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Review

Recommendations for an update of the 2010 European regulatory guideline on clinical investigation of medicinal products used in the treatment of osteoarthritis and reflections about related clinically relevant outcomes: expert consensus statement

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SUMMARY

Objective: The European Society on Clinical and Economic aspects of Osteoporosis and Osteoarthritis (ESCEO) organised a working group to evaluate the need for updating the current European guideline on clinical investigation of drugs used in the treatment of osteoarthritis (OA).
Design: Areas of potential attention were identified and the need for modifications, update or clarification was examined. Proposals were then developed based on literature reviews and through a consensus process.
Results: It was agreed that the current guideline overall still reflects the current knowledge in OA, although two possible modifications were identified. The first relates to the number and timing of measurements required as primary endpoints during clinical trials of symptom-relieving drugs, either drugs with rapid onset of action or slow acting drugs. The suggested modifications are intended to take into consideration the time related clinical need and expected time response to these drugs – i.e., a more early effect for the first category in addition to the maintenance of effect, a more continuous benefit over the long-term for the latter – in the timing of assessments.
Secondly, values above which a benefit over placebo should be considered clinically relevant were considered. Based on literature reviews, the most consensual values were determined for primary endpoints of both symptom-relieving drugs (i.e., pain intensity on a visual analogue scale (VAS)) and disease-modifying drugs (i.e., radiographic joint-space narrowing).

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Conclusions: This working document might be considered by the European regulatory authorities in a future update of the guideline for the registration of drugs in OA.

Introduction

Osteoarthritis (OA) is a common, slowly progressive condition that may affect all joint structures, and is a major cause of pain and chronic disability in the elderly[1]. Current treatment includes non-pharmacological and pharmacological therapies that are taken into account in a recent algorithm developed to advise on the possible stepwise approach to the sequence of interventions[2].

Symptomatic drugs are usually divided into drugs with a rapid onset of action such as paracetamol or other analgesics and non-steroidal anti-inflammatory drugs (NSAIDs) – (being either non-selective or selective COX-2 inhibitors) – or intra-articular injections of corticosteroids, and Symptomatic Slow Acting Drugs for OA (SYSADOAs) such as glucosamine and chondroitin sulfate or intraarticular hyaluronic acid. Drugs with potential beneficial effect on the joint structure (Disease Modifying OsteoArthritis Drugs, DMOADs) may be developed in the future: these may or may not have a direct effect on symptoms and they may delay the disease process, as preliminarily suggested by currently available SYSADOAs showing some hints of modification of joint structure[3,4,5].

A first European regulatory document aimed at providing advice for the development of drugs in OA was issued in 1998[6]. The latest version of the Committee for Medicinal Products for Human Use (CHMP)/European Medicines Agency (EMA) guidance[7], adopted in 2010, is a revision of that document.

The first version of the guideline[6] was derived from a report by the Group for Respect of Ethics and Excellence in Sciences (GREES)[8]. This group has been thereafter providing recommendations for an update based on a critical analysis of the available science[9–11].

A substantial part of these proposals were taken into account in the 2010 current version of the CHMP/EMA guidance[7].

Several elements of the guideline are the subject of much debate. They are mainly related to the cut-off values that should define a clinically relevant symptomatic or structural improvement and to the timing of assessments that should be collected throughout confirmatory clinical trials.

For this reason, under the auspices of the European Society on Clinical and Economic aspects of Osteoporosis and Osteoarthritis (ESCEO), a special section of the GREES was convened in May 2014 to discuss these issues in the light of recent data and expert opinion. The consensus view, which might be possibly considered in future guidelines, is presented in this discussion paper.

Methods

As in previous initiatives and publications, the GREES/ESCEO working group consisted of clinical scientists expert in the field of OA in academia and consulting for drug development within the pharmaceutical industry, and representatives of national or European licensing authorities giving their contribution on a personal basis.

As a general methodology, the group reviewed the current version of the CHMP/EMA guideline in detail[7].

The members of the working group were asked to assess the possible need for revision of the guideline in view of their knowledge of the field and of the clinical literature, in order to identify the areas of potential attention. The group judged that there was no need to revise any of the first four sections within the CHMP/EMA document (including disease definition, drug categories and patient selection). Conversely, there was general consensus that specific parts within the methods for assessing efficacy section (Section 5) for both symptom modifying and structure modifying drugs, with particular respect to the clinical relevance of the changes on the primary endpoint(s) and the timing of assessment, may be in need of clarification. This would inevitably affect also the section on the design of the studies (Section 6.2) with particular regard to confirmatory trials, while the guideline sections on 'early studies in man' (Section 6.1) or the 'clinical safety evaluation' (Section 7) were not explicitly covered by the discussion.

Members of the group (SR, OB and GH-B) were therefore asked to prepare a full review of the literature on these topics and to present the results at the May 2014 meeting. After the presentations, a comprehensive discussion was hold within the group and shared conclusions were reached.

Results

Table I summarizes the proposed changes to the current guideline document, as extensively reported below.

Primary endpoint and design of clinical studies of symptom modifying drugs

Symptom modifying drugs act on pain and potentially on functional disability. According to the CHMP guideline, Phase III pivotal studies should have a randomised, double-blind, parallel group design. A three-arm study with placebo and a most appropriate active comparator is recommended for symptom modifying drugs: the nature of the active comparator can be discussed between the regulatory authority and the sponsor e.g., in a scientific advice procedure. Long-term efficacy data (e.g., on an open label extension) as well as data after stopping therapy should be provided. Importantly, the absence of deleterious effects on joint structure should be established from imaging (e.g., radiographic) data obtained over at least one year.

The recommended primary endpoint for clinical development of symptom modifying drugs is pain attributable to the target joint. Pain referring to a recent period, ideally the past 24 or 48 h, should be self-assessed by the patient using a validated method (e.g., the visual analogue scale-VAS, Likert scale…). Validated multidimensional tools with pain subscale index are also acceptable. Functional disability may be considered as an important co-primary endpoint, again with validated disease-specific and joint-specific instruments. However, if functional disability is not a co-primary endpoint and benefit is only shown for pain, at least the absence of deterioration of physical function should be demonstrated.

In the opinion of the working group, some specific clarifications and recommendations were considered necessary and are given below for the development of drugs with rapid onset of actions and SYSADOAs, respectively.

Symptom modifying drugs with rapid onset of action

The current guideline recommends that the primary endpoint, i.e., the change from baseline in pain intensity and optionally

Table I
Proposed modifications to the current CHMP/EMA guideline on the clinical investigation of medicinal products used in the treatment of OA (CPMP/EWP/784/97). Sections 1–4 and 7 do not require modifications

Current content	Proposed modification
5. Methods to assess efficacy	
5.1 Medicinal products intended to improve symptoms	
Primary endpoint	
• Pain attributable to the target joint is the primary endpoint.	• Unchanged
• Pain self-assessment by a validated method (e.g., VAS, NRS, Likert) separately on motion at rest, or validated multidimensional tools subscale index, referring to a recent past (e.g., 24–48 h), as absolute difference vs baseline.	• Unchanged
• The difference vs placebo should be predefined and justified based on published trials.	• A rounded MPCI 10 mm average value on a 100 mm VAS is acceptable as threshold for clinically significant difference vs placebo at the patient group level.
• Functional disability co-primary optionally, or at least show no deterioration.	• Unchanged
Secondary endpoints	
• Course of pain intensity (e.g., AUC).	• Unchanged
• Percentage of responders per predefined definition (including PASS, MCII, OARSI criteria).	• Responder criteria are important at the individual patient level: MCII is the preferred concept and PASS is helpful for assessing maintenance of improvement; OARSI/OMERACT criteria as alternative, but do not distinguish between pain and function. Clinically relevant improvement at a 10–20% difference vs placebo depending on drug class (SYSADOA and symptomatic drugs with rapid onset of action, respectively).
• Other secondary endpoints	• Unchanged
5.2 Medicinal products intended to slow or prevent structural damage	
• Radiographic JSN as primary endpoint, with technical recommendations for assessment.	• Unchanged
• MRI as potential alternative surrogate endpoint still subject to validation, similarly to biochemical markers.	• Watch out for ongoing initiatives to qualify biochemical markers and especially MRI as an imaging biomarker offering surrogacy over shorter periods and in smaller trials than with JSN.
6. Strategy and design of clinical trials	
6.1 Early studies in Man	• Unchanged
6.2 Therapeutic confirmatory studies	
6.2.1 Study design	
Modification of symptoms	
• Studies should have randomized, double-blind, three-arm (placebo and active comparator) design.	• Unchanged
• Primary efficacy endpoint at a time-point showing maximum effect vs placebo, with maintenance confirmed for at least 3 months, for symptom modifying drugs with rapid onset of action.	• Most trials powered for primary endpoint significance vs placebo at 12–13 weeks, but several patients may need very short-term pain relief (2–4 weeks). • Three classes among drugs with rapid onset of action: a) very short-term pain relief, primary endpoint at 2–4 weeks (no worsening at 12 weeks); b) both very short-term and maintenance of pain relief, co-primary end-points at 2–4 and 12 weeks (issues in powering the studies); c) relief of persistent pain, primary endpoint at 12 weeks (effects at 2–4 weeks should be described).
• For SYSADOA, evaluation after at least 6–12 months.	• Pain intensity at multiple time-points, at least two consecutive assessments (≥4 weeks apart) or 50% of the assessments (including the last one in either case), over 6–12 months.
• Structural changes to be monitored for at least one year to exclude deleterious effects on the joint.	• Unchanged
• Data after stopping therapy should be obtained.	• Unchanged
Modification of structure	
• Studies should have randomized, double-blind, parallel group design, not shorter than 2 years	• Unchanged
• Clinical endpoints, e.g., time to virtual or actual joint replacement, preferable. If structural changes (JSN) are primary endpoint, magnitude of clinically relevant effect should be predetermined.	• Radiographic JSN ≥0.5 mm corresponds to the lowest difference exceeding the measurement error and is a relevant threshold to demonstrate activity at the individual patient level, in that significantly correlates with recourse to TJR in several studies. At the patient group level, these studies have shown that the mean reduction in JSN ranges from 0.10 to 0.36 mm vs placebo over 2–3 years.
6.2.2 Choice of control	• Unchanged
6.2.3 Concomitant interventions	• Unchanged

Abbreviations: NRS = Numeric Rating Scale; AUC = Area Under the Curve; MCII = Minimum Clinically Important Improvement; SYSADOA = Symptomatic Slow Acting Drugs in Osteoarthritis; TJR = Total Joint Replacement.

functional disability, should be assessed at a time-point appropriate to show the maximum effect over placebo. However, the guideline adds that the maintenance of effect should be evaluated after at least 3 months. Consequently, most clinical trials aiming at demonstrating the benefit of drugs rapidly acting on symptoms of OA are powered to reach statistical significance for the comparison of the drug vs placebo at 12 or 13 weeks only[12–16].

Although OA is a chronic disease, it shows fluctuating levels of pain over time. For this reason, heterogeneous results for non-selective or COX-2 selective inhibitors NSAIDs have been shown in clinical trials[17] and several studies have failed to show clinically relevant outcomes measured at 3 months[18,19]. Moreover, from the patient's perspective it would seem appropriate to have different therapeutic options, including a treatment with a demonstrated acute analgesic effect in addition to maintenance of improvement.

In systematic reviews of randomised clinical trials in knee OA patients and as acknowledged by the current CHMP guideline, the time-point of maximum effect over placebo was determined to be

2–4 weeks for systemic NSAIDs or analgesics and 1–3 weeks for intra-articular steroids injections and topical NSAIDs, respectively[17,20]. Indeed, these drug classes are intended to rapidly decrease pain/inflammation during the symptomatic phases of OA.

Furthermore, in clinical trials, the possibility of detecting a symptomatic benefit over placebo is more likely early in the course of the study than at 3 months, due to the self-healing effect: in OA clinical trials, placebo responses on pain have been shown to be considerable[21,22] and may increase over time[23]. Last but not least, several patients may actually need drugs that provide very short-term pain relief. Therefore, the clinical relevance of this time-point at 3 months appears questionable for this class of drugs, especially for those with a particularly fast and relevant onset of action, that in several instances may even better serve patient's needs. Thus, the group felt it may be at least as important to demonstrate a decrease in pain intensity in the first weeks of treatment as it is after 3 months, as long as the characteristics of the new drug indicate that this is a potentially achievable target. Two to 4 weeks appear as a reasonable target for the demonstration of pain reduction, depending on the drug tested.

The working group proposal is that the benefit of most analgesic drugs over placebo on pain assessed at 2–4 weeks after the initiation of treatment might be considered an alternative primary endpoint. The currently recommended benefit at 3 months may remain a co-primary endpoint as evidence for the maintenance of the effect of the drug, or in exceptional cases even as a secondary endpoint if appropriately justified (e.g., depending on the indication claimed, or the characteristics of the drug and keeping in mind that the extent of the difference between groups may be smaller at 3 months than at 2–4 weeks for the reasons above, thus with issues in appropriately powering the studies).

Drugs whose mechanism of action suggests a strong maintenance of effects, may retain the currently recommended primary endpoint at 3 months (but the effects after 2–4 weeks should be described). In such a way, there may be three classes within symptom modifying drugs with rapid onset of action: a) those that provide very short-term pain relief, with trial primary endpoint after 2–4 weeks (and at least no worsening over placebo on 12-week data collected as secondary endpoint); b) those providing both very short-term pain relief and maintenance of such effect after 12 weeks (two co-primary endpoints); c) those whose primary endpoint for pain relief is at 12 weeks, as currently recommended (but whose effects after 2–4 weeks should be described). Appropriate classification should be reflected in the drug labelling.

OA pain intensity should be measured by patient's self-assessment with validated methods such as the Visual Analogue Scale (VAS), which is enough sensitive to distinguish small differences. The guideline requires the demonstration of a statistically significant and a clinically meaningful superiority vs placebo on pain intensity to justify efficacy. However, there is no further indication of where this clinically relevant superiority threshold should be set at a patient group level or at an individual patient level.

At the patient group level, the Minimum Perceptible Clinical Improvement (MPCI) could be considered: a value of 9.7 mm on the 100 mm normalised pain subscale of a multidimensional tool such as the WOMAC (Western Ontario and McMaster Universities) index[24] (a copyrighted instrument, therefore not publicly available) has been shown to represent the MPCI in patients with knee or hip OA[25]. Thus, a rounded 10 mm value on a 100 mm pain VAS is accepted by the scientific community as a threshold for a clinically significant difference as compared with placebo[26]. Indeed, it has been shown to be an achievable target for symptom modifying drugs with rapid onset of action, e.g., NSAIDs at the peak of their effects after 2–4 weeks of treatment[20]. Such threshold may be used as primary outcome in pivotal trials and thus for sample size calculation. Clearly, the final decision on product approval will depend on the overall assessment of the benefit and harm related to the new specific agent.

At the individual patient level, the most widely accepted and preferred concept to define a responder is the Minimal Clinically Important Improvement (MCII, i.e., "feeling better")[27,28]. A responder rate based on the MCII could be chosen as an important secondary endpoint. Also, the Patient Acceptable Symptom State (PASS, i.e., "feeling good") could be used to calculate the rate of responders[29] especially when assessing maintenance of improvement after 3 months. Another method for determining a clinically relevant responder would be to use the OARSI/OMERACT responder criteria[30]. However, they cannot distinguish between pain and function.

The difference between the rates (percentages) of defined responders between test and placebo group should show a relevant clinical benefit for a substantial part of treated patients to justify the treatment. Such difference should be pre-determined and at least approximately 20% over placebo.

Further improvement of study design could be reached by requiring a flaring design in knee OA patients[31] and considering the documented differences in the outcome between knee and hip OA by assessing the locations separately[19].

SYSADOAs

The current guideline recommends that for SYSADOAs the primary endpoint for symptoms should be assessed after at least 6–12 months of treatment. It is unclear whether the extent of improvement after such a long treatment course should be similar to that suggested for rapidly acting symptomatic agents and whether a single assessment at the end of treatment is sufficient.

With respect to the latter, the position of the working group was that the assessment of pain intensity at multiple time-points, reflecting a sustained clinical benefit, would be more appropriate and relevant for this class of drugs than a rather random outcome measurement of improvement at only one single time point.

Insofar as OA may be associated with remitting and relapsing symptoms, intermediate measurements should be taken into account in the evaluation of slow-acting drugs, as well as consistency between various assessments.

This statement is in accordance with data showing that the consistency of pain at two time points, not only its severity, can predict the need for total knee replacement[32]. The association was consistent across each level of pain severity. In line with this concept of consistency between multiple measurements, the sustainability and persistence of symptoms were considered important components for "virtual joint replacement" (VJR), a composite index proposed as a surrogate outcome for OA progression in clinical trials[33].

The multiplicity of assessments however raised several issues, including the questions of the number of measurements and when they should be performed. In 6–12-month clinical trials, the number of assessments of pain and function is generally from 3 to 6, distributed over the treatment period in the most appropriate manner according to the characteristics of the medicinal product and of the trial.

The group suggested that within the context of confirmatory trials for SYSADOAs, a statistically significant improvement should be detected at least on the last two consecutive assessments as long as they are sufficiently spaced, e.g., not less than 4 weeks apart. Alternatively, a significant improvement might be seen on at least 50% of the assessments including the last one. In any case, there should be no clinically relevant worsening at any of the time points.

A final remark with regards to the interpretation/evaluation of the results is that the multiplicity of measurements should be taken into consideration in the preparation of the statistical analysis plan[34].

Also for SYSADOAs, the current CHMP-guideline recommends that the mean difference in the change in pain intensity vs placebo should be statistically significant and clinically relevant. It is generally admitted that the expected extent of improvement is smaller with SYSADOAs than with drugs with rapid onset of action[35,36]. Published clinical trials show symptomatic improvement in the 5–6 mm range on a 100 mm VAS[37–42]. Average changes in this range translated in a clinically relevant higher proportion of responder patients according to MCII, PASS, or OARSI/OMERACT criteria. The working group suggested at least 5 mm as a clinically relevant threshold for a SYSDAOA in the difference with placebo at the patient group level, also considering that the required sustained benefit might increase the precision of measurements (see above), that such an effect would allow the control of the disease symptoms over much longer treatments and finally, in view of the generally better safety of SYSADOAs compared with faster acting medications. At the individual patient level, the same parameters considered for symptom modifying drugs with rapid onset of action should be used for calculating responder rates, aiming at a difference with placebo in the 10–20% range as suggested in pivotal trials of existing SYSADOA[42].

Primary endpoint and design of Disease Modifying Drugs for Osteoarthritis (DMOADs)

Structural modification of the joint is considered to be the most important determinant of disease progression. Joint Space Narrowing (JSN), measured on conventional X rays, is currently the only validated primary outcome measure to show progression of OA[7,43]. The surrogacy of JSN has been established in 8-year studies where it has been shown to correlate with the need for joint replacement in knee OA[44,45]. It is assumed that this could also be valid for hip OA. The working group agrees therefore on the current guideline stating that radiographic JSN is an acceptable surrogate outcome measure for OA disease modification and is still the gold standard compared with other methods including magnetic resonance imaging (MRI) or biochemical markers. The group also agrees on the current technical recommendations within the guideline for appropriate radiological assessment. However, if a clear consensus admits that JSN is the most appropriate structural measure[46,47], a threshold value above which a reduction of JSN should be considered as clinically relevant has not been validated. Nevertheless, a minimum radiographic JSN of 0.5 mm or more over the duration of the trial (i.e., 2–3 years) in the individual patient has been suggested to be a relevant threshold to demonstrate efficacy[26,48]. This value corresponds mostly to the lowest difference in joint space width exceeding the measurement error: while, pragmatically, the measurement error should be study-specific, the current guidelines state that the magnitude of the drug effect should be predetermined based on previously established findings. The group agrees on this statement (also in view of the need of predetermining the sample size of the trial) and it appears therefore logical to base the choice on the available literature. In this respect and notably, patients with radiographic minimum JSN $\geq$0.5 mm over 3 years have a statistically significant, three-to fourfold increase in risk of joint replacement over up to 8 years[11,44]. However, none of the considered thresholds of mean JSN (0.2–0.8 mm) was significantly related to the clinical outcome. In a number of studies, individual patients considered having a clinically relevant radiographic progression are those with a minimum JSN $\geq$0.5 mm[5,48–52]. Conversely, it is more difficult to determine what should be a clinically relevant difference in JSN at a patient group level, since many patients do not vary at all, even during a 2–3 years period of observation, and since the distribution of radiographic joint space changes does not follow a Normal law. Published clinical trials generally show a group mean reduction of JSN with glucosamine[3,4,50], chondroitin sulfate[5,50,53] or strontium ranelate[49] ranging from less than 0.10 to 0.36 mm over 2 or 3 years. Such average changes are clinically relevant in that they seem to predict total joint replacement over longer periods of observation[54]. As discussed above for SYSADOA pain relief assessments, the consistency of the trend of JSN over the duration of the trial could be important to consider, as it has been shown that taking into account more measurements and not only the last one, may be more relevant as a predictive tool of future knee surgery in the individual patient.[44]

While radiographic JSN is the currently accepted primary endpoint at the regulatory level for a DMOAD, it is acknowledged that it is an imperfect surrogate of disease progression. First of all, it may reflect modifications in other structures, e.g., meniscal extrusion and degeneration, while not addressing changes at other joint tissues, e.g., synovitis or bone marrow lesions. In addition, small sensitivity to change may require several hundred patients in 2–3 year trials to show relevant changes over placebo. For this reason initiatives are in progress such as the one by the Foundation for NIH OA Biomarkers Consortium[55] to qualify new biochemical or imaging biomarkers that may be predictive of radiographic (and pain) progression over shorter treatment periods and in smaller scale trials. In particular, MRI may become the imaging modality of choice in the future if its validity and responsiveness is proven. MRI measures currently investigated include quantitative cartilage morphometry, bone marrow lesions and other joint structure changes on semi-quantitative analysis, bone shape/attrition and subchondral bone area[55].

Discussion

The current CHMP European guidance on clinical investigation of drugs for the treatment of OA overall is still in line with the current scientific knowledge and only a few points that deserve discussion were identified. They mainly relate to the number and timing of measurements of the primary endpoints performed during clinical trials with symptom modifying medicinal products with rapid onset of effect and SYSADOA, and the need to define more precisely the required clinically relevant benefit thresholds for both symptom modifying and structure modifying agents.

For symptom-relieving drugs, the guideline recommends that an improvement in pain intensity should be demonstrated primarily at 3 months for drugs with rapid onset of action and at 6 months or 12 months for SYSADOAs. The suggested modifications are intended to take into account the expected time-related main clinical need and time response of these drugs – i.e., a more acute effect for the first class of drugs in addition to maintenance of effect, a more sustained effect for the latter – in the timing of assessments.

For drugs providing very short-term pain relief, symptomatic benefit should be demonstrated as primary endpoint after 2–4 weeks of treatment, to be possibly adapted to the pharmacokinetic and pharmacodynamic characteristics of the drug tested, with the maintenance of efficacy after a 3-month treatment period as a co-primary endpoint or as a secondary endpoint if appropriately justified. In the important subset of patients with persistent pain, the primary endpoint should continue to be collected at 3 months, thus giving preference to maintenance of effects. The exact product characteristics should be described in the drug labelling. As differences in the extent of pain reduction between knee and hip OA patients are identified this should be considered by appropriately assessing these patients separately.

For SYSADOAs, the working group suggests multiple assessment time points to better show sustained benefit. Significant benefit over placebo should be shown on at least two consecutive assessments including the last one over a 6–12-month treatment, or 50% of the assessments including the last one with no clinically relevant worsening at any time point.

A second aspect of the discussions concerned the threshold value above which a benefit over placebo should be considered as clinically relevant. Although none of the proposed thresholds is officially validated and further confirmatory data are needed, the most consensual values based on a literature review were identified for each class of drugs. For symptomatic drugs, the mean difference of changes in pain intensity between the active drug and placebo at the patient group level should be at least 10 mm on a 100 mm VAS or on the normalised pain subscale of an appropriate multidimensional tool (e.g., the WOMAC index) for a drug with a rapid onset of action. For a SYSADOA such average difference should be at least 5 mm, but it should be shown at repeated time points. At the individual patient level, several responder criteria have been proposed as secondary endpoints, including preferentially the MCII, or the PASS (especially for documenting maintenance of effects), or the OARSI/OMERACT criteria. The difference with placebo in responder rate should be between 10% and 20% depending on the drug class (SYSADOA or rapid onset of action, respectively). For DMOADs, the reduction in the proportion of patients with radiographic minimum JSN of more than 0.5 mm over the duration of the trial is suggested as a relevant threshold to demonstrate efficacy at the individual patient level. Conversely, it is more difficult to propose an average difference with placebo in the change from baseline at the patient group level, although available trials[3,4,5,49,50,53] show that this may range from less than 0.10 to 0.36 mm over 2–3 years and be clinically relevant[54]. New initiatives are ongoing[55] that may establish MRI as a better surrogate of OA progression.

Much remains to be established in OA. The research agenda includes better understanding of underlying mechanisms of the disease, and consensus on the definition of clinical outcomes.

Author's contribution

OB, JYR organized the meeting. SR, OB, GHB performed the literature review. All authors have taken part in the discussion and meeting and have critically analysed and approved the final manuscript.

Competing interests

All authors have completed the International Committee of Medical Journal Editors (ICMJE) uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf.

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