



Recommendations for the Reporting of Harms in Manuscripts on Clinical Trials Assessing Osteoarthritis Drugs: A Consensus Statement from the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO)

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Abstract

Background There is strong evidence of under-reporting of harms in manuscripts on randomized controlled trials (RCTs) compared with the volume of raw data retrieved from these trials. Many guidelines have been developed to tackle this, but they have failed to address some important issues that would allow for standardization and transparency. As a consequence, harms reporting in manuscripts remains suboptimal.

Objective The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) aimed to deliver accurate recommendations for better reporting of harms in clinical trials manuscripts on anti-osteoarthritis (OA) drugs. These could help to better inform clinicians on harms recorded in RCTs and further help researchers conducting meta-analyses.

Methods Using the outcomes of several systematic reviews on the safety of anti-OA drugs, we summarized the ways in which harms have been reported in OA RCT manuscripts to date. Next, we drafted some recommendations and initiated a modified Delphi process that involved a panel of clinicians and clinical researchers to build an expert consensus on recommendations from the ESCEO for the reporting of harms in future manuscripts on RCTs assessing anti-OA drugs.

Results These recommendations emphasize that all treatment-emergent adverse events (AEs) should always be taken into account for harms reporting, with no frequency threshold, and describe how specific AEs should be reported; they also provide a list of the most relevant organ systems to be considered according to each class of drug for reporting of harms within the results section of a manuscript. Irrespective of the drug, the ESCEO recommends that total, severe and serious AEs and withdrawals due to AEs should always be reported; guidance on the reporting of specific events pertaining to each category is provided. The ESCEO also recommends the reporting of information on drug effect on biological parameters, with specific guidance.

Conclusions These recommendations may contribute to improve transparency in the field of safety of anti-OA medications. Pharmaceutical companies developing drugs for OA, and researchers conducting clinical trials, are encouraged to comply with them when reporting harms-related results in manuscripts on RCTs. The ESCEO also encourages journals to refer to the ESCEO recommendations in their instructions to authors for the publication of manuscripts on trials of anti-OA medications.

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1 Introduction

Drug safety is a critical public health issue but, unfortunately, harms-related data collected from randomized controlled trials (RCTs) are not adequately reported in manuscripts [1]. In fact, there is strong evidence of important dissimilarities between published and unpublished adverse

Key Points

These are the first recommendations for harms reporting in clinical trial manuscripts on drugs specific to osteoarthritis (OA); however, they may also apply to other diseases, particularly for anti-OA drugs that are also used in other fields.

The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) safety working group emphasizes that all treatment-emergent adverse events (AEs) should always be considered for harms reporting, with no frequency threshold; any interpretation of a relationship between an AE and the treatment studied should only be included in the discussion section of the manuscript, when comparing the results with findings from other clinical trials or meta-analyses.

Clear and specific guidance is provided for the reporting of each type of AE, with particular emphasis that all specific severe and serious events should always be reported; henceforth, information on adverse drug biological effects should also be reported.

event (AE) data from the same study and of published data being systematically under-reported [2–5]. Many reasons are proposed to explain the practice of under-reporting of AEs, including an emphasis on efficacy rather than harms, a lack of statistical significance, and restrictions on manuscript length [6–9].

Several initiatives have been undertaken in an attempt to tackle the inadequate reporting of harms in manuscripts on RCTs. These include the development of an extension of the Consolidated Standards of Reporting Trials (CONSORT) statement specifically dedicated to harms reporting [10]. However, this more general guidance, primarily dealing with how AE information should be reported in various sections of the manuscript, fails to provide clear instruction on which “type” of AE should be described in the results section and how to uniformly report harms across studies. Consequently, despite the release of the CONSORT-harms extension statement, practices around reporting of AE results were still found to be inadequate and inconsistent [11–13]. Thus, additional recommendations to improve AE reporting in clinical trial publications have been developed to complement the CONSORT-harms extension statement by providing guidance on the reporting of clinically informative harms-related data [14]. These recommendations specify deaths, serious AEs and dropouts due to AEs as the harms that should always be reported, whatever the intervention or the

population being studied. However, for the reporting of other AEs, the authors suggest multiple strategies, which include reporting AEs according to clinical relevance, reporting the most common AEs (using a threshold of occurrence), or grouping AEs according to organ systems [14]. While representing progress compared with the CONSORT-harms extension statement, this left the choice of reporting harms-related data to author preference, which might not allow comparability between different trials on the same drug or between various trials on different classes of drugs for the same disease; in addition, combining the results reported using such different reporting systems in a meta-analysis may not prove meaningful.

Further to the release of the CONSORT-harms extension statement in 2004 [10] and prior to the publication of the recommendations by Lineberry et al. [14] in 2016, both of which were rather broad and not disease/drug-specific in nature, two recommendations specific to the reporting of harms with some pain medications were published in 2013 [15, 16]. Interestingly, the authors of these recommendations raised and addressed many of the most important points that should be considered for comprehensive reporting of relevant AEs in manuscripts. However, these recommendations failed to clarify some issues that we consider essential with regard to standardization and transparency in the reporting of AEs. Notably, although not specifically dedicated to the reporting of harms in OA, these guidelines on the reporting of harms for pain medications apparently did not help to improve the reporting of AEs in manuscripts on OA, a disease in which pain is an important outcome [17–19]. As an illustration, manuscripts on randomized trials in OA published in 2018 still lack completeness and consistency in the reporting of AEs [20–23].

While some progress has been made in the reporting of AEs in clinical trial manuscripts in recent years [15, 16], it is still recognized that considerable improvements are needed [24–26]. The need for disease-specific guidance on AE reporting has been identified to enable consistency in the disclosure of harms across RCT manuscripts [13] by standardizing the reporting of harms-related results. Such specific guidance does not exist in the field of musculoskeletal diseases, and particularly for OA.

To close this gap, a working group of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), through publication of this document, aims to complement the existing recommendations on the reporting of clinical trials. The ESCEO recommendations provide specific, clear, practical and standardized guidance on the reporting of harms in manuscripts on RCTs assessing anti-OA drugs. These recommendations are limited to manuscripts for publication of RCTs in scientific journals; therefore, sponsors of clinical trials should continue to adhere to regulatory

guidelines for reporting AEs arising from clinical trials to regulatory authorities worldwide [27–29].

2 Methods

Recently, the ESCEO commissioned several systematic reviews and meta-analyses of randomized, placebo-controlled trials to reassess the safety of various anti-OA medications, including topical nonsteroidal anti-inflammatory drugs (NSAIDs), symptomatic slow-acting drugs for OA (SYSADOAs) and intra-articular hyaluronic acid (IAHA) [30–32]. For this purpose, the MEDLINE, Cochrane Central Register of Controlled Trials, and Scopus databases were comprehensively searched. The methodology and the outcomes of these systematic reviews have been extensively described in each manuscript. From the articles included in each systematic review, we collected information on how AE data were reported; details on how AE-related results were reported in each article retrieved from the systematic review processes can be found in the tables describing the characteristics of the included studies in each specific manuscript reporting the outcomes of these new meta-analyses (in this supplement) [30–32]. For the purpose of preparing the ESCEO recommendations for the reporting of harms in future manuscripts on trials on anti-OA medications, we summarized the ways in which harms-related data have been reported across the articles retrieved for these new ESCEO meta-analyses, and report here the common sub-standard harms reporting practices found in these prior manuscripts on RCTs on anti-OA drugs.

On the basis of this, and considering the difficulties encountered in pooling the published data for the purpose of meta-analysis, we conceived a draft of a general framework for harms reporting in clinical trial manuscripts. To build expert consensus guidance on the reporting of harms-related data in future anti-OA medication trial manuscripts, we initiated a two-stage modified Delphi process [33–35] that involved experts from the ESCEO working group on the safety of anti-OA medications.

This working group included rheumatologists, specialists in physical medicine and rehabilitation, clinical epidemiologists, endocrinologists, pharmacologists, orthopedic surgeons, geriatricians, specialists in public health and health economics, preclinical scientists and representatives of patients with OA. The working group took place on 1 December 2017 in Geneva, Switzerland, where the results of the new meta-analyses on the safety of anti-OA medications were first presented. The majority of the working group members have been clinical investigators for anti-OA medication trials and/or clinicians. All 20 of the members of the ESCEO working group on the safety of anti-OA medications were invited to take part in the consensus-making process.

The Delphi process aimed at reaching consensus on a final general framework for the reporting of harms-related data in manuscripts. An additional consensus was also to be made on the most relevant organ systems to be considered for the reporting of harms within the results sections of manuscripts on RCTs according to each drug class, to take into account journal space constraints [8, 15] and the fact that all AEs arising from a clinical trial cannot be reported within the results section of a manuscript.

The first round of the modified Delphi process consisted of reviewing, commenting on, and improving the first draft of the general framework designed by the lead author (GH). The working group members were asked to add any other subjects they would judge necessary to include in the general framework. This first round took place from 26 July to 31 August 2018. The new ideas were summarized, and the original draft was adapted using the contributions from the working group members. The new draft of the general framework was then submitted to all working group members who contributed to the first round of the consensus-making process for review and consensus. They were asked to consider the relevance, feasibility and usefulness of each item and rate it on a scale of 0–10, expressing their level of agreement on each specific item (0 being “strongly disagree” and 10 “strongly agree”). They were asked to rate the item as highly as they thought it should be recommended. The second round took place from 26 September to 18 October 2018. During this round, the working group members were also asked to select from a list the system organ classes (SOCs) they thought the most relevant (absolutely essential) for harms data reporting within the results section of a manuscript according to each class of drug in OA. The rationale for SOC selection was the mechanism of action of the drug and organ systems that might reasonably be harmed by a specific class of drug [14]; physicians’ and patients’ safety concerns about each drug class were also to be taken into account for selection.

Regarding the general framework for harms reporting, the median rating (within the 25th and 75th percentiles [P25 and P75]) was determined for each item following the second round of the Delphi process to measure the overall degree of agreement on each item. Prior to the calculation of the median ratings, when a working group member rating was < 7 for an item, the responders were asked to comment on their rating so we could understand why they did not express strong agreement with this specific item. Based on these comments, the content of the item was rephrased without modifying the main idea of the recommendation in the specific item. However, the working group member was not asked to give a new rating to the item. A draft of the manuscript describing the ESCEO recommendations for harms reporting in future publications on clinical trials on anti-OA medications was subsequently prepared and submitted to

all ESCEO safety working group members for review. All members of the working group agreed with the final version of this consensus paper.

3 Results

3.1 Adverse Event (AE) Reporting Practices in Prior Anti-osteoarthritis (OA) Medication Trial Publications

The articles selected for the ESCEO meta-analyses on the safety of some anti-OA medications [30–32] hide important divergence in the reporting of AEs, which we report here. As previously stated, these meta-analyses were aimed at assessing the AEs associated with the use of topical NSAIDs, SYS-ADOAs and IAHA for the management of OA. The main different ways in which harms-related data were reported in the retrieved articles are summarized in the following six subsections and in Table 1. These diverse reporting practices, which have also been described in other systematic reviews on drugs for other diseases [15, 16], preclude any objective comparison of AEs and AE frequencies between various studies on the same medication, as well as between studies on different drugs for the same disease. Pooling of these kind of diversely reported data is inadequate in

meta-analyses [15] or, at least, might lead to a systematic underestimation of harms. Thus, any objective assessment of harm/benefit balance in such context is compromised.

In addition to the main harms-reporting practices summarized hereunder, we also found that, although the total numbers of participants who withdrew from the trials due to AEs or who experienced any severe or serious AEs at least once during the trials were usually reported in the manuscripts, the specific events pertaining to each of these categories were not always reported. In almost all of the articles, we found no reported data about drug effects on biochemical and biological parameters such as full blood count, hemoglobin, and biochemical markers of liver injury and renal function.

3.1.1 Treatment-Emergent vs. Treatment-Related AEs

In some articles, harms were reported as “treatment-emergent AEs” (TEAEs) [36–38], defined by the International Conference on Harmonization (ICH) as events “that emerge during treatment having been absent pre-treatment, or that worsen relative to the pre-treatment state” [39]. Other manuscripts reported only AEs judged by the investigators as “treatment-related AEs” (TRAEs) [40–42]. Finally, many other cases did not clearly specify whether the reported AEs were “treatment emergent” or “treatment related” [43, 44].

Table 1 Summary of adverse event reporting practices in past osteoarthritis trial manuscripts

| Reporting practice | Description |
|---|---|
| Reporting only AEs considered treatment related | Reporting of only AEs judged by clinical investigators as related or probably related to treatment, instead of reporting all AEs that emerge or worsen during treatment (TEAEs) |
| Defining a threshold for AE reporting | Reporting only the AEs that are the most common. Usually, a threshold for harms reporting was chosen by the authors, which varied widely across manuscripts: 2%, 3%, or 5% were most frequently used |
| Reporting harms frequencies at SOC level only or only for some specific events | For example, reporting the number of patients who experienced any gastrointestinal disorder at least once (SOC-level frequency) per group, without details of specific events. Conversely, reporting only the frequencies of some specific gastrointestinal disorders (e.g., diarrhea, flatulence, abdominal pain) |
| Summary report and reporting of total numbers of AEs | Reporting profile limited to short statements such as “the rates of AEs were the same between the treatment and placebo groups,” without clearly reporting the frequencies in each treated group. Sometimes, instead of reporting the AEs and their frequencies (i.e., number of patients reporting each event at least once), authors reported the numbers of AEs experienced during the trial (e.g., “ten AEs were reported in the intervention group and 12 in the placebo group”) |
| Combination of many of these previously described reporting profiles in a single manuscript | For example, reporting the frequencies of some specific AEs considered “treatment related” only when a defined percentage of participants (e.g., > 2%, > 5%, or other) experienced these events |
| Heterogeneity in AE coding systems used | Various AE coding systems were used for harms reporting (e.g., the WHO-ART, the MedDRA, the COSTART). Many manuscripts did not specify the coding system used |

AE adverse event, COSTART Coding Symbols for Thesaurus of Adverse Reaction Terms, MedDRA Medical Dictionary for Regulatory Activities, SOC system organ class, TEAE treatment-emergent adverse event, WHO-ART WHO – Adverse Reaction Terminology system

3.1.2 Relevance of AEs: A Threshold for AE Reporting

Reporting AEs according to frequency of occurrence was very common. Many articles reported only AEs experienced by at least a given percentage of patients in either group (treatment or control). The most common threshold percentages were 2% (i.e., AEs occurring in $\geq 2\%$ of patients in either group) [36, 45], 3% [37], or 5% [46–48].

3.1.3 System Organ Class (SOC) vs. Specific AE Reporting

Many articles reported AEs by SOC, providing for each SOC the number of patients who experienced any AE related to that SOC. Sometimes only partial or no details on specific AEs pertaining to each SOC were included [42, 49, 50]. By contrast, other articles reported only a small number of selected specific AEs [47, 51] without providing the overall SOC-related frequencies when many specific AEs pertained to the same SOC.

3.1.4 Reporting in Summary Form and/or Reporting of the Number of AEs

The majority of manuscripts on the efficacy and safety of anti-OA medications reported AE data only in summary form. This summary was usually formulated as: “The most commonly reported AEs in the intervention and control groups were xxx” and/or “There was no statistically significant difference between the intervention and control groups” and/or “There were no serious AEs in either group” [52–54].

Alternatively, rather than listing the AEs and providing the number of patients who experienced each event at least once (the frequency), some manuscript authors reported only the numbers of AEs experienced during the trial [52, 55, 56]. This was usually stated in the form of “The total numbers of AEs in the intervention and placebo groups were # and ## AEs, respectively” or “The numbers of AEs in the two treatment arms were similar: ### AEs occurred in the intervention group and #### AEs in the placebo group.” This kind of information is not relevant in terms of knowledge about harms associated with a given treatment.

3.1.5 Combination of Many of the Previous Reporting Profiles in a Single Manuscript

Very often, many of these previously described reporting practices were combined in a single manuscript. Sometimes, “TRAEs in a defined percentage of patients” [42, 45, 57] or “TEAEs in a defined percentage of patients” [36–38] were reported, and these threshold percentages varied between manuscripts reporting data from various RCTs on the same drug. Other cases provided a narrative summary of treatment-related (and/or treatment-unrelated) AEs in the results

section of the manuscript to describe harms associated with drugs [40, 58].

3.1.6 AE Coding Systems

Different coding systems were used for the assessment and reporting of AEs in the studies included in the new ESCEO meta-analyses. These included the WHO-Adverse Reaction Terminology (WHO-ART) system [55, 58], the Medical Dictionary for Regulatory Activities (MedDRA) [38, 59, 60] and the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) [44, 61]. Most manuscripts did not specify the AE coding dictionary used [43, 62–64].

3.2 The ESCEO Recommendations for Harms Reporting in Future Manuscripts on Studies Assessing Anti-OA Drugs

In total, 20 individuals were first invited to the modified Delphi process (round 1); 15 responded, representing 75% of the original experts contacted. Based on comments from these experts during this first round, the six items originally designed as a general framework for harms reporting were rephrased or improved, leading to a new draft with eight items. Only the 15 experts who completed the first round were then invited to take part in round 2 of the modified Delphi process; all of these participants (100%) rated each recommendation on a scale of 0–10, where 10 represented the highest level of agreement on the item.

For the eight items of the general framework for harms reporting, the median rating of the working group members was 9 ($P_{25} \geq 7$; $P_{75} = 10$) for four items, 8 ($P_{25} \geq 6$; $P_{75} \geq 9$) for three items, and 7 ($P_{25} = 6$; $P_{75} = 8$) for one item. This suggests a high level of agreement on each item. As planned, the working group members who rated an item as < 7 were contacted and asked to comment on their rating. Based on these comments, the item was rephrased for a better consensus on the final version of the recommendation without changing its main theme.

Regarding the SOCs to be considered for AE reporting within the results section of manuscripts, the votes of the members of the working group were counted. For each drug class/group, the SOCs that received $\geq 50\%$ of the votes ($\geq 7/14$ voters) were retrieved. Some additional SOCs with six votes were also ultimately included by consensus. For the SYSADOAs, “eye disorders” was not originally selected (only three votes initially) but was ultimately added to the SOCs list by consensus. Indeed, a recent RCT on glucosamine reported an increase in intraocular pressure in patients with OA, particularly in older patients [65].

3.2.1 General Framework for Harms Reporting Within the Results Sections of Manuscripts on Anti-OA Drugs

The members of the ESCEO working group on the safety of anti-OA medications agreed on a general framework of recommendations for better reporting of harms in studies assessing drugs for OA. This is summarized in Table 2 and discussed in detail here.

The ESCEO working group first focused on the types of AEs to be reported within the results section of manuscripts and how these should be reported to allow for capturing of all relevant harms. While it is understandable that AEs may differ according to individual drugs and pharmacological classes, reporting the same type of information, in the same way, from various trials of the same drug or of drugs pertaining to the same class appears to be essential. The CONSORT-harms extension statement recommends to “present the absolute risk per arm and per AE type, grade, and seriousness” [10]. However, the “AE type” is not clarified, with the result that manuscript authors may not report the same type of information for different trials on the same drug, and even for trials on different drugs for the same disease. To allow for consistency in the future, and for comparability, the ESCEO proposes a general framework for harms reporting consisting of always reporting AEs by body system.

The other source of variation in the reporting of AEs in clinical trial manuscripts is the coding dictionary used. For the meta-analyses commissioned by the ESCEO to assess the safety profile of various anti-OA medications, almost all of the full safety reports received from pharmaceutical companies and investigators used the MedDRA coding system. Other authors have also reported that MedDRA was one of the most commonly utilized systems for harms reporting around the world [66, 67]. Thus, for consistency in this regard, the ESCEO recommends use of the MedDRA coding system (<https://www.meddra.org/>) when reporting harms from drugs for OA [68, 69]. However, if another coding system is used (which is not recommended), the ESCEO recommends that this coding system and the reason for not using MedDRA should always be clearly stated in the manuscript. Regardless of the coding system used, the ESCEO recommends that, for each SOC, at least the five most frequent (more if necessary) specific AEs with their frequencies (i.e., the number of participants per arm who experienced each specific AE at least once) are reported. These AEs should be reported whether or not the difference between the intervention and control groups is statistically significant. When the MedDRA dictionary is used for AE reporting, as recommended by the ESCEO, specific AEs should be reported using MedDRA “preferred terms” [68, 69].

Finally, regarding the types of AEs that should be reported, the ESCEO recommends always reporting the total number of patients who experienced at least once

any severe AE (highest grade in severity—mild, moderate, severe—for the non-serious AEs) and any serious AE (an AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect) [27]. As well, the total number of patients who withdrew from the trial due to AE(s) and the overall number of patients who experienced any AE (total AEs) at least once during the trial should always be reported, irrespective of the drug. These reports should be made regardless of the SOC. As for the specific AEs for reporting by SOC, at least the top five specific events that led patients to withdraw from the trial should be reported, as well as the top five total AEs. By contrast, ESCEO safety working group members emphasized that all specific severe and serious AEs should always be reported.

The ESCEO safety working group members are aware that the recommendation to report the most frequent specific events (in the intervention group) pertaining to an SOC might pose a different problem. Indeed, the most frequent events might not be clinically relevant, and some more clinically relevant events might be sparse. To avoid missing any clinically relevant information, the working group members recommend separately reporting any other specific event that would be judged as clinically relevant by the clinicians conducting a trial and that would not have been captured by the reporting of serious or severe AEs, or withdrawals due to AE(s), as recommended hereunder. However, as has been seen in studies on diacerein for patients with OA, the most well-known safety issues related to that compound were the most frequent events reported in the full clinical trial reports, particularly regarding gastrointestinal and urinary system disorders [48, 70]. On the other hand, even though the most frequent specific events pertaining to an SOC are not clinically relevant, knowing them may also be important. In fact, this could help physicians to warn patients that they might experience such events (in case of a causal relationship with the treatment) but that they are not severe or serious.

The approach that consists of reporting AEs by body system along with frequencies for specific events pertaining to each body system is supported by the following rationale: when only specific AEs are reported with multiple events pertaining to the same organ class (e.g., vomiting, nausea, diarrhea, abdominal pain), it is impossible to know whether many of them have been experienced by a single patient. In this case, a meta-analysis on the harms related to a specific SOC (e.g., gastrointestinal) will not be feasible or might lead to double counting. Furthermore, for a given drug, when authors of different clinical trials choose to report only the frequencies for specific AEs (and not the SOC level frequencies), each of these authors may not be interested in reporting the same specific events. In such a case, comparing results from various studies might not be easy, because the

Table 2 Summary of the ESCEO general framework recommendation for the reporting of harms in articles reporting outcomes of clinical trials on drugs to be used in osteoarthritis

| Item | Description of the recommendation | Comment on the recommendation |
|------|--|---|
| 1 | All TEAEs must be considered for harms reporting. Any claim of TRAEs should be banned from the results section of a manuscript reporting outcomes of a single RCT | Do not consider a threshold for AE reporting (e.g., AEs occurring in $\geq 2\%$ of patients) as it may lead to a loss of harms-related information (some serious and other clinically relevant AEs may occur in $< 5\%$ or 3% or even $< 1\%$ of patients), and no argument would support any choice of threshold. Interpretations of causality (i.e., TRAEs) should only be made in the discussion section of manuscripts |
| 2 | Always report AE data by body system, providing for each body system the number of participants who experienced any AE related to that body system at least once (the frequency). These data should be separately reported for each arm of the RCT | The absolutely essential body systems that should be considered for AE reporting within the results sections of manuscripts, according to each class of anti-OA drugs, are described in Table 3 |
| 3 | Use the MedDRA coding system when reporting harms for drugs to be used in OA | For consistency in organ systems and description of specific events across studies, we recommend the use of the internationally accepted MedDRA coding dictionary |
| 4 | For each MedDRA SOC, always report at least the five most frequent specific AEs with their frequencies; use the MedDRA preferred terms for specific events | The relevant AEs that would not be captured here will be captured within recommendations 5 and 6 |
| 5 | Always report the total number of patients who experienced at least once during the clinical trial: <ol style="list-style-type: none"> 1. any AE ("total AEs") 2. any "severe AEs" 3. any "serious AEs", as well as 4. the total number of patients who withdrew from the trial due to AE(s) For "total AEs" and "withdrawals due to AE(s)" (1 and 4), the five most frequent specific events should also be reported. For "severe AEs" and "serious AEs", always report all specific events. Report the number of participants who experienced each specific event at least once. These data should be separately reported for each arm of the randomized trial | All severe and serious events need to be captured, rather than just the top five |
| 6 | Report separately any clinically relevant AEs that would not be captured on the basis of items 4 and 5 of the current recommendations, considering all TEAEs | This reporting should be done, irrespective of the SOC (consider all MedDRA SOCs) |
| 7 | Report information on drug effects on any biological parameter that may be relevant to the drug mechanism of action or potential for any adverse biological effects. For consistency, the following parameters should always be measured: serum level of urea and creatinine, AST and ALT, full blood count (white and red blood cells, platelets) and hemoglobin. When reporting information about drug effects on biochemical and other biological parameters, numbers of trial participants with <i>abnormal changes in these parameters at all timepoints</i> , from baseline to end of treatment, per arm should be reported | Do not consider a change in the normal range. A change from the normal to the abnormal range should be considered as abnormal change. For patients with abnormal values at baseline, a change of at least 1.5 times from the baseline value (worsening), should be considered as abnormal change |
| 8 | Harms-related data must always be reported in a table within the results sections of manuscripts on RCTs; additional text description of harms-related results in this section is optional | Examples of tables for harms reporting are presented in the Electronic Supplementary Material to this paper |

AE adverse event, ALT alanine aminotransaminase, AST aspartate aminotransaminase, ESCEO European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases, MedDRA Medical Dictionary for Regulatory Activities, OA osteoarthritis, RCT randomized controlled trial, SOC System organ class, TEAE treatment-emergent adverse event, TRAE treatment-related adverse event

same events (of interest) might not be reported by different authors.

The second main issue addressed by the ESCEO working group on the safety of anti-OA medications was the thresholds usually chosen by authors to report harms-related data and the choice to report TEAEs or TRAEs. On these points, the working group members recommend that harms should always be reported considering all TEAEs. This excludes any practice consisting of choosing a threshold of occurrence for AEs reporting and/or reporting only the AEs judged as “treatment-related” by clinical investigators, i.e., only based on the judgement of clinicians. As noted by Lineberry et al. [14] in their paper on recommendations to improve AE reporting in clinical trial publications, such judgement by clinicians is subjective and not adequate in the context of randomized, double-blind, controlled clinical trials. Notably, the ESCEO experts recommend that these claims of “treatment-related” or “treatment-unrelated” AEs be avoided, particularly for new drugs for which a “definitive” conclusion regarding the safety profile requires results from several trials, considering Hill’s causal criteria [71, 72]. For all drugs (old and new), the working group members recommend that the interpretation of a relationship between an AE and the study drug should only be made in the discussion section of the manuscript, comparing the results obtained from the RCT with those reported from other trials and meta-analyses [71, 73]. This applies also for suspected unexpected serious adverse reactions (SUSARs) [74], which regulators compel clinical trial sponsors to report through expedited reporting during the course of clinical trials [27–29]. In fact, reporting SUSARs implies an assessment of causality (based on clinicians’ judgments), which the ESCEO discourages from the results sections of manuscripts. Since SUSARs are by default “serious” in nature, they should be reported along with all other serious AEs in the results section as recommended, without any distinction. However, if a serious event qualified as a SUSAR occurred in the course of an RCT, it should be mentioned in the manuscript conclusions (both the conclusion of the main text and that of the summary).

It should be noted that it is extremely difficult (even impossible) to draw a definitive conclusion regarding the safety of drugs in the context of a single clinical trial. Indeed, RCTs are not usually powered to detect differences in AE rates between the intervention and placebo groups but to test hypotheses on efficacy outcomes [16, 75–77]. In such context, a real statistically significant difference can exist but might not be detectable [75, 76]. That is why it would not be adequate to base any conclusion on the results of statistical comparison of harms data between the intervention and control groups [15, 77–80]. Furthermore, a statistically significant or non-significant difference might merely be due to sampling error, a direct result of having drawn a sample from a population [81–83]. On the other hand, the risk of

bias in RCTs (systematic errors) may more severely affect the results [82, 84–86]. Hence, results from several trials and meta-analyses are required to adequately estimate the risk of AEs [15, 77, 80, 87] and to “definitively” conclude on the safety of drugs. What would be appropriate in the context of a single clinical trial, and strongly recommended by the ESCEO, particularly for serious AEs (including SUSARs), is that the characteristics of each patient reporting any serious AE (demographic characteristics, clinical characteristics, concomitant drug use, comorbidities, etc.) and the context in which the event occurred are thoroughly assessed. This information should be reported in the discussion section of the manuscript to support the interpretation on relatedness of the event with the studied medication, for each single patient involved. Such an interpretation should always be cautious, reporting in terms of probability of relatedness (strong, weak or uncertain), rather than making strong statements such as “treatment related,” “treatment-unrelated” or “treatment is safe.”

Finally, the ESCEO working group members reached consensus on the recommendation that clinical trial manuscripts should also include information on drug effect on biological and biochemical parameters for both approved and experimental drugs in OA. The relevant biological parameters may differ according to the drug, depending on the drug mechanism of action and the potential for any other adverse biological effects. However, for comparability between drugs and across studies, the ESCEO safety working group recommends that information on drug effects on liver and renal function parameters, as well as on blood cells and hemoglobin, should always be reported whatever the drug, and provide specific guidance on how this information should be reported (see item 7 in Table 2). Regarding the relevance of biological parameters according to drug type, reporting data on glycemia may be important for the SYSADOAs for example, particularly for glucosamine and chondroitin. In the case of biological drugs, it would also be important to collect and report data on antibody immune responses. Data on these particular biological parameters, which are specific to drug types, should be reported on the same model as for the biological parameters that should always be reported irrespective of the drug.

All safety information should be reported in a table that should be included in the results section of the manuscript (see Table 2 and the Electronic Supplementary Material [ESM]-1).

3.2.2 Recommendations on the Main Body Systems to be Considered for Harms Reporting Within the Results Section of a Manuscript

Table 3 lists the MedDRA SOCs [88] that the ESCEO recommends should always be considered for harms reporting

within the results section of a manuscript on anti-OA medications, according to each drug class.

It is important to note that limiting the reporting of body system-related AEs to these SOCs will not result in a loss of information regarding the relevant AEs that would have occurred in the other SOCs. In fact, recommendation number 6 (other clinically relevant AEs) (Table 2) should help capture any other clinically relevant AE that would not have been captured with all the other recommendations. The approach recommended in Table 3 allows for consistency in reporting across several manuscripts, while also considering the space limitations imposed by journal requirements.

4 Discussion

These ESCEO recommendations for the reporting of harms in manuscripts on studies assessing anti-OA drugs complement previous guidelines, particularly the extension of the CONSORT-harms extension statement [10, 14]. The ESCEO recommendations are dedicated to the reporting of clinical trials in OA, focusing on how harms should be reported in the results sections of manuscripts, and the MedDRA SOCs that should be of primary interest for reporting within this section, according to the drug studied. However, these recommendations may also apply to other diseases, particularly those that share the same drugs with OA.

Both the ESCEO recommended general framework and the list of the minimal organ systems to be considered for harms reporting (Tables 2 and 3) should be taken into account when reporting harms associated with anti-OA medications in clinical trial manuscripts. These recommendations are expected to help standardize harms reporting in manuscripts on clinical trials in OA and will allow for better harm/benefit assessment for each medication. They may also contribute to closing the credibility gap surrounding harms reporting and improve the confidence of patients and doctors in anti-OA medications. It is important to note that the current ESCEO recommendations are not to be interpreted as basis for drug approval; as previously stated, they intend to promote transparency and standardization in harms reporting in manuscripts, providing clinicians and clinical researchers (particularly those performing meta-analyses), with more accurate data for comparison of harms results across studies on various anti-OA drugs as well as across various studies on the same drug.

One of the challenges in the implementation of these recommendations may be the manuscript length policies of medical journals [8, 15], since reporting harms-related data as recommended by the ESCEO would require one to two A4 pages (maximum) (see example tables in ESM-1). Indeed, as suggested by Mansi et al. [89], reporting AE data more transparently in the results sections of manuscripts

may require that journals revisit their manuscript length policies; however, this should not be impossible for journals to accommodate, since many manuscripts allocate at least the same amount, if not more space, to authors' names and affiliations as to the reporting of AEs [1, 90]. In addition, in manuscripts of systematic reviews or meta-analyses, tables describing the characteristics of included studies already take up to three pages within the results section [91].

To circumvent the space limitation issue in the comprehensive reporting of all relevant harms within the results sections of manuscripts [16], the idea of reporting AEs (or some of the harms data) as supplementary material on journal websites has emerged [8, 26]. The ESCEO considers that this could indeed be a good idea but is concerned that it might be interpreted as a lack of interest in drug safety as compared with efficacy, since efficacy results are usually extensively reported within the results sections. Of course, the ESCEO does not believe this was the reason for such a suggestion and does consider safety of equal importance to efficacy. In addition, the ESCEO strongly recommends that harms-related data, as agreed by the working group members, should be reported within results sections. However, were it not possible to report all harms-related results in the main body text because of space constraints, the ESCEO considers that the SOC-level and specific AEs pertaining to each SOC as recommended (items 2 and 4, Table 2) may be reported as supplementary material, with comprehensive reference to it in the main article text. In this case, the limitation to the reporting of AEs for the SOCs listed in Table 3 no longer applies; SOC-level and specific AEs pertaining to each SOC should therefore be reported considering all MedDRA SOCs.

Pharmaceutical companies developing OA drugs, and researchers conducting clinical trials, are expected to play their part fully in the implementation of these recommendations besides adhering to guidelines for reporting clinical trial results in regulatory submissions. Until now, and contrary to media reports, the pharmaceutical industry has not been solely responsible for the practice of under-reporting of AE data in manuscripts [92]. Rather, harms reporting in manuscripts in industry-funded studies was found to be better than in non-industry-funded studies [6, 11, 26]. In addition, recent research found that compliance with transparency policies by pharmaceutical companies was better than that by academic organizations and non-commercial funders of clinical research [93–95]. The greater adherence of pharmaceutical companies to recommendations may be explained by the requirements of regulatory authorities [15, 16, 26], with which academic researchers are not required to comply, rather than any suboptimal adherence of academic researchers to transparency policies.

It can thus be expected that pharmaceutical companies, who are the main sponsors of trials in OA, will easily and

Table 3 The ESCEO recommendations regarding the main (essential) organ systems to be considered for adverse event reporting within the results sections of manuscripts on clinical trials on anti-osteoarthritis medications

| Treatment or treatment category | MedDRA SOCs [88] |
|--|--|
| Topical treatments (NSAID or other) | Skin and subcutaneous tissue disorders General disorders and administration site conditions Infections and infestations Pregnancy, puerperium and perinatal conditions Neoplasms benign, malignant and unspecified (incl. cysts and polyps) |
| Oral NSAIDs (including COX-2 inhibitors) | Cardiac disorders Gastrointestinal disorders Vascular disorders Renal and urinary disorders Blood and lymphatic system disorders Hepatobiliary disorders Respiratory, thoracic and mediastinal disorders Pregnancy, puerperium and perinatal conditions Surgical and medical procedures Product issues Neoplasms benign, malignant and unspecified (incl. cysts and polyps) Immune system disorders Skin and subcutaneous tissue disorders |
| SYSADOAs (including glucosamine, chondroitin, diacerein, ASU, oral HA, etc.) | Gastrointestinal disorders Skin and subcutaneous tissue disorders Pregnancy, puerperium and perinatal conditions Blood and lymphatic system disorders Endocrine disorders Hepatobiliary disorders Renal and urinary disorders Product issues Eye disorders |
| Intra-articular treatments (HA, corticosteroids, PRP, etc.) | Infections and infestations General disorders and administration site conditions Surgical and medical procedures Skin and subcutaneous tissue disorders Endocrine disorders Pregnancy, puerperium and perinatal conditions Injury, poisoning and procedural complications Musculoskeletal and connective tissue disorders Product issues Vascular disorders Gastrointestinal disorders |
| Opioids | Psychiatric disorders Nervous system disorders Gastrointestinal disorders Hepatobiliary disorders Pregnancy, puerperium and perinatal conditions Cardiac disorders Respiratory, thoracic and mediastinal disorders Injury, poisoning and procedural complications Renal and urinary disorders Product issues |
| Other new anti-OA medication | The ESCEO safety working group members recommend that information on all SOCs be reported (except “social circumstances”) for any new anti-OA drug that does not pertain to any of the categories listed above. Specific SOC lists will be issued by the ESCEO for each future new drug, at the appropriate time |

ASU avocado soybean unsaponifiable, COX cyclooxygenase, ESCEO European Society for Clinical and Economic Aspects of Osteoporosis Osteoarthritis and Musculoskeletal Diseases, HA hyaluronic acid, MedDRA Medical Dictionary for Regulatory Activities, NSAID non-steroidal anti-inflammatory drug, OA osteoarthritis, PRP platelet-rich plasma, SOC system organ class, SYSADOA symptomatic slow-acting drugs for OA

spontaneously comply with the new recommendations. The ESCEO also hopes that authors of non-commercial studies will improve their practice and better comply with transparency policies in future by particularly adhering to the current recommendations.

Many authors have previously suggested that improvement in harms reporting in manuscripts strongly depends on journal editors and reviewers [10, 16]. The ESCEO shares this point of view and encourages journals to refer to these new recommendations in their ‘instructions for authors’ for publications of manuscripts on anti-OA medication trials, alongside the instruction to refer to the CONSORT-harms extension statement. The lack of implementation of recommendations that have been published further to the CONSORT-harms extension statement might be due, in part, to a lack of awareness. Thus, the ESCEO commits to raising awareness among journals to include these new recommendations in their ‘instructions for authors’ and to ask that peer reviewers of manuscripts on OA drugs pay particular attention to this.

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Compliance with Ethical Standards

All authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to this version to be published.

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