Implications of OMERACT Outcomes in Arthritis and Osteoporosis for Cochrane Metaanalysis

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ABSTRACT. The Cochrane Collaboration has established a set of methods for pooling multiple studies assessing the same intervention. Assessing the same endpoints in all studies is important to allow different trials to be combined using metaanalysis. OMERACT can play a key role in establishing consensus on the use of common endpoints that are credible to clinicians. We describe the data that need to be included in individual trial reports for metaanalyses to be carried out. (*J Rheumatol 1997;***24:1206–7**)

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Cumulative metaanalysis of clinical trials can profoundly affect medical care and the setting of health care policies in the following circumstances: (a) where an insufficiently large sample size of individual studies results in high risk of beta or type 2 error, e.g., in osteoporosis many trials are powered based on having designated their primary endpoint as bone density, which is far too small to detect differences in fracture rates. Pooling may result in large enough sample sizes to define a statistically significant difference in fracture reduction; similarly, this can be applied to pooling toxicity endpoints where the frequency is low in any one study; (b) where different trials have different results, e.g., efficacy of different nonsteroidal antiinflammatory drugs in osteoarthritis (OA); (c) and even where a number of trials show a statistically significant benefit. There is often major variation in the estimates of the magnitude of this benefit — pooling provides a "best estimate" useful to clinicians and patients in making informed decisions about diagnosis and therapy, economists in cost-effectiveness analysis, and policy makers in making resource allocation decisions. Hormone replacement therapy is a good example: estimates being quoted for its effect on osteoporosis, heart disease, and breast cancer vary widely; the Cochrane Collaboration musculoskeletal group are currently implementing metaanalyses for this reason.

The Cochrane Collaboration is an international multidisciplinary organization dedicated to conducting and maintaining databases of systematic reviews of randomized controlled trials in all areas of health care. Its objective is to create and maintain a database of systematic current reviews of intervention studies accessible to consumers and health care providers as an electronic journal (online and on disk) through the Computer Disk Systematic Reviews[2,3]. The Cochrane Musculoskeletal Group (CMSG) is the largest, with subgroups for rheumatoid arthritis (RA), OA, osteoporosis, back pain, gout, lupus erythematosus, systemic sclerosis, vasculitis, soft tissue rheumatism, and musculoskeletal injuries[4]. The CMSG aims to review all controlled trials of interventions in musculoskeletal disorders using standardized methodology.

The need for metaanalysis in musculoskeletal disorders is increasing. In head-to-head studies of 2 or more active agents, used for ethical reasons, and in economic evaluations of drugs of choice, large sample sizes are needed to achieve statistical power to detect a minimal clinically important difference; for example, fracture reduction in primary prevention trials of osteoporosis; or clinical improvement from combination therapy compared to monotherapy[5].

The variety of endpoints and lack of agreement on a core set of outcomes in trials has made it difficult or impossible to implement Cochrane metaanalyses to compare and combine the results of various trials. It is OMERACT's mission to develop consensus on a minimal core set of outcomes for the major musculoskeletal conditions. OMERACT III is meeting this challenge by developing the core set of disease-specific clinical and quality of life endpoints for OA and osteoporosis, to later be ratified by the international community. This was accomplished for RA during OMERACT I[6]. Once a core set has been agreed on, it will not be necessary to transform formulae to convert different scales to a common metric. Thus, it will then be possible to combine data from the endpoints in Cochrane systematic reviews and metaanalyses.

A group of twenty scientists from 9 countries met in Potsdam to assess the science of metaanalysis and systematic reviews and to arrive at a consensus on methodologic guidelines for systematic reviews of randomized trials[7]. For the purposes of their document, they specified the following definitions[8]:

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Systematic Review = Overview = the application of scientific strategies that limit bias to the systematic assembly, critical appraisal, and synthesis of all relevant studies on a specific topic.

Metaanalysis = Quantitative Overview = a systematic review that employs statistical methods to combine and summarize the results of several studies.

To further minimize bias in systematic reviews, we need to develop a standardized format for presentation of data with the key elements needed for pooling/metaanalysis of the OMERACT core outcomes. We propose basing this on the Potsdam guidelines. The following elements are proposed:

1. The search strategy should be extensive and reproducible. Hand searching and checking citation lists of retrieved articles should also be carried out. Relevant details about inclusion and exclusion criteria should be presented, along with the details pertaining to data extraction such as study design, dosage, duration of treatment, and quality. The data extraction process should be described and be conducted in a fashion that is unbiased and reproducible.
2. Both qualitative and quantitative results should be presented. Point estimates and 95% confidence intervals of the individual trials should be tabulated for individual trials.
3. The results should be statistically combined into a measure of relative risk, absolute risk, or effect size where applicable. Since effect sizes are difficult for readers to interpret, a possible solution would be to turn the effect size into the original unit of measurement (bone density result).
4. Heterogeneity should be tested for and, when evident, this should be adequately accounted for. Where significant heterogeneity exists, pooling of the individual trials may not be advisable. Sensitivity analysis can be used to test the robustness of results relative to the quality of the primary studies and shifts in event rates.
5. Publication bias should be assessed, since negative trials are not usually published and not including these trials in the results can lead to an overestimation of point estimates. There are a variety of techniques for attempting to estimate and minimize this[3].
6. Journal articles reporting the data from individual clinical trials need to provide the following information, which is critical for the data to be used subsequently for a metaanalysis:

Discrete data. For discrete data, we need to agree on criteria for the presence or absence of each outcome. For example, how is a vertebral fracture defined, using morphometry or semiquantitative techniques? Instead of reporting the number of outcomes, the number of patients with each outcome should be reported (e.g., the number of patients who sustained a vertebral fracture). All patients entered in the study should be accounted for, with documentation of the number of completers, numbers and reasons for discontinuation (especially if due to adverse drug effects), and losses to followup. This makes it possible to calculate a pooled estimate, such as an odds ratio, and to accurately test for homogeneity among various studies. Outcomes should be listed for both intention to treat and efficacy analysis in all trials. Reproducibility of measurement should be maximized by agreeing on data to be submitted. For example, when interpreting hand radiographs in RA, standardization of the methods to perform and interpret the radiographs should be agreed upon.

Continuous data. For continuous data, criteria for standardized data acquisition should be established. For example, when data is obtained through an interviewer administered questionnaire, pre-training of the interviewers should be conducted to improve reproducibility.

In the report or manuscript, data must be documented in a format that allows easy calculation of effect size or comparable measure of change. For example, with bone mineral density in osteoporosis it is essential to include data at baseline and end of treatment; (sample size (N), mean, standard deviation/standard error); change score data (mean, standard deviation) should be expressed as the absolute difference or the percentage of baseline or percentage change from baseline. This should also be documented for subgroups.

Metaanalysis for evaluating adverse effects[9] should be based on a standardized method of reporting adverse effects.

A consensus among rheumatologists on core and research outcomes in OA and osteoporosis and explicit guidelines for pooling data in systematic reviews will significantly improve the quality of systematic reviews in the area of musculoskeletal disorders. We also need to accept common guidelines on methodology in conducting meta-analyses. Rheumatology has played a key role in the development of core endpoints and we should continue to ensure these are used in individual trials and that metaanalyses in musculoskeletal disease are conducted with the necessary methodologic rigor.

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