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Special Article

Quality of reporting of meta-analyses: the QUOROM statement. Will it help?

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The number of meta-analyses of randomized clinical trials (RCTs) has increased markedly in recent years. This method of aggregating different and often conflicting results from similar randomized clinical trials has achieved a significant position in providing useful information for evidence-based medicine.

In parallel with this development there has been an increased focus on methodology in this field. Several aspects have been discussed and explored including the influence of study design, combinability of trial results, control of bias, statistical analysis, and applicability of the results [1].

As a sequel to the CONSORT initiative to improve quality of reporting of RCTs [2], a recent report has been published in the Lancet presenting a checklist to ensure high quality of reporting of meta-analyses (the QUOROM statement) [3]. This was the result of a 2-day conference in 1996 with the participation of 30 experts (clinical epidemiologists, clinicians, statisticians and researchers conducting meta-analyses as well as editors interested in meta-analysis). Since documentation could only be found for eight of the 18 items dealt with, the authors do not consider the QUOROM statement to be the final truth. Thus the authors invite interested readers, reviewers, researchers and editors to use the QUOROM statement and to generate ideas for its improvement. The QUOROM statement is available on The Lancet's website: htp://www.thelancet.com.

The QUOROM statement [3] comprises the following 18 items:

1. The **title** should identity the report as a meta-analysis (or systematic review) of RCTs.
2. The **abstract** should use a structured format applying these sections:
   3. Objectives: describing the clinical question explicitly.
   4. Data sources: describing the databases (i.e. list) and other information sources.
   5. Review methods: describing the selection criteria (i.e. population, intervention, outcome, and study design); methods for validity assessment, data abstraction, and study characteristics, and quantitative data synthesis in sufficient detail to permit replication.
   6. Results: describing the characteristics of the RCTs included and excluded, qualitative and quantitative findings (i.e. point estimates and confidence intervals) and subgroup analyses.
   7. Conclusion: describing the main results.
8. **Introduction** describing the explicit clinical problem, biological rationale for the intervention, and rationale for review.

Methods

   9. Searching: describing the information sources in detail (e.g. databases, registers, personal files, expert informants, agencies, hand-searching), and any restrictions (years considered, publication status, language of publication).
   10. Selection: describing the inclusion and exclusion criteria (defining population, intervention, principal outcomes, and study design).
   11. Validity assessment: describing the criteria and process used (e.g. masked conditions, quality assessment, and their findings).
   12. Data abstraction: describing the process or processes used (e.g. completed independently, in duplicate).
   13. Study characteristics: describing the type of study design, participants' characteristics, details of intervention. outcome definitions, affiliations, and how clinical heterogeneity was assessed.
   14. Quantitative data synthesis: describing the principal measures of effect (e.g. relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data, how statistical heterogeneity was assessed; a rationale for any a priori sensitivity and subgroup analyses; and any assessment of publication bias.

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Results

15. Trial flow: providing a meta-analysis profile summarising trial flow: (A) potentially relevant RCTs identified and screened for retrieval; (B) RCTs retrieved for more detailed evaluation; (C) Potentially appropriate RCTs to be included; (D) RCTs included; (E) RCTs with usable information, indicating for each step the number of RCTs and the reasons for exclusion.
16. Study characteristics: presenting descriptive data for each trial (e.g. age, sample size, intervention, dose, duration, follow-up period).
17. Quantitative data synthesis: report agreement on the selection and validity assessment; present simple summary results (for each treatment group in each trial, for each primary outcome); present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (e.g. 2×2 tables of counts, means and SDs, proportions).

18. Discussion: Summarize key findings, discuss clinical inferences based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (e.g. publication bias); and suggest a future research agenda.

How is the quality of reporting of meta-analyses in hepatology according to the QUOROM statement? To get an indication of this, the 15 latest hepatologic meta-analyses [4–18] were identified in a Medline search. Thirteen were based on summarized trial results ('classical' meta-analyses) and two were based on individual patient data [6,8]. Ten were published in major journals (Journal of Hepatology, Hepatology and The Lancet) [4–8,11–13,16,18]. Three were published in supplement issues [5,14,17]. Seven dealt with therapies for hepatitis C [4–10], five with therapies for portal hypertension [11–15], two with antibiotic prevention of bacterial infection [16–17] and one with therapy for cholestatic liver disease [18]. The centres of origin were Palermo [7,9,10,15], Paris [4,11,13,16,17], London [12,14,18] and Seattle [5] Two were European co-operative studies [6,8].

The 15 meta-analyses were assessed according to the 18 QUOROM points. Since in some of these points there are a number of subpoints, some judgement had to be made in order to decide if the point could be considered fulfilled or not. The result of this crude pilot assessment is shown in Table 1 for the total sample and for a few subsamples.

In the total sample the fulfilment was not complete for many of the points. There were no obvious systematic differences between meta-analyses dealing with treatments for hepatitis C and those dealing with treatments for portal hypertension (Table 1). However, meta-analyses of the 'classical' type published in regular issues of major journals were complying to a high degree with the QUOROM points (Table 1).

Some of the points which scored low concern the abstract. Part of the explanation is probably space restrictions imposed by the journals. The specified details are therefore being referred to the paper proper. Some journals (e.g. Hepatology) do not use a structured abstract format.

Among the points concerning the methods, especially the validity assessment of the individual trials (point 11) scored rather low. This point is important, especially the degree of allocation concealment throughout the trial (see below). In a substantial number of meta-analyses, the flow of trials (point 15, see above for definition) was not adequately reported according to the QUOROM statement.

The meta-analyses based on individual data [6,8] scored particularly low on selection (point 10) and on trial flow (point 15). Since these analyses are dependent on the authors of the identified RCTs giving access to the individual data, some kind of selection bias cannot be ruled out. Furthermore, unbalanced designs [8] relying heavily on adjustment procedures using complex statistical methods may be another difficulty to deal with. Even when using individual data and powerful statistical methods, the inclusion of only randomized studies should still be an essential requirement.

The fact that the fulfilment of the QUOROM points seems to be associated with the journal of publication and the type of issue (regular or supplement) is unfortunate. Any publi-

Table 1
Percent of hepatologic meta-analyses fulfilling the 18 QUOROM main points

QUOROM main point	Subsample			
	Total	A[a]	B[b]	C[c]
1. Title	93	100	80	100
Abstract				
2. Structured format	40	57	60	57
3. Objectives	73	71	80	100
4. Data sources	80	100	60	86
5. Review methods	20	14	20	29
6. Results	73	86	80	86
7. Conclusion	80	86	100	86
8. lntroduction	100	100	100	100
Methods				
9. Searching	87	100	80	100
10. Selection	73	71	80	100
11. Validity assessment	67	57	80	86
12. Data abstraction	87	100	80	100
13. Study characteristics	87	86	80	100
14. Quantitative data synthesis	100	100	100	100
Results				
15. Trial flow	47	57	40	71
16. Study characteristics	87	86	80	100
17. Quantitative data synthesis	57	100	100	100
18. Discussion	93	100	80	100

[a] Treatments of hepatitis C ($n = 7$) [4–10].
[b] Treatments of portal hypertension ($n = 5$) [11–15].
[c] Classical meta-analyses published in regular issues of major journals ($n = 7$) [4,7,11–13,16,18].

cation should adhere to the highest criteria of reporting and the QUOROM statement should be a reminder to editors, reviewers and authors in this respect.

Improvement of the quality of reporting of meta-analyses will be a step forward, but to improve the reliability of their information, the quality of the individual RCTs, which form the basis of the meta-analyses, needs improvement. This is the main task.

A survey of RCTs in two major hepatologic journals revealed considerable weaknesses in a large proportion of the published RCTs [19,20] including: inadequate reporting of allocation sequence, inadequate allocation concealment, inadequate blinding, lack of intention-to-treat analysis, missing sample-size calculations, and a small number (<20) of patients per intervention arm.

Allocation concealment and its maintenance throughout the study is of major importance for the reliability of the RCT results. Inadequate reporting of allocation concealment is associated with an overestimation of the intervention effect of up to 30% [21]. Because of its marked influence, insufficient allocation concealment needs to be identified and adjusted for in some way in the meta-analyses.

Publication bias due to a favoured publication of the positive trials is another very important source of bias in meta-analyses. A thorough search of the literature is mandatory but identification of unpublished RCTs may be extremely difficult and the necessary extra effort may not be successful. A recent survey including 252 RCTs within a given domain shows that the percentage of positive RCTs varies with the country of origin e.g. Austria 89%, Italy 89%, France 83%, Germany 63%, UK 60%, Sweden 59%, USA 53%, Finland 50%, Denmark 50%, the Netherlands 33%, Canada 27%, a probably explanation being varying degrees of publication bias [22]. One example of likely publication bias in hepatology concerns the effect of interferon in chronic hepatitis B where a large meta-analysis based on published and unpublished RCTs [23] demonstrated a significantly smaller effect than in meta-analysis based on published data only [24].

In another field it has been demonstrated that the type of affiliation or sponsoring of the investigator was strongly associated with the conclusion of a review article [25]. Some of the hepatologic meta-analyses reviewed mentioned specifically that the investigator was not supported financially by any pharmaceutical company, government agency or other grants. This point is important.

One aspect which is not included in the QUOROM statement is the comparability between the intervention groups in the original RCTs. Imbalance in respect to variables associated with the measured outcome may be a significant problem in the smaller trials [26] of which there are many in the field of hepatology. This emphasizes the importance of presenting a thorough description (including all variables which may be associated with the outcome) of each intervention group in the original RCTs. If an imbalance favours the new intervention, the trial may be positive without the intervention being effective. If the imbalance disfavours the new intervention, the trial may be negative without the intervention being ineffective. RCTs with the former type of imbalance will be published more often than RCTs with the latter imbalance type. Therefore publication bias will tend to be more pronounced if a significant number of the RCTs have a small sample size. A decrease of the intervention effect with the sample size (e.g. in a so-called 'funnel plot') is indicative of publication bias and such an assessment should always be performed in a meta-analysis. If publication bias is detected, the overall intervention effect can be considerably overestimated and some kind of effect-adjustment would be necessary. This implies that even more weight should be given to the largest RCTs at the expense of the small RCTs, and exclusion of the most positive, smallest RCTs from the analysis could be justified.

It may to some degree be possible to adjust for some imbalance in important prognostic variables if these are reported in the RCTs [27]. If considerable heterogeneity exists between the RCTs, more special methods may be applied [28]. However, there is a limit to how much information can be extracted from reported summarized RCT data. More elaborate results may be obtained by combining RCT databases and performing meta-analyses using the individual data from the RCTs [6,8,23]. This will make possible a more comprehensive analysis with adjustment for any confounding variables, and a study of the intervention effect in special subgroups may be performed more reliably. However, the superior approach is to perform primary RCTs having the necessary large sample size to make such analyses possible within the same RCT. Therefore, large multicenter – or even better – large multinational RCTs will provide the best chances for progress in this field. Such studies will tend to have a higher quality and the chance of publication will be high even if the results are negative. We may hope that such co-operative studies will be more common in the future.

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