Reviewer's report

Title: Health-related quality of life as an endpoint in oncology phase I trials: a systematic review

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Reviewer: Galina Velikova

Reviewer's report:

This article presents a systematic review of phase I trials that have incorporated quality of life as an endpoint.

Major comments

In the background section the authors have made a good justification why quality of life might be helpful in Phase I trials. The authors state that quality of life questionnaires can capture moderate toxicity experienced over a long period of time. However, they could provide further elaboration on the fact that in Early Phase trials, the methodology is very strict and regulated. Often the side-effects of the drugs are not known and therefore it is difficult to choose a quality of life instrument. It could be argued that further evidence is needed on the usefulness of quality of life instruments in Early Phase trials before they are recommended.

Line 91 - the authors should justify the statement that "doses recommended based on current MTD definition are higher than needed" and add a reference.

Line 104 - the objective of this study is stated as to assess the current use of health-related quality of life as an endpoint in Phase I trials. The authors should be more specific here and state that this covers both primary and secondary endpoints as per their subsequent search strategy. Furthermore, it may be useful to specify what their hypothesis was. Did they expect to see many Phase I trials with health-related quality of life endpoints or not.

The results are perhaps not surprising. Interestingly two trials had quality of life as a primary endpoint. The majority (60%) had MTD as the primary endpoint as perhaps expected. This is a relatively small systematic review. It will be helpful for the reviewers to provide more information on the two trials that included health-related quality of life as a primary endpoint but then didn't use it subsequently to determine MTD subsequently. Why did they not use it and what other measure did they employ instead?

In table 2, I would like to see more information on whether, in any of the listed studies with the statistical methods employed, the information was useful and influenced any decisions or subsequent Phase II trials. In the two trials that had quality of life as primary endpoint, how was MTD determined? Did quality of life results help in any of these trials?
In the discussions, the authors seem to suggest from line 201 onwards that NCI PRO CTCAE should be added to the current reporting using CTCAE to define MTD. It appears that they argue that in addition to NCI PRO CTCAE, health-related quality of life should be measured to determine the impact of the toxicities on patients' lives. This point could be expressed more clearly and strongly.

The general impression of this article is that it doesn't bring much additional information to what an oncologist would expect. It will be useful if the authors could express their opinion whether in any of these trials health-related quality of life contributed and how it was interpreted to make the case for its future inclusion more routinely. Even one example where it has changed the decision-making would be extremely helpful. This could lead to some more specific suggestions as to how this field could be moved forward. At present, the article does not provide good direction for the future apart from the recommendation for more methodological research.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Unable to assess

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

No

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable
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