Reviewer's report

Title: Lack of Treatment-Related Mortality Definitions in Studies of Children, Adolescents and Young Adults with Lymphomas, Solid Tumors and Brain Tumors: a Systematic Review

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Reviewer: Sara Ghaderi

Reviewer's report:

The authors performed a systematic review of studies enrolling children, adolescents and young adults with lymphomas, solid tumors and brain tumors in which an anti-cancer intervention was randomized, or all study designs in treatment-related mortality was a primary or secondary outcome. The authors address an important issue that is generally well written. I have, however, several comments to consider:

Major Compulsory Revisions

Comment 1: The title of the paper should be clearer. The study mainly focuses on clinical trials and this should be understood from the title of the paper.

Comment 2: The authors focus on definition of TRM. I would have like to see a suggestion from them that how TRM should be defined.

Comment 3: The main issue for me is that the authors do not clearly distinguish between early and late mortality. Early mortality is commonly believed to be treatment related while late mortality is mainly due to late effects. It is very important to clarify this.

Comment 4: In the Background, line 27, authors state that survival rate is now about 80%. This is to my knowledge, 5-year survival rate and it should be clarified here.

Comment 5: In line 31-32 the authors states “As cure rates continue to improve, TRM is predicted to account for a growing proportion of deaths in this population.” Is there any reference for this statement?

Comment 6: In line 36, the authors state that reducing treatment intensity may reduce TRM. However, increase in 5-year survival in this group of patients is due to improved medical treatments which include use of multi-modal therapies with higher intensity. Is there any reference for this statement? How can treatment intensity be reduced without affecting survival rate?

Comment 7: In line 38, the authors talk about improving disease control. Causes of cancer in young individuals are generally unknown. Therefore this statement can’t be correct, what the authors mean here?

Comment 8: In line 117, it is referred to a single study. I miss a reference to this specific study here.

Comment 9: In line 149, it is stated that the early death is define as deaths
occurring 6 weeks after start of treatments. As mentioned before, it is necessary
to distinguish clinical trials from other studies such as cohort studies. In cohort
studies, early deaths are usually defined as deaths occurring 5-years after
diagnosis.

Comment 10: My concern for defining TRM is accuracy of cause of death. This
can vary from country to country or even from hospital to hospital within the same
country. To distinguish between treatment-related deaths and disease-related
deaths is not an easy task. This issue must be addressed in the discussion.

**Level of interest:** An article whose findings are important to those with closely
related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
'I declare that I have no competing interests.