Reviewer's report

Title: Systematic evaluation of the methodology of randomized controlled trials of anticoagulation in patients with cancer

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Reviewer: Gary Lyman

Reviewer's report:

General Comments:
1. The authors provide a strong rationale for a study appraising the quality of RCTs of anticoagulation in patients with cancer given the recent considerable interest in this topic and the number of trials reported and ongoing.

2. The author(s) have been involved with several Cochrane reviews of various related topics and utilized searches related to those reviews as a basis for identifying RCTs for this report.

3. It is difficult to disagree with the conclusions of the authors that there are important and probably frequent methodological limitations of the RCTs reported in this field as with many topics in medicine

4. It is also difficult to disagree with the conclusions of the authors, calling for greater methodologic rigor in the conduct and reporting in future RCTs to avoid many of the limitations discussed

5. Nevertheless, this report, itself, suffers from several methodologic lapses that will need to be addressed as discussed below.

6. In addition, a careful rereading of the paper will identify a number of language/grammar/typo issues that should be addressed in any revised manuscript.

Specific Recommendations:
1. While the authors refer to searches conducted in previous Cochrane reviews, these were conducted over varying periods of time and it is not clear that they were all current as of February 2010.

2. The readers should not be asked to go to the Cochrane library for the methodologic details of the search algorithm and the inclusion and exclusion criteria utilized in this report. This information should be included in the methods section of the paper.

3. In the methods section, the authors state that the specific topics covered included all for which RCTs were conducted in the field but they fail to mention VTE thromboprophylaxis trials in ambulatory patients with cancer which represent neither treatment studies nor survival studies but were designed for the primary purpose of reducing the risk of VTE in that setting. This needs to be clarified.
4. Again, the detailed electronic search algorithm(s) and eligibility criteria should be provided in the methods section of this paper.

5. A Quorom diagram or similar summary of the numbers of articles excluded and reasons for exclusion should be provided as called for in the XXXXXXXXXX.

6. Lines 3 and 5 under Data extraction (page 6) contain incomplete sentences.

7. It is not entirely clear to this reviewer and therefore may not be to some readers, how the risk of bias was assessed using the scales described to distinguish ‘definitely’ from ‘probably’ or ‘not clear’ from ‘inadequate’. Perhaps the description of this phase can be expanded upon in the methods.

8. From this reviewers clinical perspective, the authors understate the challenges of RCTS of anticoagulation in the cancer setting adhering to some of the quality measures critically assessed. The ability to conduct double (or triple) blinded RCTs in the setting of patients with active cancer, already at increased risk of bleeding and frequently undergoing invasive procedures, eg, surgery, catheters, interventional biopsies, radiation and chemotherapy with associated thrombocytopenia, makes this a very challenging area for clinicians caring for such patients. This should be discussed from a more balanced perspective.

9. Along a similar vein, with standard treatments established by previous RCTs as effective and safe, the appropriate comparator for a new therapeutic will often be the established standard rather than placebo.

10. With increasing evidence that unsuspected PEs have real clinical relevance and likely the same impact on survival as symptomatic PEs, the relative value of screening in such trials takes on a more complicated tenor and should be discussed again from a more balanced perspective. In the hands of experienced imaging centers, false positive scans should be few and US should generally be confirmed before initiating treatment thus avoiding some of the author’s arguments.

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

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

No conflicts of interest to report