Reviewer’s report

Title: Treatment strategies in colorectal cancer patients with initially unresectable liver-only metastases, the randomised phase 3 CAIRO5 study of the Dutch Colorectal Cancer Group (DCCG)

Version: 3 Date: 23 January 2015

Reviewer: Susan Dutton

Reviewer’s report:

I support the publication of study protocols, but these should adhere to the SPIRIT 2013 Statement which provides guidance for protocols of clinical trials (see http://www.spirit-statement.org/ for details and access to the relevant publications)

Major Compulsory Revisions

The SPIRIT 2013 Statement which provides guidance for protocols of clinical trials has not been adhered to and therefore there are many items that are missing from this article which prevent carrying out a full review:

1. It is helpful if the title state that it is a study protocol
2. No details of randomisation, either sequence generation (method of randomisation and stratification factors) or allocation concealment
3. No details of who will be blinded in the trial - from my reading this may be the Central Review Panel, but the make up of this panel is not explicitly stated or whether it is independent or not.
4. The sample size is included, but in the methods section it state that cross-over between antibody regimens after treatment failure (still unresectable at 12 weeks). Has this cross-over been taken into account in the sample size calculation. Please make it clear that there are two separate embedded trials for the patients with/without KRAS mutations and therefore the number of events is required for each comparison, not overall. It is not clear how long patients will be followed up for, will this be one year after last patient enters the study?
5. There is no mention of Data management including data collection methods, and data monitoring.
6. There is no description of planned statistical analysis for any of the outcomes. As a minimum details for the primary outcome should be included.
7. There is no description on the collection of safety data - some of these treatment combinations are likely to throw up complications.
8. There is no description on any trial monitoring committees such as a data monitoring Committee and/or Trial Steering Committee who would usually be in place to monitor safety of the participants and conduct of the trial.

Minor essential considerations:
The length of a treatment cycle is not specified and whether this is the same for all regimens.

The current article seems to have 2 copies of Figure 1.

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

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare I have no competing interests