Author's response to reviews

Title: Combining curcumin (C3-complex, Sabinsa) with standard care FOLFOX chemotherapy in patients with inoperable colorectal cancer (CUFOX): study protocol for a randomised control trial.

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Author's response to reviews: see over
Dear Sir,

RE manuscript 7724556615805439

Thank you for the consideration of the article ‘A phase I/IIa study combining curcumin (C3-complex, Sabinsa) with standard care FOLFOX chemotherapy in patients with inoperable colorectal cancer: The CUFOX trial’.

Both the reviewer’s and editor’s comments are addressed below. Any additions to the text have been highlighted in the revised article.

Reviewer’s comments

1) **What is the rationale to add curcumin to the chemotherapy for inoperable CRC? Why not start from stage III?**

Assessment of new drugs or new combinations of drugs is almost always undertaken in the metastatic setting, as this allows changes to measurable disease to be quantified via CT. Stage III CRC is usually treated via surgery, with only a small number receiving neo-adjuvant intervention. Use of stage III patients would limit quantifiable outcome measures to that of PFS and OS.

2) **What is the rationale for dosage selection of curcumin?**

The dose selection of curcumin was based on a number of previous studies that have assessed safety and tolerability of curcumin in patients with colorectal cancer. Three of these studies have been undertaken at the University of Leicester.


The Tolerated Dose of 2 g daily oral curcumin was chosen for three reasons. Firstly, the pilot study (reference (a) above) showed that whilst compliance was excellent
(92%) amongst patients receiving 2.35 g taken in 5 daily capsules, participants would be reluctant to take larger doses which would necessitate a greater number or larger size of capsule. Furthermore, side effects of nausea associated with chemotherapy regimens may make larger capsule numbers prohibitive, and so limit compliance.

Secondly, adverse events may increase at doses in excess of 4 g, particularly when in combination with chemotherapy (observed in pancreatic cancer studies of curcumin + gemcitabine). Despite curcumin having been administered at doses of up to 12 g per day in healthy volunteers with minimal AE’s, AE’s of a mainly gastrointestinal nature (diarrhoea, nausea) often manifest in the colorectal cancer cohort. This suggests that greater caution must be observed in patient cohorts, particularly in those whose chemotherapy regimens incorporate 5-FU which is already associated with dose-limiting gastro-intestinal side effects such as diarrhoea.

Finally, the dose required to exert a pharmacological effect in humans remains unknown. A mouse model of polyp prevention demonstrating efficacy of curcumin (Perkins et al. Cancer Epidemiol Biomarkers Prev. 2002) proposed that 1.6 g per day delivered in a single dose to humans is likely to be sufficient. Curcumin has been detected in plasma of patients receiving 2 g daily oral curcumin (Carroll et al. Cancer Prev Res. 2011) and HPLC analysis of portal blood and hepatic tissue, suggests that 3-4 g may be sufficient for activity in organs distal to the gut (Garcea et al. Br J Cancer. 2004).

Two g once a day in 4 capsules per day, was expected to be a well-tolerated amount of curcumin yet also possess the potential to invoke a clinical response. At higher doses participant compliance was likely to decrease and adverse events increase. Whilst 3 or even 4 g daily curcumin might be an attractive TD, maintaining good patient compliance for 6 months with 6-8 daily capsules was less likely.

3) Curcumin is a mix, could it be a pure compound based capsule?

More recently, new formulations of curcumin are appearing with as high as 99% purity, eliminating other common curcuminoid constituents that are present in the Sabinsa C3 complex such as demethoxy and bis-demethoxy curcumin. Evidence for clinical use of the pure compound is growing, and so it may be of potential use for future studies. However, as this study was the first of its kind to combine curcumin with FOLFOX-based chemotherapy, it was decided to use the current formulation which has an extensive history of use in pre-clinical studies and clinical trials and has a well-established side effect profile.

4) Please provide the safety data for curcumin in the references.

As curcumin is not classed as a medicinal product, there is no standard Investigational Medicinal Product Dossier (IMPD) available. This was created specifically for the trial by the authors, based on the best of our knowledge taking account of the published pre-clinical and clinical trial data.

Much of this information is summarised in the review below, which was written in conjunction with the relevant trial paperwork. This review is already referenced as
in this article and refers to all relevant curcumin studies in gastrointestinal disease that report side effect profiles or potential efficacy.


5) Please follow up the format of SPIRIT, a standard reporting format of protocol.


Editorial requests

1) Title format now as requested.
2) Email addresses of all authors included on title page.
3) Funding information moved to the acknowledgements section.
4) Date of trial registration included at end of abstract.
5) Written informed consent statement included and highlighted in methods section.
6) Trial status section now included after discussion.
7) Abbreviations list included after trial status.
8) Author contributions mentioned individually.

I hope that this suitably addresses all of the comments.

Best wishes

Lynne Howells (corresponding author)