Reviewer's report

Title: Cost-minimization analysis of XELOX and FOLFOX4 for treatment of colorectal cancer to assist decision-making on reimbursement

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Reviewer: chris Twelves

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Joint review by:
1. Dr Chris Twelves, Professor of Clinical Pharmacology and Oncology & Head, Clinical Cancer Research Groups Leeds Institute of Molecular Medicine & St James’s Institute of Oncology, UK.

2. Dr Peter Hall, Clinical Research Fellow, Section of Oncology and Clinical Research & Associate Research Fellow, Academic Unit of health Economics, University of Leeds, UK.

Reviewer's report

This original research article presents the costs associated with treatment of advanced colorectal cancer with two alternative chemotherapy regimens: 1. XELOX, 2. FOLFOX4. The study is undertaken in Hong Kong and is presented as a cost-minimisation analysis. The conclusion is that XELOX is the more cost-effective treatment option.

Overall the paper is very worthwhile. To our knowledge this is the first time such data has been published from a Hong Kong perspective. In particular it will be of use to those wishing to undertake a full cost-effectiveness analysis from a Hong Kong perspective. It may also be of some use to policy makers and healthcare providers in Hong Kong. The manuscript is clearly written in good english. (We note that a professional writing company has assisted, funded by Roche who manufacture capecitabine) We have a number of concerns which should be addressed before we believe this manuscript is suitable for publication.

- Major Compulsory Revisions

1. We feel that the conclusion "XELOX is a more cost-effective treatment option" is not valid on the basis of this study alone. This could be addressed in one of two ways:

   a) The authors could undertake a formal systematic review and (if appropriate) meta-analysis of the available data comparing the efficacy of XELOX with FOLFOX. Only then if equivalence could be statistically demonstrated between the two regimens should a cost-minimisation analysis be undertaken. The transferability of the resulting efficacy conclusions to the Hong Kong population
should also be formally assessed with supporting evidence.

b) The authors could present this study as a cost analysis without inference about comparative clinical efficacy. The conclusion that XELOX is a more cost-saving (as opposed to cost-effective) treatment could then be made. This approach would be our recommendation.

2. The data presentation should be split clearly into unit cost data and resource use data. Each of these data points should also have an adequate representation of variability such as variance, standard error or confidence intervals. The overall cost-estimates should be presented with confidence intervals (e.g. based on a bootstrapping method).

3. Inadequate detail of the sensitivity analyses are provided to enable meaningful review. For example, when oxaliplatin was removed from the review, was this limited to removing oxaliplatin drug costs or where costs of administration and associated toxicity also removed? We feel this section should be clarified and expanded upon.

- Minor Essential Revisions

1. The healthcare costs are presented over the duration of chemotherapy treatment plus 28 days for XELOX or FOLFOX4. It would be helpful if the mean time is explicitly stated. In fact, the follow-up time horizon for the study should really be the same between arms, ideally over the lifetime of the patients.

2. Recruitment took place over a four year period therefore a discount rate / adjustment for inflation acceptable to Hong-Kong decision makers should be applied to costs. The base year for the analysis should also be specified.

3. The retrospective power calculation in the discussion does not add validity and should be omitted - it is not a substitute for proper analysis of the data.

4. The authors refer to the comparative efficacy of XELOX and FOLFOX as "no poorer" and "at least as effective as." The definition of equivalence needs to be consistent.

- Discretionary Revisions

1. Much of the additional cost with FOLFOX4 comes from the additional hospital days associated with administration. Can the authors confirm that inpatient administration is standard in Hong-Kong and that ambulatory infusion pumps for 5FU administration at home are not used?

2. Community healthcare costs have not been considered such as nursing care at home or primary care costs - do these exist in Hong Kong? Are cost associated with admission to an alternative hospital recorded?

3. To complete the societal costs some consideration should perhaps be given to lost carer time. Also, it is unlikely that clinic attendance or hospital admission would incur additional lost productivity costs in this patient group, the majority of
whom are likely to be either retired or unable to work due to the burden of their disease. To accurately include this it would be necessary to look at the actual time spent at work.

4. There are 30 patients in each arm. This seems to be too much of a coincidence given that recruitment was defined by a set time period. Can the authors explain this?

5. There are clearly strong reasons for selection bias between arms of this study. Could the authors explore the likely impact of this on the results and include a relevant sensitivity analysis?

**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:**

PH is employed by the University of Leeds to provide independant data review of a research project funded by Roche and has undertaken research supported by the UK Department of Health.

CT has received honoraria from Roche as a member of advisory boards and speaker's bureau.