Author's response to reviews

Title: Aspirin for Dukes C and High Risk Dukes B Colorectal Cancers - The ASCOLT study: study protocol for a Multi-centre, Double Blind, Randomised Placebo Controlled Phase III Trial

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Version: 2 Date: 5 December 2011

Author's response to reviews: see over
1 December 2011

To : Editor Trials Journal

Dear Editor,

**Re: Reply to Reviewer’s Queries**

We thank the Reviewer for his kind comments and queries. We have attempted to answer them below and make the necessary inclusions into the Manuscript. If there are any further questions, we will be happy to address them.

**Question 1.** Please explain a little bit more about “direct web randomization”. Please outline step by step what happens.

**Response:** The steps for direct web randomization are as follows:

2. The following information will be entered and the patient will be stratified by:
   - Study centre
   - Tumour type (Dukes C colon, high risk Dukes B colon cancer & rectal cancer sub-groups)
   - Type of adjuvant chemotherapy received (exposed/ not exposed to oxaliplatin)
3. The randomisation system will then determine the treatment arm and provide the subject number to be used for the patient.
4. The site monitor/CRA will be informed immediately in the event that the web randomisation is not successful.

*We have amended the text of the Manuscript to include these comments.*

**Question 2:** You say that “non-proportional hazards models (which allow for the effects of covariates to vary over time) would be considered when the proportional hazards assumption is not valid”. You need to be more explicit here. Will these be additional, secondary analyses? Or will you
test proportional hazard and then report something else as the main analysis if the proportional hazards does not hold?

**Response**: The non-proportional hazard models will be used as an alternative (main analysis) to the proportional Cox model in case the proportional hazard assumption does not hold. This assumption will be checked by using graphical methods and statistical tests during the modelling. Results from non-proportional models such as stratified Cox model or Cox model with time-dependent covariates will then be reported (depending on the appropriateness of each model to the actual data).

*We have amended the text of the manuscript to include this comment.*

**Question 3**: No information is given as to how compliance will be analyzed. If I was on this trial, I’d go out and buy some aspirin and take it just in case I was in the placebo group. There isn’t much downside, and it might save my life. How will you be monitoring for that kind of thing?

**Response**: The author brings up a salient point. Whilst this may be a problem in the West, the likelihood of subjects going out to buy aspirin off the shelf in Asia is much lower. Most Asian patients are not familiar with the drug Aspirin (paracetamol is most often used) and are much less likely to consume off the shelf medication without doctor supervision. Virtually all aspirin consumed in Asia is prescription aspirin. Asian patients are also extremely adverse to toxicity and the experience so far with the study is that the majority of patients are extremely apprehensive about the risk of gastrointestinal and cerebral hemorrhage. The minority of patients who express the desire to take Aspirin outside the clinical trial are given a prescription and are not recruited onto the study.

The Analysis of compliance is as such “if there was no early discontinuation of the study treatment and for each scheduled follow-up visit throughout the treatment duration of 3 years, positive compliance is found when \( \frac{\text{exposure days for that visit}}{\text{days between the two visits since last visit}} \geq 70\% \) - where exposure days is calculated as days between the two visits since last visit minus days off medication during that visit.” Compliance will be considered unknown if it cannot be calculated because of missing data. Dose delays information on the CRF will not be taken into account in the measure of compliance. The number of patients discontinuing randomized investigational product, as well as the reason for discontinuation will also be summarized and listed.

For the Monitoring of compliance, all sites are doing a pill count for the return drugs – to assess compliance and as part of drug accountability. For patients who are non-compliant, the study coordinator will inquire further as to the reason for “missed days”, side effects and reinforce the need for daily dosing.

**Question 4**: How can be sure all the sites including future sites have internet access?

**Response**: All sites will need internet access since the treatment kit allocation is also via web. The study CRA will ensure that the respective site has the necessary access before launching the study.

Thank you again,

Sincerely,