GCIG Harmonization Committee - Statistical Section
Thursday, May 31, 2012, 5:00pm – 6:00pm
LaSalle I Room, Doubletree Magnificent Mile Hotel, Chicago

MINUTES

Chair: Mark F. Brady (brady@gogstats.org) - GOG
Co-Chairs Elect: Jim Paul (james.paul@glasgow.ac.uk) – SGCTG
Byung Ho Nam (byunghonam@ncc.rc.kr) – KGOG

Present:
Jane Hook (j.hook@ctu.mrc.ac.uk)– MRC
Val Gebski (val@ctc.usyd.edu.au) – ANZGOG
Byung Ho Nam (byunghonam@ncc.rc.kr) – KGOG
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Dongsheng Tu (dtu@ctg.queensu.ca)– NCIC
Jim Paul (james.paul@glasgow.ac.uk) – SGCTG
Kathryn A. Winter (kwinter@ccr.org) – RTOG
Alexander Reuss (Alexander.reuss@kks.uni-marburg.de) – AGO
Mark F. Brady (brady@gogstats.org)- GOG

Welcome & Introductions (C.O.I. declaration)

No conflicts of interest were declared.

1. Study Designs for Targeted Therapies and Biomarker-Adaptive Threshold Designs

Alexander Reuss prepared a presentation and led the discussion on a procedure for evaluating a treatment with a possible biomarker-defined subset effect. Many of the new and interesting anti-cancer agents are molecularly targeted and they may only be effective in a subset of those patients who are traditionally enrolled into disease-specific clinical trials. If the agent is only effective in a subset of the patient enrolled onto a trial, then statistical tests that assess the treatment effect in the entire sample appreciably lose statistical power. Enrichment designs can be used to restrict the enrollment to those patients who are likely to respond to treatment and hence increase the statistical power of the study. Enrichment designs, however, require that the agent's mechanism of action be well understood and there must be an analytically validated biomarker to identify those patients who are apt to respond. The trial statistician needs to consider the important interplay among the biomarker's sensitivity, specificity and prevalence when designing these types of studies.

The challenge in designing trials for targeted agents becomes more complex when there are no validated markers, but non-validated biomarker candidates. In this case, consideration can be given to an adaptive design which attempts to incorporate a clinical validation for the biomarker into the study design. Dr. Reuss reviewed two approaches that have been proposed by Jiang et al, 2007 and control the overall type I error in a study:

The first approach tests for treatment an effect in all patients is conducted at a reduced significance level, α_1. If the test is statistically significant, then for the purpose of formal evaluation, the procedure stopped and the null hypothesis of no treatment effect for the randomized patients as a whole is rejected. Otherwise, an algorithm is applied to test for treatment effect in a biomarker-defined subset of patients at a significance level of $\alpha_2=\alpha - \alpha_1$ (where α is typically .05). This procedure controls the probability of making any false-positive claim at the pre-specified level α. For instance, to preserve the ability of this procedure to detect an overall effect, α_1 could be allocated 80% of α, and the remaining 20% to α_2. This approach has merit in that it is simple, and statistical valid, however, it is conservative in the sense that more powerful approaches could be considered. It also requires a previously specified cutoff value for the biomarker-defined sensitive patients.

A second procedure involves testing the null hypothesis of no treatment effect in the subset of patients who are biomarker positive, where biomarker positivity is determined by a cutoff value, c. The procedure is performed once for each unique value of all of the observed biomarker measurements obtained in the trial. Notice that when c is set to the lowest observed value then this would be equivalent to testing for a treatment effect in the entire population. Jiang et al recommend testing the null hypothesis with a likelihood ratio test statistic, S. They also recommend reweighting the test statistic by adding a constant R (~=2.2) to S, giving T. The final test statistic is the maximum value of T. The p-value associate with this value of T is then obtained from estimating the distribution of T from repeated permutations of the observed data.

2. Proposal for discuss topics at future meetings:

a. The PFS/OS controvery for phase III clinical trials.
b. Dose intensity (Ruess)

3. New Buisness

None.