Reviewer's report

Title: What does a modified-Fibonacci dose-escalation actually correspond to?

Version: 2 Date: 23 March 2012

Reviewer: Oke Gerke

Reviewer's report:

Thank you for the opportunity to review this interesting and well written manuscript. The research question posed by the authors is well defined and of interest to researchers involved in phase I testing of cancer drugs. The methods used are appropriate and well described, the data presentation is sound. However, the search strategy of those 327 trials extracted should be detailed more (e.g. search engines, keywords searched; minor essential revision). You may consider to prepare a complete list of these trials as electronic supplementary document to this paper (discretionary revision).

The discussion and conclusions are well balanced and adequately supported by the data. Limitations of the work could only relate to the search strategy which is deemed appropriate anyway. So, limitations were not to be stated here anyway. On the other hand, the authors point out the interesting spin-off finding that astonishingly few phase I cancer trials did use more advanced methods than the traditional 3+3 dose escalation trial design. Taking into consideration that quite a number of publications over the last two decades did show the superiority of CRM class models over 3+3 with respect to accuracy and efficiency, this is a disillusioning finding.

The authors do clearly acknowledge other manuscripts upon which they are building. Title and abstract do accurately convey what has been found, and the writing is acceptable, although minor spelling errors were found, but these can easily be taken care of (minor essential revisions). See below a list of some errors found.

List of major compulsory revisions: none listed

List of minor essential revisions:
(1) p.1: check both e-mail addresses
(2) p.3, l.2: ‘recommended dose for of a new compound’ - just ‘for’, no ‘of’
(3) p.3, l.3: ‘[1, 2.’ - missing parenthesis
(4) p.3, l.3+5: ‘phase II’ versus ‘phase-II’, would prefer phase II
(5) p.3, l.6: delete abbreviation ‘RDP2’ as there only is one other occasion of the corresponding term anyway.
would have the advantage of describing the design of clinical cancer trials, both traditional and methodological phase I as well as both phase I, phase II and phase III trials.


(8) p.4, l.2-5: specify search strategy by giving more details like search engines, key words searched and so on.

(9) p.4, l.8: ‘into 5 categories’ as only 5 categories are listed thereafter – or is the genuine Fibonacci sequence the 6th category?

(10) p.5, l.4-5: ‘The median number of dose-levels explored was 5 (range 1 – 12).’ Isn’t the range of dose levels explored from 2 to 12 (see Table 2)?

(11) p.5, l.4-5: Propose to add a notion that 4 out of 81 studies actually only investigated 2 dose levels (in order to support reading of Table 1), e.g. after ‘The median number of dose-levels explored was ….’

(12) p.5, l.11: ‘from the fifth dose-level (5.32 instead’ - instead of ‘five’

(13) p.5, l.13: re-check sequence (rounding errors) ‘2.00, 1.50, 1.33, 1.33, 1.47, 1.53, 1.32, 1.24, 1.18, 1.26, 1.33, 1.33’

(14) p.5, l.14: ‘(see 8th column of Table 3).’- it's the 4th col.

(15) p.6, l.8: ‘in 3 and 2%’ - 3% and 2%

(16) p.6,l.19: genuine (instead of Genuine)

(17) p.10, header to table: ‘phase I1 trials’ - phase 1 trials OR phase I trials

(18) p.10: frequencies add up to 198 (instead of 197). add percentages to frequencies

(19) p.11, legend to table: ‘n: number of studiesd reaching’ - studies

List of discretionary revisions:

(20) complete list of all 327 trials considered as electronic supplementary document to this paper.

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

**Quality of written English:** Needs some language corrections before being published

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

**Declaration of competing interests:**

I declare that I have no competing interests.