Reviewer’s report

Title: Flexible trial design in practice: stopping arms for lack-of-benefit and adding research arms mid-trial in STAMPEDE: a multi arm multi stage randomised controlled trial

Version: 1 Date: 14 May 2012

Reviewer: Charlie Goldsmith

Reviewer’s report:

In general, this paper is well done. However, there are a series of issues that should be considered to improve the paper.

1. P(age) 3, l(ine) 20. Insert [new arms] between [These] and [are].
3. P 4, l 40. Since no data are shown in this paper that the design is more efficient and more cost effective, this statement should be made more speculative until the data can be cited.
4. P 4, l 43. Include the date the first patient was randomised for the complete trial as well as the new arms.
5. P 6, l 76. Suggest replacing [manpower] by [personnel] to make this statement gender neutral.
6. P 6, l 77. Some other benefits could be a longer time for companies to generate profit under their patent life as well as getting therapies out to patients sooner.
7. P 7, l 80 and 81. Suggest underlining the letters that led to STAMPEDE.
8. P 7, l 93. This reviewer thinks the lack of benefit is not the same as lack of sufficient activity and so the brackets and [equivalently] should be eliminated.
9. P 8, l 101. Suggest deleting [in a pairwise fashion] since comparing each active versus the control is a pair.
10. P 8, l 109 and 116. Be consistent in the use of the word [program], either one will do.
12. P 9, l 130. Insert [(TSC)] after [Committee]. Please define all short forms the first time they are used.
13. P 9, l 139. Delete [in order] before [to] as the words are redundant in English.
15. P 10, l 170. Insert [(PIS)] after [Sheets].
16. P 10, l 171. Insert [each centre’s] between [the] and [Ethics].
18. P 11, l 195. Suggest replacing [failed to] by [did not]. The former suggests it should have; however, the trial should have equipoise. Suggest including the 95% Confidence Interval here as well.

19. P 11, after l 203. Trials does not allow footnotes.

20. P 12, l 206. Delete [Patient Information Sheet ()] since it should be defined the first time it is used. See 15 above.

21. P 12, l 211. Insert the number of patients.

22. P 13, l 241 and 242. This suggests that some patients will have their data included in the trial twice. Also, it violates the principle of Intent to Treat and trial randomisation integrity, so will need to be accommodated in a revised analysis.

23. P 13, l 250. Add an [s] to [arm] to read [arms].

24. P 13, l 252. Arms that stop early for benefit generally overestimate the treatment effect. This should be discussed as a possible weakness.

25. P 14, l 267. Rewrite as [addition when there are robust and convincing scientific hypotheses.]

26. P 14, l 280. Provide R(eference)s for these possible benefits rather than an opinion.

27. P 15, l 303. Replace [Trial Management Group] by [TMG] since this should be defined on P 14, l 259 which appears to be the first time it is used.

28. P 16, l 326. Is there a R to the survey results?

29. P 16, l 330 to 334. Are there any other packages that do these calculations? Were these two packages validated by peer review? If so can they be cited?

30. P 17, l 339. Suggest coding by line type as well as color as they did not come through when I printed them in black & white.

31. P 17, l 341. Suggest rewriting as […] when there are more research …].

32. P 17, l 353 to 356. If these are available, then could be added as appendices.

33. P 20, l 429. Can this be documented that it deserves to be called major?

34. P 20, l 434. Can this be documented?

35. P 20, l 446. Provide a R for minimisation.

36. P 20, l 447. Relist or R the stratification factors.

37. P 21, l 455. List them with registration numbers.

38. P 21, l 464. Insert [arms] between [further] and [that].

39. P 21, l 471. Add an [s] to [provide] to read [provides].

40. P 21, l 474. Provide a R to results.

41. P 22, l 486. Is there a R to this?

42. P 22, l 489. Provide some data to justify the increase.

43. P 22, l 492. Replace [that] by [and].

44. P 23, l 504. Replace [significant] by [major] or some other word that does not
imply this has statistical significance.

45. P 23, l 506. Replace [effective] by [efficient].

46. P 24. The following short forms are not in this list: yr, pts, CYPO, CRPC, ASCO, PSA, NICE, SAKK, tot, ctrl, ev, R&D, AS1, AS2, Ppn. For yr, why not use the standard short form y?

47. P 27, Ritchie. Why not make [Reviewed and approved final manuscript] last rather than second to be consistent with the rest?


A random sample of 10 Rs was checked for citation accuracy. Trials likes to publish all authors up to 30 before using et al. So add authors for R 3, 4, 5, 15, 16, 17, 18, 19, 20, 21, 23, 24, 25, 26, 28, 29, 30.

49. P 31, R 6. Insert the date of last access.

50. P 32, R 7 appears to be correct.


52. P 32, R 9 and 10 appear to be correct.


54. P 33, R 14 could not be verified.

55. P 34, R 22 appears to be correct.

56. P 35, R 27 appears to be correct.

57. P 35, R 30, 1709. Insert the volume and page numbers.

58. Table 1, l 7 and 8. The sentence from [The number … allocation ratio] does not seem to be needed.

59. Table 1, l 10 Suggest deleting [pairwise].

60. Table 2, l 16. Replace [wk] by [w] and add [d = day]; with the corresponding changes in the Table above.

61. Table 3, bullet 2. Since [or] logically includes [and] delete [and/].

62. Table 3, bullet 7, l 5. Suggest rewrite as [700 patients/year when 500 patients/year were targeted].

63. Figure 4, last line. Suggest rewrite as [approval (approved)]. It appears to be weekly intervals even though the graph (small ticks) seems to be daily.