Author's response to reviews

Title: The Effectiveness of Early Lens Extraction with Intraocular Lens Implantation for the treatment of Primary Angle Closure Glaucoma: A Randomised Controlled Trial.

Authors:

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Version: 3 Date: 10 February 2011

Author's response to reviews: see over
10-Feb-11

Dear Editor:

Please find below the answers to the Reviewer’s comments.

Yours sincerely,

Augusto Azuara-Blanco
Corresponding author and EAGLE Principal Investigator

Reviewer’s report

Title: The Effectiveness of Early Lens Extraction with Intraocular Lens Implantation for the treatment of Primary Angle Closure Glaucoma: A Randomised Controlled Trial.

Version: 2 Date: 11 January 2011

Reviewer: Charlie Goldsmith

Reviewer’s report:
In general, this protocol is well done; however, there are few suggestions to possibly improve it for the benefit of readers.

1. Title P(age), l(ine) 4. Please insert the date of registration and the date the first patient was randomized.
   Added

2. Title P, l 6. While a study group is the claimed authorship, the list of team members, steering committee members and additional member were listed on P8. Should any others be part of the authorship?
   We have added one collaborator who is part of the study group, Dr. Jemaima Che-Hamzah

3. This reviewer thinks it would be helpful to have an appendix of short forms used in the study. For example, it looks as if [IOP] is not defined yet used on P 2, p(aragraph) 2, l 5.
   Added (see below, Appendix 1)

4. P 2, p 3, l 6. Provide a reference for the details of the drugs used, such a form, dosage, frequency etc. that may be of interest to a potential reader.
   Added, (see below, Appendix 2)

5. P 3, p 2, l 1. Suggest replacing [recent] by [2006]. Recent fades with time; however, the date is always relevant.
   Replaced

6. P 3, p 4. Since there are really 3 questions and apparently 3 hypotheses, it would be helpful to state it as such, and whether they will separately or simultaneously tested.
   The three hypotheses will be analysed separately, as specified in the preceding paragraph (labelled “outcomes”)

Added
7. P 3, p 5, l 2. There is no need to have both the [at least 50 years old] on l 2 as well as 5th b(ullet). 
    Corrected

8. P 3, p 5, b 1, l 7. Since [or] logically includes [and], drop [and/]. Corrected

9. P 3, p 5, b 1, l 6. Rewrite as [P < 0.05], with a space on either side. Corrected

10. P 3, p 5, b 1, l 9. Rewrite as [> 21 mm Hg]. Corrected

11. P 3, p 5, b 3, l 1. Drop [and/]. Corrected

12. P 3, p 5, b 3, l 2. Rewrite as [# 30 mm]. Corrected

13. P 3, p 6, b 1, l 2. Rewrite as [-15 dB] or (ii) cup-disc-ratio # 0.9. Corrected

14. P 4, p 2, l 6. Each of these instruments should be briefly described to give a reader information on scoring and interpretation. The EQ-5D should also be referenced. 
    Agreed, see below (Appendix 3)

15. P 4, p 2, l 2. Provide a reference to the website that does this as well as any reviews of its veracity.
    Standard libraries are used to build the website and internal testing of data input is performed by CHaRT.
    CHaRT is an accredited trials unit with accredited randomisation standard operating procedures (including testing).
    http://www.charttrials.abdn.ac.uk/

16. P 4, p 2, l 5. Provide levels for ethnicity and centres. The other minimisation factor levels are clear. Also, provide a reference to minimisation.
    The minimisation levels are: Ethnicity - Chinese or non-Chinese; Gender- Male/Female; Diagnosis - PAC or PACG; centre

    Modified as follows: “treatment would be aiming for a target IOP between 15-20 mmHg depending...”

18. P 6, p 3, l 4. Is the plan to compute the QALYs over 3 years? If so, state it. Is any discounting going to be used?
    Yes, the plan is to compute the QALY over 3 years. Annual discount rate of 3.5% will be used to discount health outcome and cost, which is based on the recommendations of the UK treasure and suggested by NICE (NICE: Guide to the Methods of Technology Appraisal, April 2004). This information has been added to the paper.

19. P 6, p 5, b 3. Since incidence is a time related rate, what time will be used? Annual?
    Yes. Information added

20. P 6, p 8, l 2. Rewrite as [> 10].
    Corrected

21. P 6, p 10, l 3. Is there a reference to the charter and responsibilities of the DMC?
22. P 7, p 1, l 6. Reference the forms of imputation analysis that will be used with any missing data. It would also be useful to know what types of sensitivity analyses are planned, with suitable references.

The following comments and reference have been added to the paper:
The methods that would be used include expectation maximisation algorithm, multiple imputation, general linear mixed models, techniques based on survival analysis (Ostenbrink 2003 - Oostenbrink, J.B., Maiwenn, J. and Maureen P.M.H Rutten-van Molken (2003) Methods to Analyse Cost Data of patient who withdraw in Clinical Trial Setting. Pharmacoeconomics, 21 (15): p. 1103-1112). The specific missing data approach will be pre-specified once the pattern of missingness has been determined.

23. P 7, p 1, l 12 to 14. For these 2 sub-group analyses, will interactions be tested? And is there a reference as to why these subgroups should be tested?
See above answer to Q. 22.

24. P 7, p 2. Apart from redundancy, what else will be done to add to the validity of the scale?
Sensitivity to change in severity of disease will be measured. This has been added to the analysis section.

25. P 7, p 3, l 5. What is the reference for 0.05 minimum clinically important difference in QALYs? And the 15% in l 15, just like the 2 mm Hg in l 12.
- No reference for 15% as it was based on expert consensus
- Reference for 2 mmHg is current reference # 24 (Leske 2003)

A random sample of 10 R(eference)s was checked for accuracy. Also, Trials tries to publish all authors, not just the first 6 et al. This reviewer also likes to see the issue number as it makes finding the reference easier for a reader.
Modified as requested

26. P 9, R 1,l 2. Insert [(11)] after [85]. Corrected

27. P 9, R 2, l 2. Insert [(3)] after [90]. Corrected

28. P 9, R 3, l 1. Insert [(10)] after [87]. Corrected

29. P 9, R 5, l 2. Insert [(8)] after [84]. Corrected

30. P 9, R 7, l 2. Insert [(2)] after [ 86]. Corrected

31. P 9, R 9, l 3. Insert [(8)] after [112]. Corrected

32. P 9, R 12, 15. Insert the rest of the authors. Corrected

33. P 10, R 18. This reviewer could not reference this source. Is it accurate?
Yes, it is accurate

34. P 10, R 21, l 3. Insert [(4)] after [107]. Corrected
35. P 10, R 23, l 1. Insert the other 2 authors, and on l 3 insert [(3)] after [113]. Corrected

36. P 10, R 24, l 1. Replace [et al] by [Early Manifest Glaucoma Trial Group] and in l 3, insert [(1)] after [121]. Corrected

Appendix 1. Glossary of abbreviations
Appendix 2. Possible treatments for glaucoma (eye drops)

- CHOLINERGIC AGENTS: PILOCARPINE (TDS or QDS)
- BETA ADRENERGIC ANTAGONISTS (QD or BDS)
- ALPHA AGONISTS
  - APRACLONIDINE (TDS)
  - BRIMONIDINE (BDS or TDS)
- CARBONIC ANHYDRASE INHIBITORS
  - DORZOLAMIDE (BDS or TDS)
  - BRINZOLAMIDE (BDS or TDS)
- PROSTAGLANDINS
  - LATANOPROST (QD)
  - TAFLUPROST (QD)
  - BIMATOPROST (QD)
  - TRAVAPROST (QD)
Appendix 3. Patient reported outcomes used in EAGLE: description, scoring and interpretation

EQ-5D

EQ-5D is a generic health status instrument developed by EuroQOL Group that can be used for clinical and economic evaluation as well as population based survey. EQ-5D consists of the EQ-5D descriptive system which provides a simple descriptive profile of health in five dimensions: mobility, self-care, usual activities, pain, and anxiety/depression, each with three levels. The EQ-5D also includes a visual analogue scale on which patients rate their own health between 0 (best imaginable health state) and 100 (worst imaginable health state).

A single summary index can be generated by applying a formula that attaches values to each level in each dimension. Therefore, patient’s health state can be classified into one of the 243 theoretically possible health states (e.g. value of full health is 11111). These value sets are obtained using result of EQ-5D visual analogue scale valuation or the time trade-off (TTO) valuation of a representative sample of the population in several countries.

Reference for EQ-5D


Website: http://www.euroqol.org

NEI-VFQ 25

The NEI-VFQ 25 is a widely used vision-specific patient reported outcome measure. It measures the impact of vision problems on vision-targeted functioning and health related quality of life (HR QOL). NEI-VFQ 25 consists of 25-items with 11 subscales and a single general health rating question. A standard algorithm was used to calculate the scale scores which have a possible range from 0 to 100 whereby 100 is the best possible score and 0 the worst. A composite NEI-VFQ 25 score can be generated by averaging the eleven scores (except the general health rating question). A higher score represents better visual functioning.

Glaucoma Utility Index

The Glaucoma Utility Index (GUI) is a glaucoma-specific preference based (utility) measure developed for economic evaluation. GUI provides a descriptive profile in six dimensions: central and near vision, lighting and glare, mobility, activities of daily living, eye discomfort and other effects of glaucoma and its’ treatment, each with four levels. A single summary index can be generated where patients’ health state can be classified into one of the 4096 theoretically possible health states. Value sets are obtained by using results of discrete choice experiment (DCE) of a representative sample of glaucoma population.
Appendix 4. Charter and responsibilities of the Data Monitoring Committee

A Data Monitoring Committee (DMC) has been established. The DMC is independent of the study organisers. During the period of recruitment to the study, interim analyses will be supplied, in strict confidence, to the DMC, together with any other analyses that the committee may request. This may include analyses of data from other comparable trials. In the light of these interim analyses, the DMC will advise the TSC if, in its view:

a) the active intervention has been proved, beyond reasonable doubt*, to be different from the control (standard management) for all or some types of participants, and

b) the evidence on the economic outcomes is sufficient to guide a decision from health care providers regarding recommendation of early lens extraction for PACG.

The TSC can then decide whether or not to modify intake to the trial. Unless this happens, however, the TSC, PMG, clinical collaborators and study office staff (except those who supply the confidential analyses) will remain ignorant of the interim results.

The frequency of interim analyses will depend on the judgement of the Chairman of the DMC, in consultation with the TSC. However, we anticipate that there might be three interim analyses and one final analysis.

The Chairman is Mr David Garway-Heath, with Dr David Crabb, and Professor Baljean Dhillon. Terms of reference for the DMC are available on request from the EAGLE study office.

* Appropriate criteria for proof beyond reasonable doubt cannot be specified precisely. A difference of at least three standard deviation in the interim analysis of a major endpoint may be needed to justify halting, or modifying, such a study prematurely (Peto R et al, Br J Cancer 1976;34:548-612).