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Title

Cost-effectiveness of Erythropoietin in Traumatic Brain Injury (EPO-TBI):
A multinational trial based economic analysis

Running title

Cost-effectiveness of the EPO-TBI trial

Authors

Rachel J Knott, Ph.D.[1]
Rachel.knott@monash.edu
Level 2, 15 Innovation Walk, Monash University Clayton Campus, Victoria 3800 Australia
Ph: 61 3 9905 0772
Fax: 61 3 9905 8344

Anthony Harris, M.Sc.[1]
Anthony.harris@monash.edu
Level 2, 15 Innovation Walk, Monash University Clayton Campus, Victoria 3800 Australia
Ph: 61 3 9905 8380
Fax: 61 3 9905 8344

Alisa Higgins, M.P.H.[2]
lisa.higgins@monash.edu
Level 3 553 St Kilda Road, Melbourne Victoria 3004 Australia
Ph: 61 3 9903 0348
Fax: 61 3 9903 0071

Alistair Nichol, M.B., Ph.D.[2,3,4]
alistair.nichol@monash.edu
Level 3 553 St Kilda Road, Melbourne Victoria 3004 Australia
Ph: 61 3 9903 0390
Fax: 61 3 9903 0071

Craig French, M.B., B.S.[5,6]
craig.french@wh.org.au
160 Gordon Street, Footscray Victoria 3011 Australia
Ph: 61 417 538 464
Fax: 61 3 8345 7610

Lorraine Little, M.Bioethics[2]
lorraine.little@monash.edu
Level 3 553 St Kilda Road, Melbourne Victoria 3004 Australia
Ph: 61 3 9903 0513
Fax: 61 3 9903 0071

Samir Haddad, M.D.[2,7]
samir.haddads55@yahoo.com
606 Broadway, Paterson, NJ 07514, USA
Ph: 1 (973) 523 1800
Fax: 1 (973) 689 3081

Jeffrey Presneill, M.B., B.S., Ph.D.[2,3,8]
intensive@fastmail.com.au
PO Box 2149 Royal Melbourne Hospital Victoria 3050 Australia
Ph: 61 419 783 899
Fax: 61 3 9342 8812

Yaseen Arabi, M.D.[2,9]
yaseenarabi@yahoo.com
PO Box 22490, Riyadh Kingdom of Saudi Arabia
Ph: 966 (11) 801-1111 Ext 18855/18877
Fax: 966 11 8011111x18880

Michael Bailey, Ph.D.[2]
Michael.bailey@monash.edu
Level 3 553 St Kilda Road, Melbourne Victoria 3004 Australia
Ph: 61 417 391 513
Fax: 61 3 9903 0071

D James Cooper, M.D.[2,3]
Jamie.cooper@monash.edu
Level 3 553 St Kilda Road, Melbourne Victoria 3004 Australia
Ph: 61 419 770 051
Fax: 61 3 9903 0071

Jacques Duranteau, M.D., Ph.D.[10]
jacques.duranteau@aphp.fr
78, rue du Général Leclerc, 94275 Le Kremlin Bicêtre France
Ph: 33 1 45 21 34 41
Fax: 33 1 45 21 28 75

Olivier Huet, M.D., Ph.D.[2,11]
olivier.huet@chu-brest.fr
Bd Tanguy Prigent, 29609 Brest Cedex France
Ph: 33 2 98 34 72 88
Fax: 33 2 98 22 34 98

Anne Mak, B.Sc.Pharm., Grad.Dip.Pharm.[2,3]
a.mak@alfred.org.au
55 Commercial Road, Prahran Victoria 3181 Australia
Ph: 61 3 9076 8343

Fax: 61 3 9076 3305

Colin McArthur, M.B.Ch.B.[2,12]
colinm@adhb.govt.nz
Private Bag 92 024, Auckland Mail Centre 1142, Auckland NZ
Ph: 64 21 722 781
Fax: 64 9 307 4927

Ville Pettilä, M.D., Ph.D.[2,13]
ville.pettila@hus.fi
Topeliuksenkatu 5, Helsinki P.O. Box 266, FIN-00029 HUS, Finland
Ph: 35 8 5042 71715
Fax: 65 6 357 7715

Markus Skrifvars, M.D., Ph.D.[13]
markus.skrifvars@hus.fi
Haartmaninkatu 9, 000290 HUS, Helsinki Finland
Ph: 35 8 4051 37862
Fax: 35 8 9471 74125

Shirley Vallance, M.P.H.[2,3]
s.vallance@alfred.org.au
55 Commercial Road, Prahran Victoria 3181 Australia
Ph: 61 3 9076 8034
Fax: 61 3 9076 2343

Dinesh Varma, M.B., B.S.[3]
d.varma@alfred.org.au
55 Commercial Road, Prahran Victoria 3181 Australia
Ph: 61 3 9076 2536
Fax: 61 3 9076 2343

Judy Wills, D.M.U., A.S.A.R.[2,3]
j.wills@alfred.org.au
55 Commercial Road, Prahran Victoria 3181 Australia
Ph: 61 3 9076 2536
Fax: 61 3 9076 2343

Rinaldo Bellomo, M.D.[2,5,6,14]
Rinaldo.bellomo@austin.org.au
Studley Road, Heidelberg Victoria 3084 Australia
Ph: 61 3 94965992
Fax: 61 3 9496 3932

for the EPO-TBI Investigators and the ANZICS Clinical Trials Group*

Affiliations

[1]Centre for Health Economics, Monash Business School, Monash University, Melbourne, Victoria, Australia

[2]Australian and New Zealand Intensive Care Research Centre, School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia

[3]The Alfred, Melbourne, Victoria, Australia

[4]University College Dublin-Clinical Research Centre, St Vincent's University Hospital, Dublin, Ireland

[5]Western Health, Melbourne, Victoria, Australia

[6]University of Melbourne, Melbourne, Victoria, Australia

[7]King Abdulaziz Medical City, National Guard Health Affairs, Riyadh, Kingdom of Saudi Arabia

[8]University of Queensland and Royal Brisbane and Women's Hospital, Brisbane, QLD

[9]King Saud Bin Abdulaziz University for Health Sciences and King Abdullah International Medical Research Center Riyadh, Kingdom of Saudi Arabia

[10]Département d'Anesthésie-Réanimation, Hôpital de Bicêtre, Assistance Publique des Hopitaux de Paris, Hôpitaux Universitaires Paris-Sud, Université Paris-Sud, Paris, France

[11]Department of Anaesthesiology and Intensive Care Medicine, CHU La Cavale Blanche, Brest, France

[12]Auckland City Hospital, Auckland, New Zealand

[13]University of Helsinki and Helsinki University Hospital, Helsinki, Finland

[14]Austin Hospital, Melbourne, Victoria, Australia

*The Erythropoietin in Traumatic Brain Injury (EPO-TBI) trial is a collaboration of the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group and the Australian and New Zealand Intensive Care Research Centre. A complete list of investigators in the EPO-TBI trial is provided in Box A1 of the Appendix.

Corresponding author:

Alisa Higgins

Email: lisa.higgins@monash.edu
Level 3 553 St Kilda Road, Melbourne Victoria 3004 Australia
Ph: 61 3 9903 0348
Fax: 61 3 9903 0071

Abstract

The EPO-TBI multinational randomised controlled trial found that erythropoietin (EPO), when compared with placebo, did not affect 6 month neurological outcome but reduced illness severity-adjusted mortality in patients with traumatic brain injury (TBI), making the cost effectiveness of EPO in TBI uncertain. The current study uses patient-level data from the EPO-TBI trial to evaluate the cost-effectiveness of EPO in patients with moderate or severe TBI from the healthcare payers' perspective. We addressed the issue of transferability in multinational trials by estimating costs and effects for specific geographical regions of the study (Australia/New Zealand, Europe and Saudi Arabia).

Unadjusted mean QALYs (95%CI) at six months were 0.027 (0.020 to 0.034; p<0.001) higher in the EPO group with an adjusted QALY increment of 0.014 (0.000 to 0.028; p = 0.04). Mean unadjusted costs (95%CI) were $US5,668 (-9,191 to -2,144; p = 0.002) lower in the treatment group; controlling for baseline IMPACT-TBI score and regional heterogeneity reduced this difference to $2,377 ($-12,446 to 7,693; p = 0.64). For a willingness-to-pay threshold of $US50,000 per QALY, 71.8% of replications were considered cost-effective. Therefore, we did not find evidence that EPO was significantly cost-effective in the treatment of moderate or severe TBI at 6 month follow-up.

Trial registration:
ClinicalTrials.gov NCT00987454
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Keywords

Traumatic Brain Injury, Erythropoietin, Cost-effectiveness, multinational trial, QALYs.

Introduction

Traumatic Brain Injury (TBI) is a major cause of death and disability - especially amongst younger people; and its incidence is rising sharply.[1, 2] For those who survive TBI, lifelong disability is common, and the impact on quality of life can be significant.[3, 4] The costs of TBI on the healthcare system and the wider economy are also substantial – in the USA, for example, total costs have been estimated at over US$60 billion annually.[5] For these reasons, the discovery of cost-effective interventions is an important objective.[6]

The Erythropoietin in Traumatic Brain Injury (EPO-TBI) study was a multinational, double-blind, randomised controlled trial (RCT) that assessed the effectiveness of erythropoietin (EPO), a neuroprotective agent, in a heterogeneous population of patients with moderate or severe TBI.[7] EPO is approved by the Food and Drug Administration (FDA) but not indicated for TBI. While the EPO-TBI trial did not demonstrate that EPO was effective in reducing the number of patients with moderate or severe neurological dysfunction at six months post-injury (defined by a Glasgow Outcome Scale – Extended (GOS-E) of 1-4).[7] it showed a significant decrease in illness severity-adjusted mortality at 6 months, making it uncertain whether EPO is a cost-effective intervention in TBI in terms of quality adjusted life years (QALYs). Accordingly, we aimed to assess the quality of life and resource use from the perspective of the healthcare payer over 6 months of the EPO-TBI trial and estimate the cost-effectiveness of EPO in TBI. We hypothesized that EPO would be a cost-effective treatment for TBI.

Methods

Overview

The EPO-TBI trial was a prospective, randomized, parallel-group, double-blinded trial conducted in 29 participating hospital sites across seven countries (Australia, New Zealand, France, Finland, Germany, Ireland and Saudi Arabia). The design, methodology and results of the EPO-TBI trial have been described in detail previously.[7, 8] In brief, 606 patients aged between 15 and 65 presenting with moderate or severe TBI were stratified according to severity, and randomised to receive either epoetin alfa 30,000 IU (Eprex Janssen-Cilag Pty Ltd, Titusville, NJ, USA) (n=308) or placebo (0.9% sodium chloride) (n=298) in the intensive care unit (ICU) within 24 hours of injury. Second and third doses were administered at weekly intervals conditional on patients remaining in the ICU. Follow-up was conducted at approximately six months by trained local staff via structured telephone interviews with patients where possible, or with a proxy if patients were unable to answer (interviewers were blind to the patient's treatment allocation). The trial commenced in May 2010 and patient recruitment ended in November 2014, with follow-up finalised in May 2015. Ethics approval was obtained at all participating hospitals and informed consent was obtained from the patient or their legal representative.

Health outcomes

Effectiveness in the current study was considered in terms of quality-adjusted life years (QALYs), where 1 QALY is equal to one year in full-health[7] These were measured using utility scores derived from the EQ-5D-3L,[9] which was administered at follow-up, and valued using the UK time-trade-off tariff.[10] All patients were assumed to have a utility score of zero at randomisation in accordance with other studies recruiting patients in critical care.[11, 12] Patients who died were given a utility of zero at follow-up. Quality of life is also reported in terms of the proportion of limitations for each EQ-5D-3L dimension, and the physical components score (PCS) and mental components score (MCS) of the SF-

12,[13] which was also administered at follow-up. Since the primary analysis found no difference in the proportion of patients with a GOS-E of 4 or less at follow-up, we did not examine this outcome.[7]

Patients with missing EQ-5D-3L information were removed from the analysis since they represented less than 5% of the sample in each arm.[14] A sensitivity analysis was conducted assuming best and worst case scenarios (i.e. utility scores of 1 and 0 at follow-up, respectively) for these patients, as well as those lost to follow-up.

Resource use and costs

Data on resource use at different levels of care were recorded at discharge from the index hospitalisation, and again at follow-up for subsequent health-care resource use (including readmissions, rehabilitation and other care facilities). Information was available for length of ventilation, time in ICU, transfusion of red blood cells, hospital (ward) days, rehabilitation days, and time spent in high and low level care facilities and transitional living centres. Additionally, information on whether carers were required for patients that returned home was inferred from item 2b of the GOS-E[15] at follow-up.

Resources were translated into costs by multiplying the relevant country-specific unit cost by use for each patient in the analysis; where unit costs were obtained from hospital staff where possible, or national databases.[16-25] Detailed information on all costs and sources is provided in a supplementary web-appendix (Table A1). All costs are reported in 2014 prices using national consumer price index statistics from relevant countries.[26-28] Purchasing power parity (PPP) statistics from the Organisation for Economic Co-operation and Development (OECD) were used to translate costs to a common currency (United States Dollars, $US).[29] Given the short time period, costs were not discounted.

Analysis of costs and outcomes

A statistical analysis plan was published prior to study completion.[30] We present and compare selected baseline characteristics and rates of resource use over the trial across treatment groups. Unadjusted and adjusted summary measures are presented for costs and QALYs, as are raw EQ-5D-3L profiles and SF-12 summary components scores (i.e. the PCS and MCS), across treatment groups. An incremental cost-effectiveness ratio (ICER) is also presented. Adjusted measures account for differences in the baseline probability of having a GOSE-E of 4 or less at six months, according to the extended International Mission on Prognosis and Analysis of Clinical Trials in Traumatic Brain Injury, (IMPACT-TBI). We also adjusted for fixed effects across three geographical regions (i.e. Australia/New Zealand (NZ), Europe and Saudi Arabia) to account for potential heterogeneity which may arise, for example, through regional variations in treatment patterns. Finally, we made statistical adjustments for the slight variability in the timing of collection for the resource use and outcomes data at follow-up.

Cost-effectiveness estimates are presented for the trial-wide (pooled) analysis. To address issues of transferability in this multinational trial, costs and effects across treatment groups are also presented for each of the three geographical regions, to ensure that estimates are relevant for local policy-makers.

Statistical methods

Means (with standard deviations) of the continuous raw data are compared across treatment groups using t-tests or Wilcoxon rank-sum tests as appropriate. Binary and categorical characteristics/outcomes are presented in terms of proportions and compared using two-proportion z-tests and χ^2-tests (or Fisher exact tests), respectively. We use a 5% level of statistical significance.

For the adjusted cost analyses we used generalised linear models (GLM); where distribution families were selected using the Modified Park Test, and the link function using the Pearson Correlation,

Pregibon Link and Modified Homer and Lemeshow tests.[14] To derive adjusted QALYs, we first multiplied the probability of survival to six months by the adjusted EQ-5D-3L utility scores at six months. A survival function with a Weibull distribution was fitted to derive adjusted survival, and multiple linear regression was used to derive preference scores adjusted for differences in the timing of follow-up. QALYs were then evaluated by calculating the area under the curve, assuming a linear improvement/decline in quality of life from a baseline score of zero. We tested the sensitivity of this assumption against an alternate scenario where a baseline quality of life score of zero was maintained until discharge from the index ICU admission.

Region-specific estimates were obtained by interacting the treatment variable with regional fixed effects. Adjusted costs and QALYs were calculated using the method of recycled predictions (where follow-up time for survivors was standardized to six months). Bootstrap procedures were conducted to estimate uncertainty around costs and effectiveness estimates. We conducted 5,000 bootstrap replications, stratified by treatment group and geographical region. 95% confidence intervals were calculated using the bootstrap acceptability method.[14] Bootstrap replications are displayed graphically on the cost-effectiveness plane. Replications are also summarised in terms of the percentage for which (1) costs were lower amongst patients in the treatment group, and (2) EPO lead to an improvement in QALYs. Finally, cost-effectiveness is expressed in terms of the percentage of replications for which EPO is cost-effective at six months, based on a hypothetical maximum willingness-to-pay threshold of $US50,000 per QALY. To be (two-tailed) 95% confident that EPO is cost-effective, 97.5% of replications must fall below this limit.[14] Cost-effectiveness acceptability curves are also presented; these illustrate the percentage of the joint distribution of costs and QALYs from treatment that are cost effective over a range of reasonable willingness-to-pay thresholds from $US25,000 to $US150,000. All analysis was conducted in STATA version 14.

Results

A total of 606 patients were randomized to receive EPO (epoetin alfa n=308) or placebo (n=298). Three patients in the treatment group and four in the control group were lost to follow-up and excluded from the analysis. A further three patients in the treatment group withdrew consent for use of their data. Table 1 presents selected characteristics for the sample followed to the end of the trial. 15 of the 302 patients in the treatment group, and 14 of 294 patients in the control group had missing EQ-5D-3L information and were removed from the analysis (for characteristics of this group compared to the analysis sample, refer to Table A2 in the online appendix). Thus, 567 patients were included in the cost-effectiveness analysis (Figure A1).

<Table 1 here>

Resource use

Resource use across treatment and control groups until death or follow-up is summarised in Table 2 for both the trial-wide sample and subsamples according to region. Some variation in treatment patterns is evident among the different regions. For instance, ICU days, ventilation days and rehabilitation days were higher in Europe compared to Australia/NZ and Saudi Arabia, while ward days in Europe were lower. Across treatment groups, ward length of stay was slightly higher in the group that received treatment in the Australia/NZ subsample ($p = 0.02$), and carer days were greater in the treatment group for the European subsample ($p = 0.01$). Other measures of resource use did not vary significantly across treatment groups.

<Table 2 here>

Outcomes at follow-up

Tables 3 and A3 of the appendix summarize outcomes at follow-up. For the trial-wide sample, the unadjusted proportion of deaths in the treatment group was lower compared to the control group,

but not significantly (0.11 (32/287) vs. 0.16 (46/280), p = 0.07). For the regional sub-samples, the proportion of deaths in Australia/NZ was significantly lower in the treatment group (0.08 (12/154) vs. 0.17 (25/148); p = 0.02); while for Europe and Saudi Arabia, deaths did not significantly differ across treatment and control groups.

<Table 3 here>

EQ-5D preference indices at follow-up were higher in the treatment group but not significant (0.58 (95%CI: 0.54 to 0.63) vs. 0.51 (0.46 to 0.56); p = 0.07); this effect was largely driven by the higher proportion of deaths in the control group. There were no significant differences in preference scores across treatment groups for the regional sub-samples.

Costs and QALYs

Tables 4 and 5 report unadjusted and adjusted costs (in $US2014) and QALYs to six months, respectively. While mean unadjusted costs (95%CI) were $5,668 (-9,191 to -2,144; p = 0.002) lower in the treatment group compared to the control group, this effect diminished after controlling for baseline IMPACT-TBI score and regional heterogeneity, resulting in a difference in adjusted costs of $-2,377 ($-12,446 to 7,693; p = 0.64) between the two groups. Although there was considerable heterogeneity in costs across regions, there were no significant differences in adjusted costs amongst treatment and control groups for the regional sub-samples.

<Tables 4 and 5 here>

Unadjusted mean QALYs (95%CI) at six months for the trial-wide sample were 0.131 (0.125 to 0.136) in the group receiving EPO and 0.104 (0.098 to 0.109) in the control group, yielding an increment of 0.027 (0.02 to 0.034; p < 0.001). After adjustment, QALYs were 0.128 (0.116 to 0.140) in the treatment group compared to 0.114 (0.100 to 0.128) in the control group, resulting in an adjusted QALY increment of 0.014 (0.000 to 0.028; p = 0.04).

Mean adjusted QALYs were higher in the treatment group for Australia/NZ and Saudi Arabia, though these differences were not statistically significant. QALYs did not vary across treatment groups for Europe. The results for incremental QALYs were robust to sensitivity analyses examining best/worst case scenarios for patients lost to follow-up and patients with missing EQ-5D-3L information; as well as the alternate assumption that quality of life improved/declined from the time of discharge of the index ICU admission, as opposed to baseline (see Appendix Tables A4-6).

The point estimate for the ICER was -$167,269 per QALY (95% CI -$2,224,260 to $10,578,103). Scatter plots of the bootstrap replications for incremental costs and effects are displayed in Figure 1. Focussing first on the trial-wide sample, EPO increased QALYs for 97.7% of replications, though costs were lower amongst patients in the treatment group for only 67.3% of replications, indicating a high degree of uncertainty around estimates for cost. For a willingness-to-pay threshold of $US50,000 per QALY, 71.8% of replications were considered cost-effective. Increasing the willingness to pay threshold up to $US150,000 did not increase this percentage by a substantial amount, as shown in Figure 2.

<Figure 1 here>

Within-trial costs in the EPO group were lower than the control group in 34.0% of replications for Australia/NZ, 73.7% for Europe, and 94.1% for Saudi Arabia. EPO increased QALYs in 96.6% of replications for Australia/NZ, 90.7% for Saudi Arabia, and only 53.7% for Europe. At six months post indexation, the percentage of bootstrap replications that were acceptable for a cost-effectiveness ratio of $US50,000 were 38.9% for Australia/NZ, 73.7% for Europe, and 95.0% for Saudi Arabia. Once again, increasing the willingness to pay threshold did not increase the percentage of acceptable replications by a substantial amount (Figure 2).

<Figure 2 here>

Discussion

We conducted a within-trial cost-effectiveness analysis of EPO vs. placebo in patients with moderate and severe TBI using data from the EPO-TBI trial, a multinational, double-blind RCT.[7, 8] We found considerable heterogeneity in costs and to a lesser extent in QALYs between geographical regions. We found QALYs at six months to be slightly higher in the EPO group compared to the control group for the trial-wide sample; however we were unable to find evidence to support the hypothesis that EPO is a significantly cost-effective treatment for moderate or severe TBI.

The small but statistically significant increment in adjusted QALYs for the trial-wide sample of 0.014 (p=0.04) represents 5.6% of the maximum achievable QALYs at six months assuming a linear increase from a baseline score of zero (i.e. maximum possible QALYs = 0.25, or one-quarter of a year in full health). While low in magnitude, this increment is favourable compared to other recent studies examining short-term outcomes in trials where randomisation occurred in the ICU. For instance, in patients presenting with septic shock, Mouncey et al. reported a QALY increment of -0.001 (p=0.88) at 90 days in patients receiving early, goal-detected therapy compared to usual care;[11] while Taylor et al. reported no change in QALYs at 6 months in critically ill patients receiving Hydroxyethyl starch vs. saline resuscitation (p=0.33).[12]

Costs were lower (though insignificant) in the group receiving EPO for the sample overall. This effect was driven by the European and Saudi Arabian subsamples, where the EPO group spent less time on average in both ICU and the hospital ward compared to the placebo group (even though mortality was lower in the treatment group for Saudi Arabia); though these effects were not significant. Notably, daily ICU costs were substantially larger for these regions compared to Australia/NZ when considered as a proportion of hospital ward costs per day (Appendix Table A1). In Australia/NZ, on the other hand, patients in the EPO group spent more time on average in the hospital ward compared to the placebo group, which contributed to higher (though not significant) costs in this group. This is likely to reflect the higher survival rate in the EPO group for Australia/NZ.

Our paper is the first to evaluate the cost-effectiveness of EPO in patients with TBI. In a modelled economic analysis of EPO in critically ill trauma patients which used data from a variety of sources including published RCTs and observational studies, Chui et al. found the probability that EPO was cost-effective varied from 0% to 85% over a range of WTP from $25,000 to $120,000 CAD using a one year time horizon.[31] These results, in a heterogeneous group of trauma patients, are similar to ours in a TBI specific population. In addition, Chui et al. also found a significant degree of uncertainty in the cost-effectiveness estimate, primarily due to uncertainty about the mortality benefits of EPO in a trauma population.[31]

Strengths and weaknesses

This study addressed the important issues of generalizability and transferability of findings in multinational trials in three ways. Firstly, to address the problem of increased heterogeneity in the multinational setting (e.g. due to differences in patients, treatment patterns and providers across geographic regions), we estimated fixed effects models that adjusted for between-region heterogeneity.[14, 32] We also used country-specific data on resource use, price weights and outcomes, in line with current recommendations.[32] Finally, we produced cost-effectiveness estimates specific to each geographical region of the EPO-TBI trial, enhancing the relevance to regional stakeholders.

The trial was pre-planned to detect changes in the primary clinical outcome for the trial-wide sample; it was not powered to detect region-specific effects or differences in QALYs or costs.[32] This meant that considerable uncertainty was observed in the trial-wide estimates for costs, and region-specific estimates for both costs and outcomes, resulting in estimates that were very imprecise. Our data are also unlikely to have sufficient power to estimate cost-effectiveness in other important subgroups, such as patients with diffuse TBI, who were found to have lower mortality in the treated group of the primary analysis.[7] Future trials should factor multinational settings and important subgroup analyses into sample size calculations.

The results are also limited to the trial period of six months. It is not uncommon to observe continued improvement in patients with TBI beyond six months of injury,[33, 34] and the gains from treatment could well extend beyond the primary end point. Further data collection to two-year follow-up is planned and may provide evidence of cost effectiveness.

Conclusion

We found evidence that EPO slightly improves the average quality adjusted survival at six months post injury in patients with moderate or severe TBI. The effect was small and was not accompanied by any significant difference in treatment or care costs. There is insufficient evidence at this time that EPO is a cost-effective therapy to improve quality of life in a heterogeneous population of patients with moderate and severe TBI.

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Conflicts of interest

The authors declare no competing interests.

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