Clinical science

# Randomised controlled trial of adjunctive triamcinolone acetonide in eyes undergoing vitreoretinal surgery following open globe trauma: The ASCOT study

Edward J Casswell ,[1,2,3] Suzie Cro ,[4] Victoria R Cornelius,[4] Philip J Banerjee,[3,5] Tapiwa M Zvobgo,[3,6] Rhiannon Tudor Edwards,[7] Victory Ezeofor,[7] Bethany Anthony,[7] Syed Mohammed Shahid ,[3,8] Catey Bunce ,[9] Joanna Kelly,[10] Caroline Murphy,[10] Elizabeth Robertson,[3] David Charteris,[3,6] The ASCOT Investigator Study Group

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bjo-2022-322787).

For numbered affiliations see end of article.

**Correspondence to**
Edward J Casswell, Sussex Eye Hospital, Brighton, BN2 5BF, UK; edcasswell@hotmail.com

Received 24 October 2022
Accepted 15 February 2023
Published Online First 27 February 2023

## ABSTRACT

**Background/aims** To investigate the clinical effectiveness of adjunctive triamcinolone acetonide (TA) given at the time of vitreoretinal surgery following open globe trauma (OGT).

**Methods** A phase 3, multicentre, double-masked randomised controlled trial of patients undergoing vitrectomy following OGT comparing adjunctive TA (intravitreal and subtenons) against standard care (2014–2020). The primary outcome was the proportion of patients with at least 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letter improvement in corrected visual acuity (VA) at 6 months. Secondary outcomes included: change in ETDRS, retinal detachment (RD) secondary to PVR, retinal reattachment, macular reattachment, tractional RD, number of operations, hypotony, elevated intraocular pressure and quality of life.

**Results** 280 patients were randomised over 75 months, of which 259 completed the study. 46.9% (n=61/130) of patients in the treatment group had a 10-letter improvement in VA compared with 43.4% (n=56/129) of the control group (difference 3.5% (95% CI −8.6% to 15.6%), OR=1.03 (95% CI 0.61 to 1.75), p=0.908)). Secondary outcome measures also failed to show any treatment benefit. For two of the secondary outcome measures, stable complete retinal and macular reattachment, outcomes were worse in the treatment group compared with controls, respectively, 51.6% (n=65/126) vs 64.2% (n=79/123), OR=0.59 (95% CI 0.36 to 0.99), and 54.0% (n=68/126) vs 66.7% (n=82/123), OR=0.59 (95% CI 0.35 to 0.98), for TA vs control.

**Conclusion** The use of combined intraocular and sub-Tenons capsule TA is not recommended as an adjunct to vitrectomy surgery following OGT.

**Trial registration number** NCT02873026.

### WHAT IS ALREADY KNOWN ON THE TOPIC

⇒ Proliferative vitreoretinopathy (PVR) is the most common cause of recurrent retinal detachment in eyes following open globe trauma.

### WHAT THIS STUDY ADDS

⇒ Adjuvant triamcinolone did not improve visual outcomes at the time of vitrectomy following open globe trauma.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The study adds to the evidence surrounding the treatment of PVR but was limited perhaps by its broad inclusion criteria. Future PVR trial designs will need to have a clear focus on disease categorisation and the timing of intervention.

## INTRODUCTION

Ocular trauma is a leading cause of visual loss worldwide and is the most common cause of unilateral visual loss, with significant socioeconomic implications.[1] In eyes that suffer open globe trauma (OGT), retinal detachment is a frequent complication and often requires multiple surgical procedures.[2 3] Proliferative vitreoretinopathy (PVR) is the most common cause of recurrent retinal detachment in these eyes and is associated with a worse visual outcome.[4]

Corticosteroid treatment has the potential to reduce the inflammatory and proliferative components of PVR; laboratory studies have suggested that corticosteroids can downregulate the pathobiological processes of PVR development.[5–7] A previous pilot randomised controlled study suggested that the adjuvant use of corticosteroid at the time of vitrectomy in eyes that had suffered OGT was associated with an improvement in visual outcomes.[8] A randomised controlled trial (RCT) on slow-release dexamethasone in vitreoretinal surgery also suggested a positive effect from steroid adjuncts in PVR cases,[9] although other studies using oral steroids have not shown an effect.[10]

The aim of this study was to test the hypothesis that adjunctive triamcinolone acetonide (TA), given at the time of surgery, can improve the outcome of vitreoretinal surgery following open globe



**To cite:** Casswell EJ, Cro S, Cornelius VR, *et al*. *Br J Ophthalmol* 2024;**108**:440–448.

trauma. The study analysed its effect on VA and the incidence of re-detachment.

## METHODS

A phase 3 multicentre double-masked RCT was carried out between November 2014 and September 2020. The trial was registered on the Clinicaltrials.gov database on 19 August 2016. The study complied at all times with the tenets of the Declaration of Helsinki. Patients provided written informed consent before enrolment. An independent Data Monitoring Committee and Trial Steering Committee provided oversight throughout the trial. The full study protocol is detailed elsewhere.[11] During the trial, the protocol was amended to change the primary outcome from a dual outcome to a single outcome (proportion of patients with a greater than 10 letter Early Treatment Diabetic Retinopathy Study (ETDRS) letter score improvement). The co-primary outcome, ETDRS letter score at 6 months, was converted to a principle secondary outcome. This was because it was felt that ETDRS letter score would have an unusual distribution, therefore requiring a complex statistical model which may be more difficult to communicate and that a binary outcome was more clinically meaningful to clinicians and patients.

### Participants

Eligible patients were those over 18 years old who had suffered full-thickness OGT and were undergoing vitrectomy, able to give written consent, willing to accept randomisation and able to attend 6-month follow-up. Exclusion criteria were (1) age under 18 years old; (2) pre-existing uncontrolled uveitis; (3) previous diagnosis of steroid-induced glaucoma; (4) pregnant or breast-feeding women; (5) allergy or previous reaction to TA; (6) inability to attend follow-up; (7) inability to give written consent; (8) current or planned systemic corticosteroid use of a dose above physiological levels (>10 mg prednisolone). The indication for vitrectomy following OGT was at the discretion of the operating surgeon.

### Recruitment

The multicentre study was planned across 20 UK sites. Recruitment was monitored and seven more recruiting sites were added during the trial.

### Intervention

Both groups received standard surgical treatment and routine preoperative and postoperative treatment and care. Standard care involved vitrectomy, treatment of retinal detachment if present and the surgeon's choice of intraocular tamponade agent. The Adjunct Group received additional postoperative steroid combination (triamcinolone acetonide, Kenalog, E.R. Squibb & Sons, New York, USA) consisting of 4 mg/0.1 mL into the vitreous cavity and 40 mg/1 mL subtenons. The control group received standard care only.

### Randomisation, masking and assessments

Eligible participants were randomised (1:1) using a telephone service to the Emergency Scientific Medical Services global service hosted at the King's College Clinical Trials Unit. The randomisation assignments were created using permuted blocks of varying sizes with stratification by trial centre. Randomisation and treatment allocation were performed intraoperatively once the operating surgeon had confirmed that the retina was attached. Operating surgeons were masked until the end of surgery; participants and study investigators were masked to treatment allocation throughout. The trial statistician remained subgroup masked throughout the trial and analysis.

Baseline assessments were performed within 14 days prior to the study vitrectomy. Participants' study visits were at 3 and 6 months postoperatively. Adverse events were reported to the sponsor as per the study protocol. Elevated intraocular pressure was defined as >25 mm Hg.

### Outcomes

The primary outcome was the proportion of patients with an improvement from baseline to 6 months of at least 10 on the corrected VA (ETDRS letter score at a starting distance of 4 m) in the study eye. The secondary outcomes were (1) change in corrected VA score (ETDRS letter score) at 6 months after initial study surgery; (2) retinal detachment with PVR at any timepoint within 6 months; (3) stable complete retinal reattachment (without internal tamponade present) at 6 months; (4) stable macular retinal reattachment (without internal tamponade present) at 6 months; (5) tractional retinal detachment at any timepoint within 6 months; (6) the number of operations to achieve stable retinal reattachment (either complete or macula) at 6 months; (7) hypotony (<6 mm Hg) at any timepoint within 6 months; (8) raised intraocular pressure (>25 mm Hg) at any timepoint within 6 months; (9) macular pucker by 3 and 6 months and/or require macular pucker surgery at any timepoint within 6 months; (10) quality of life measured using the VFQ25, CSRI and the EQ-5D-5L questionnaire.

### Sample size

The target sample size was 300 (150 per arm) over a 3-and-a-half-year recruitment period. This was based on an assumed proportion of individuals with clinically meaningful

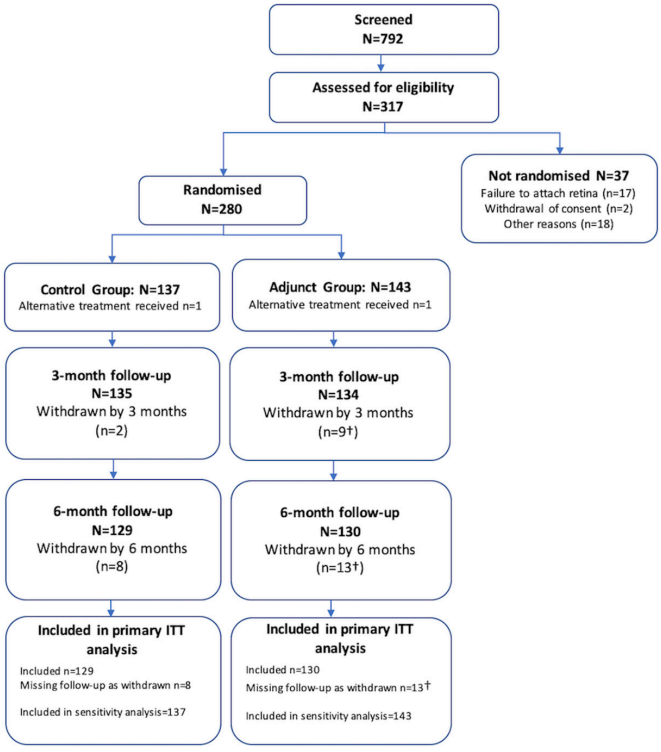



**Figure 1** CONSORT diagram. CONSORT diagram shown for the Ascot study. †Four participants who were randomised in error as ineligible and immediately withdrawn on date of randomisation. Numbers withdrawn are cumulative. ITT, intention on treat.

**Table 1** Baseline demographics

| Characteristic | Control n=137 | Missing | Adjunct n=143 | Missing | Total n=280 | Missing |
|---|---|---|---|---|---|---|
| Gender | | | | | | |
| Male | 123 (90%) | 0 | 123 (86%) | 0 | 246 (88%) | 0 |
| Ethnicity | | | | | | |
| White | 113 (82%) | 0 | 120 (84%) | 0 | 233 (83%) | 0 |
| Black | 11 (8%) | | 9 (6%) | | 20 (7%) | |
| Asian | 7 (5%) | | 11 (8%) | | 18 (6%) | |
| Other | 3 (2%) | | 3 (2%) | | 6 (2%) | |
| Mixed | 3 (2%) | | 0 | | 3 (1%) | |
| Current smoker | 55 (41%) | 4 | 51 (36%) | 3 | 106 (39%) | 7 |
| Eye injured | | | | | | |
| Right | 67 (49%) | 0 | 70 (49%) | 0 | 137 (49%) | 0 |
| Left | 66 (48%) | | 72 (50%) | | 138 (49%) | |
| Both | 4 (3%) | | 1 (1%) | | 5 (2%) | |
| Glaucoma | 2 (1%) | 1 | 2 (1%) | 0 | 4 (1%) | 1 |
| Previous eye surgery | 67 (49%) | 0 | 82 (57%) | 0 | 149 (53%) | 0 |
| Macular disease | 0 | 1 | 1 (1%) | 0 | 1 (<1%) | 1 |
| Mechanism of injury | | | | | | |
| Workplace incident | 40 (29%) | 0 | 48 (34%) | 0 | 88 (32%) | 0 |
| Road traffic accident | 5 (4%) | | 6 (4%) | | 11 (4%) | |
| Interpersonal violence | 33 (24%) | | 33 (23%) | | 66 (24%) | |
| Sports injury | 5 (4%) | | 5 (3%) | | 10 (4%) | |
| Other Injury | 16 (12%) | | 21 (15%) | | 37 (13%) | |
| Other domestic | 11 (8%) | | 10 (7%) | | 21 (8%) | |
| Domestic gardening | 5 (4%) | | 3 (2%) | | 8 (3%) | |
| Domestic DIY | 10 (7%) | | 3 (2%) | | 13 (5%) | |
| Iatrogenic | 0 | | 3 (2%) | | 3 (1%) | |
| Fall | 12 (9%) | | 11 (8%) | | 23 (8%) | |
| Previous primary repair | 95 (69%) | 0 | 110 (77%) | 1 | 205 (73%) | 1 |
| Time since primary repair (days) | | | | | | |
| Median (IQR) | 28 (12–151) | | 26 (11–108) | | 27 (12–119) | |
| Classification of Injury | | | | | | |
| Rupture | 53 (39%) | 0 | 60 (42%) | 0 | 113 (40%) | 0 |
| Penetrating | 51 (37%) | | 52 (36%) | | 103 (37%) | |
| Perforating | 4 (3%) | | 7 (5%) | | 11 (4%) | |
| IOFB | 29 (21%) | | 24 (17%) | | 53 (19%) | |
| Extent of injury | | | | | | |
| Zone 1 (cornea) | 51 (38%) | 2 | 44 (31%) | 1 | 95 (34%) | 3 |
| Zone 2 (limbus to muscle insertion) | 56 (41%) | | 54 (38%) | | 110 (40%) | |
| Zone 3 (posterior to muscle insertion) | 28 (21%) | | 44 (31%) | | 72 (26%) | |
| RAPD | | | | | | |
| Present | 17 (13%) | 2 | 26 (18%) | 0 | 43 (15%) | 2 |
| Not documented | 69 (51%) | | 71 (50%) | | 140 (50%) | |
| Visual axis corneal scar | 32 (23%) | 0 | 40 (28%) | 0 | 72 (26%) | 0 |
| Uveitis | 26 (19%) | 0 | 26 (18%) | 0 | 52 (19%) | 0 |
| Hyphaemia | | | | | | |
| Absent | 96 (70%) | 0 | 90 (63%) | 0 | 186 (66%) | 0 |
| <50% | 24 (18%) | | 26 (18%) | | 50 (18%) | |
| >50% | 17 (12%) | | 27 (19%) | | 44 (16%) | |
| Iris | | | | | | |
| Normal | 52 (39%) | 2 | 59 (42%) | 2 | 111 (40%) | 4 |
| Incomplete | 63 (47%) | | 72 (51%) | | 135 (49%) | |
| Incarcerated | 20 (15%) | | 10 (7%) | | 30 (11%) | |
| Lens | | | | | | |
| Clear | 37 (27%) | 1 | 33 (24%) | 2 | 70 (25%) | 3 |
| Cataract | 46 (34%) | | 50 (36%) | | 96 (35%) | |
| ACIOL | 0 | | 2 (1%) | | 2 (1%) | |

Continued

**Table 1** Continued

| Characteristic | Control n=137 | Missing | Adjunct n=143 | Missing | Total n=280 | Missing |
|---|---|---|---|---|---|---|
| PCIOL | 12 (9%) | | 8 (6%) | | 20 (7%) | |
| Aphakic | 41 (30%) | | 48 (34%) | | 89 (32%) | |
| Vitreous haemorrhage | 85 (63%) | 2 | 97 (69%) | 2 | 182 (66%) | 4 |
| Endophthalmitis | 2 (1%) | 1 | 3 (2%) | 0 | 5 (2%) | 1 |
| Retinal detachment | | | | | | |
| TRD | 17 (12%) | 0 | 21 (15%) | 0 | 38 (14%) | 0 |
| RRD | 49 (36%) | | 56 (39%) | | 105 (38%) | |
| Absent | 71 (52%) | | 66 (46%) | | 137 (49%) | |
| Fovea involved? (TRD and RRD only) | | | | | | |
| Yes | 41 (62%) | 0 | 44 (57%) | 0 | 85 (59%) | 0 |
| Splitting | 0 | | 1 (1%) | | 1 (1%) | |
| No | 25 (38%) | | 32 (42%) | | 57 (40%) | |
| IOFB | | | | | | |
| None | 101 (74%) | 0 | 118 (83%) | 0 | 219 (78%) | 0 |
| Intravitreal | 13 (9%) | | 18 (13%) | | 31 (11%) | |
| Intraretinal | 19 (14%) | | 7 (5%) | | 26 (9%) | |
| Intrascleral | 4 (3%) | | 0 | | 4 (1%) | |
| Presence of retinal incarceration | 25 (18%) | 0 | 38 (27%) | 0 | 63 (23%) | 0 |
| Presence of PVR C | 29 (21%) | 0 | 38 (27%) | 1 | 67 (24%) | 1 |
| Age (years) | | | | | | |
| Mean (SD) | 42.7 (15.3) | 0 | 46.8 (17.3) | 0 | 44.8 (16.5) | 0 |
| ETDRS VA in study eye (total score) | | | | | | |
| Mean, SD | 16.6 (30.5) | 0 | 10.4 (23.6) | 0 | 13.4 (27.3) | 0 |
| Median, IQR | 0.0 (0.0–11.0) | | 0.0 (0.0–0.0) | | 0.0 (0.0–1.0) | |
| Zero/very low | 98 (72%) | | 111 (78%) | | 209 (75%) | |
| >0 | 39 (28%) | | 32 (22%) | | 71 (25%) | |
| Where zero/very low, vision: | | | | | | |
| Counting finger | 10 (10%) | | 9 (8%) | | 19 (9%) | |
| Hand movement | 60 (61%) | | 54 (49%) | | 114 (55%) | |
| Perception light | 26 (27%) | | 45 (41%) | | 71 (34%) | |
| No perception light | 2 (2%) | | 3 (3%) | | 5 (2%) | |
| Where ETDRS VA>0 | | | | | | |
| Mean, SD | 58.3 (28.9) | | 46.6 (28.4) | | 53.0 (29.1) | |
| Median, IQR | 64.0 (45.0–83.0) | | 48.0 (21.0–66.0) | | 58.0 (24.0–80.0) | |
| IOP in study eye | | | | | | |
| Mean (SD) | 12.4 (7.4) | 14 | 11.7 (6.4) | 12 | 12.0 (6.9) | 26 |
| Low | 92 (75%) | | 103 (79%) | | 195 (77%) | |
| Normal | 21 (17%) | | 18 (14%) | | 39 (15%) | |
| High | 10 (8%) | | 10 (8%) | | 20 (8%) | |

ACIOL, anterior chamber intraocular lens; ETDRS, Early Treatment Diabetic Retinopathy Study; IOFB, intraocular foreign body; IOP, intraocular pressure; PCIOL, posterior chamber intraocular lens; PVR, proliferative vitreoretinopathy; RAPD, relative afferent pupillary defect; RRD, rhegmatogenous retinal detachment; TRD, tractional retinal detachment; VA, visual acuity.

improvement in VA (>10 letters) of 55% in the standard care arm and a 19% increase in the adjunct group to 75%, with approximately 7% loss to follow-up, at least 90% power and two-sided 5% type 1 error. Following slower than anticipated recruitment, the recruitment period was extended to 75 months. Over the full recruitment period, 280 eligible patients were recruited and are included within this analysis. Based on the original sample size parameters outlined above, it was established that the trial would still be adequately powered: a sample size of 280, assuming loss to follow-up of 7%, that is, 260 completers at 6 months provided 89.7% power to detect a 19% increase (55%–74%) in meaningful improvement in VA (>10 letters).

## Statistical analysis

Analysis was conducted subgroup masked (ie, group A vs B) following the ASCOT statistical analysis plan.[12] The main analysis was based on the intention-to-treat principle and included all eligible participants with follow-up in their randomised group to estimate the effect of the treatment policy (see online supplemental file). The primary analysis model consisted of a mixed logistic model with change in VA (<10, ≥10 change in 6-month ETDRS score) as the outcome and treatment arm and baseline value of the ETDRS as covariates. Treatment centre was included as a random intercept. The estimated treatment effect is reported as a subject-specific OR (conditional on centre and baseline ETDRS) with 95% CI and corresponding p value. Planned

sensitivity analyses for the primary outcome assessed the impact of missing outcome data and data collected out of window outcome. Linear (Gaussian) mixed regression models were used to analyse continuous secondary outcomes. Binary secondary outcomes were analysed using mixed logistic regression models. For count outcomes, a mixed effect negative binomial model was fitted, which allowed for overdispersion. Pre-planned subgroup analysis investigated whether the treatment effect on the primary outcome differed by retinal detachment, foveal involvement, presence of PVR or retinal incarceration and lens status. For additional details, see online supplemental file 1.

Estimates are presented with 95% CIs and two-sided p values. Statistical analysis was performed using Stata/IC V.15.2 (StataCorp) and a two-sided p value<0.05 was considered statistically significant.

## RESULTS

Site recruitment is shown in online supplemental eTable 1. Seven hundred ninety-two patients were screened, 317 were assessed for eligibility and 280 patients were randomised over 75 months. The CONSORT diagram is shown in figure 1. Four patients were withdrawn on the randomisation date from the adjunct group (two patients taking steroids, two were ineligible at the end of surgery). The remaining withdrawals were due to loss to follow-up (seven in each group) or no longer wanting to continue (one from control and two from adjunct group).

### Baseline characteristics

Baseline demographics and ocular characteristics are shown in table 1.

Participants were predominantly young white males, with poor preoperative vision (ETDRS zero or worse: 72% control and 78% adjunct) and with just under one-third suffering a Zone 3 injury (21% control and 31% adjunct). Of note, 69% of the control and 77% of the adjunct group had already undergone a primary repair, 48% of the control and 54% of the adjunct group had a pre-existing retinal detachment and PVR was present in 21%–27%, respectively. The time of vitrectomy was a median of 28 (control) and 26 (adjunct) days following the original injury. Operation and follow-up details are shown in table 2.

The groups were similar in terms of surgical gauge, need for lensectomy and silicone oil tamponade. The adjunct group had a higher rate of retinectomy and the follow-up data suggests that there was a higher rate of oil tamponade at both the 3-month and 6-month follow-up visit in the adjunct group.

### Primary outcome measure

The proportion of participants with at least a 10-letter improvement in VA over the 6-month post-vitrectomy was 43.4% (n=56/129) in the control group and 46.9% (n=61/130) in the adjunct group (unadjusted difference 3.5% (95% CI −8.6% to 15.6%)) (table 3). The baseline-adjusted OR for clinically meaningful change in VA for the adjunct relative to the control group was 1.03 (95% CI 0.61 to 1.75, p=0.908) indicating no significant difference between the treatment groups. Primary estimand attributes are shown in online supplemental eTable 2. Sensitivity analyses were performed and did not influence the outcome (see online supplemental material 1). Online supplemental eFigure 1 shows the subgroup analyses which suggested that if the fovea was detached, the adjunct increased the odds of an improvement in BCVA (OR 3.46 (95CI 1.16 to 10.36)). However, the 95%CI for this effect overlaps the treatment effect for those with the fovea on, meaning no difference

**Table 2** Operation and follow-up details

| | Treatment group | | | | | |
|---|---|---|---|---|---|---|
| | Control (N=137) | | Adjunct (N=143) | | Total (N=280) | |
| Surgeon grade (n, %) | | | | | | |
| Consultant | 77 | 56% | 95 | 66% | 172 | 61% |
| Fellow | 60 | 44% | 48 | 34% | 108 | 39% |
| Gauge (n, %) | | | | | | |
| 20G | 3 | 2% | 7 | 5% | 10 | 4% |
| 23G | 116 | 85% | 114 | 80% | 230 | 82% |
| 25G | 17 | 12% | 19 | 13% | 36 | 13% |
| 27G | 0 | 0% | 1 | 1% | | |
| 19G endoscope and 23G combined | 0 | 0% | 1 | 1% | 1 | 0% |
| 20G and 23G combined | 1 | 1% | 1 | 1% | 2 | 1% |
| PVD present (n, %) | | | | | | |
| Yes | 79 | 58% | 90 | 63% | 169 | 60% |
| No | 57 | 42% | 53 | 37% | 110 | 39% |
| Unknown | 1 | 1% | 0 | 0% | 1 | 0% |
| Lensectomy (n, %) | | | | | | |
| Yes | 48 | 35% | 56 | 39% | 104 | 37% |
| No | 89 | 65% | 87 | 61% | 176 | 63% |
| Membrane peel | | | | | | |
| Yes | 20 | 15% | 23 | 16% | 43 | 15% |
| No | 117 | 85% | 120 | 84% | 237 | 85% |
| Retinectomy (n, %) | | | | | | |
| Yes | 30 | 22% | 42 | 29% | 72 | 26% |
| No | 107 | 78% | 101 | 71% | 208 | 74% |
| Buckle (n, %) | | | | | | |
| Yes | 2 | 1% | 3 | 2% | 5 | 2% |
| No | 135 | 99% | 140 | 98% | 275 | 98% |
| Tamponade | | | | | | |
| None | 24 | 18% | 18 | 13% | 42 | 15% |
| Air | 18 | 13% | 11 | 8% | 29 | 10% |
| SF6 | 21 | 15% | 24 | 17% | 45 | 16% |
| C2F6 | 1 | 0% | 3 | 2% | 4 | 1% |
| C3F8 | 11 | 8% | 15 | 10% | 26 | 9% |
| 1300cs SO | 32 | 23% | 39 | 27% | 71 | 25% |
| 5000cs SO | 12 | 9% | 13 | 9% | 25 | 5% |
| Heavy oil | 11 | 8% | 4 | 3% | 15 | 5% |
| Other | 7 | 5% | 16 | 11% | 23 | 8% |
| Complications | | | | | | |
| Entry site break | 15 | 11% | 11 | 8% | 26 | 9% |
| Retinal break | 21 | 15% | 20 | 14% | 41 | 15% |
| Choroidal haemorrhage | 5 | 4% | 10 | 7% | 15 | 5% |
| Pre-retinal haemorrhage | 11 | 8% | 9 | 6% | 20 | 7% |
| AC haemorrhage | 7 | 5% | 10 | 7% | 17 | 6% |
| Retinal incarceration | 4 | 3% | 5 | 3% | 9 | 3% |
| Other/unknown | 10 | 8% | 18 | 13% | 28 | 10% |
| 3-Month visit | | | | | | |
| Tamponade | | | | | | |
| No | 76 | 56% | 61 | 43% | 137 | 49% |
| Gas | 5 | 4% | 0 | 0% | 5 | 2% |
| Oil | 50 | 37% | 63 | 44% | 113 | 40% |
| Unknown | 6 | 4% | 19 | 13% | 25 | 9% |
| Oil in AC | 21 | 15% | 17 | 11% | 38 | 14% |
| 6-Month visit | | | | | | |
| Tamponade | | | | | | |
| No | 86 | 63% | 73 | 53% | 159 | 57% |
| Gas | 2 | 1% | 0 | 0% | 2 | 1% |
| Oil | 38 | 28% | 57 | 42% | 95 | 34% |
| Unknown | 11 | 8% | 13 | 9% | 24 | 9% |
| Interventions during study period 6 months | | | | | | |
| Removal of oil | 32 | 23% | 26 | 18% | 58 | 21% |

Continued

**Table 2** Continued

| | Treatment group | | | | | |
|---|---|---|---|---|---|---|
| | Control (N=137) | | Adjunct (N=143) | | Total (N=280) | |
| Cataract extraction | 10 | 7% | 11 | 8% | 21 | 8% |
| IOL implantation | 17 | 12% | 14 | 10% | 31 | 11% |
| Surgical iridotomy | 11 | 8% | 13 | 9% | 24 | 9% |
| Vitrectomy | 30 | 22% | 28 | 20% | 58 | 21% |
| Membrane peel | 26 | 19% | 36 | 25% | 62 | 22% |
| Endolaser | 25 | 18% | 27 | 19% | 52 | 19% |
| Cryopexy | 8 | 6% | 13 | 9% | 21 | 8% |
| Tamponade | | | | | | |
| Air | 3 | 1% | 4 | 1% | 7 | 7 |
| SF6 | 2 | 1% | 1 | 1% | 3 | 3 |
| C3F8 | 11 | 8% | 23 | 16% | 34 | 34 |
| 1300c SO | 8 | 6% | 20 | 8% | 28 | 28 |
| 5000c SO | 6 | 2% | 1 | 1% | 7 | 7 |
| Heavy oil | 5 | 2% | 1 | 1% | 6 | 6 |
| Other | 3 | 1% | 4 | 1% | 7 | 7 |

AC, anterior chamber; C2F6, hexafluoroethane; C3F8, perfluoropropane; cs, centistokes; G, gauge; IOL, intraocular lens; PVD, posterior vitreous detachment; SF6, sulphur hexafluoride; SO, silicone oil.

in the treatment effect by fovea status cannot be ruled out. There was no difference in outcome in any of the other subgroups including retinal status and fovea status (online supplemental eFigure 1). Sensitivity analyses are shown in online supplemental eTables 3–4 & eFigure 2.

### Secondary outcomes analyses

Secondary outcomes are shown in table 3.

For the principle secondary outcome (change in ETDRS VA at 6 months), there was no significant difference between the groups (−2.65, 95%CI −9.22 to 3.92, p value=0.430). There was also no significant difference between the groups for PVR re-detachment, tractional retinal detachment, hypotony, number of operations and quality of life at 6 months. There was a significantly lower rate of stable complete retinal and macular retinal reattachment in the adjunct group compared with the control group (n=65/126, 51.6% adjust vs n=79/123, 64.2% control had complete reattachment and n=68/126, 54.0% adjunct vs n=82/123, 66.7% control had macula reattachment). Elevated IOP was more common in the adjunct group and there was a trend for increased macular pucker, also in the adjunct group.

### Adverse events

The summary of the adverse events is shown in figure 2. There was a higher rate of elevated IOP events in the adjunct group compared with the control group (58 vs 45 events, respectively) and a similar rate of hypotony. There were two case of endophthalmitis in the adjunct group. There were six cases of uveitis in the in the adjunct group compared with two in the control group.

## DISCUSSION

The ASCOT study is the first large-scale RCT to investigate the use of adjunctive medication to prevent PVR following surgery for penetrating OGT. TA was chosen on the basis of preclinical evidence of its efficacy[13] and promising results from a pilot trial.[8] The primary outcome (improvement in VA) and principal secondary outcome (change in VA) did not demonstrate a significant treatment benefit for TA. The secondary outcome measures failed to show any treatment benefit. The use of combined intraocular and sub-Tenons capsule TA is therefore not recommended as an adjunct to vitrectomy surgery following OGT.

It is notable that stable complete retinal reattachment (51.6% (65/126) TA vs 64.2% (79/123) control group) and stable macular retinal reattachment (54.0% (68/126) TA group vs 66.7% (82/123) control group) at 6 months were significantly worse for the treatment group compared with controls. These two outcomes are related and are clearly of clinical importance. Over a range of baseline parameters, the treatment group appeared to have more severe pathology on presentation. The treatment

**Table 3** Outcome data

| | Control group | Adjunct group | Difference (adjunct vs control) | OR (adjunct vs control) | P value |
|---|---|---|---|---|---|
| Primary outcome | | | | | |
| >10 ETDRS Letter BCVA gain at 6 months | 56/129 (43.4%) | 61/130 (46.9%) | 3.5% (–8.6% to 15.6%) | 1.03 (0.61 to 1.75) | 0.908 |
| Principle secondary outcome | | | | | |
| Change in ETDRS BCVA at 6 months: mean (SD) | 18.9 (29.2) | 19.4 (30.8) | –2.65 (–9.22 to 3.92) | | |
| Median (IQR) | 5 (0 to 41) | 5 (0 to 43) | Adjusted* mean difference | | 0.430 |
| Secondary outcomes | | | | | |
| Retinal PVR re-detachment | 35/124 (28.2%) | 42/124 (33.9%) | 5.6% (–5.9% to 17.1%) | 1.31 (0.76 to 2.27) | 0.327 |
| Stable complete retinal reattachment† | 79/123 (64.2%) | 65/126 (51.6%) | –12.6% (–24.8% to -0.5%) | 0.59 (0.36 to 0.99) | 0.044 |
| Stable macular retinal reattachment† | 82/123 (66.7%) | 68/126 (54.0%) | –12.7% (–24.7% to -0.7%) | 0.59 (0.35 to 0.98) | 0.041 |
| Tractional retinal detachment | 30/123 (24.4%) | 35/124 (28.2%) | 4.5% (–6.7% to 15.6%) | 1.22 (0.69 to 2.15) | 0.494 |
| Hypotony (within 6 months)‡ | 28/124 (22.6%) | 31/125 (24.8%) | 2.2% (–8.3% to 12.8%) | 1.13 (0.63 to 2.03) | 0.680 |
| Elevated IOP | 40/127 (31.5%) | 58/125 (46.4%) | 14.9% (3.0% to 26.8%) | 1.88 (1.13 to 3.15) | 0.016 |
| Macular pucker | 25/122 (20.5%) | 37/124 (29.8%) | 9.3% (–1.4% to 20.1%) | 1.65 (0.92 to 2.96) | 0.093 |
| Number of operations to achieve reattachment | 0 (0,0) | 0 (0,1) | 1.15 (0.68 to 1.94) | | 0.608 |
| Median (IQR) | | | Adjusted* incident rate ratio | | |
| VFQ-25 AT 6 months | 71.9 (20.9) | 72.0 (20.1) | 0.78 (–3.53 to 5.10)<br>Adjusted* mean difference | | 0.723 |

*Adjusted for centre.
†Without internal tamponade at 6 months.
‡Data taken from secondary outcome form and adverse events form.
ETDRS, Early Treatment Diabetic Retinopathy Study; IOP, intraocular pressure; PVR, proliferative vitreoretinopathy; VFQ, Visual Function Questionnaire.

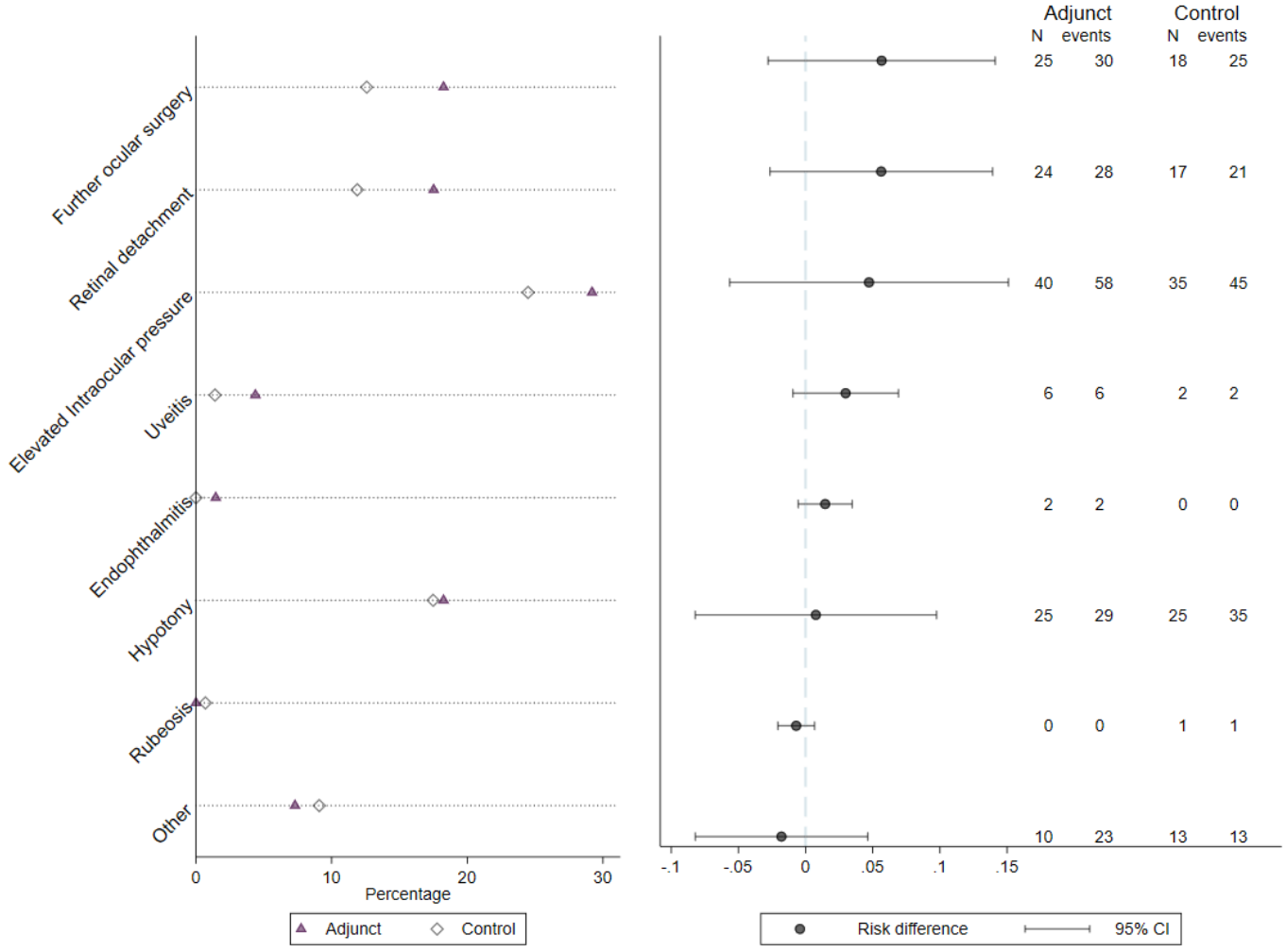



**Figure 2** Adverse events. In the control group, other adverse events were: conjunctivitis, graft opacification, swollen disc, vitreous haemorrhage, pupillary membrane, macular oedema, diplopia, total funnel inoperable retinal detachment, focal keratitis, corneal graft failure, corneal oedema, irritation and cystoid macula oedema. In adjunct group, other adverse events were: corneal abrasion, oil in anterior chamber, epiretinal membrane, epiretinal membrane, central macular subretinal bleed, cystoid macular oedema, proliferative vitreo-retinopathy, cataract formation, macular hole, irritation (x2), macular oedema, photophobia (x2), foreign body sensation (x2), pain (x2), watering eye (x2), keratitis at central cornea, intermittent headaches and loose corneal suture.

group, by chance, had a higher level of previous primary repair (77% vs 69%), previous eye surgery (57% vs 49%), zone 3 injuries (31 vs 21%), vitreous haemorrhage (69% vs 63%), retinal incarceration (27% vs 18%), pre-existing retinal detachment (tractional and rhegmatogenous) (54% vs 48%) and pre-existing PVR (27% vs 21%). Although none of these parameters demonstrate a marked difference, taken together they may account for a difference in outcome between the groups. Nevertheless, a negative effect of TA as an adjunct to vitrectomy surgery for OGT cannot be discounted although the pathobiological mechanism for this is unclear. These findings support the conclusion that TA should not be routinely recommended as an adjunct in OGT cases.

Experimental studies have demonstrated that TA has the potential to downregulate the retinal response to injury and reduce the incidence of PVR.[14] The potential for TA to produce a beneficial clinical effect on PVR is supported by pilot and small scale clinical studies suggesting a reduction in the inflammatory response and PVR in retinal detachment and trauma cases.[8 15–17] The reasons for the failure of TA to produce a treatment effect therefore need to be considered. It is possible that in OGT cases where there is extensive blood-ocular barrier breakdown and a markedly upregulated drive towards PVR, the pharmacological effect of TA (at the dosage used in the study) is insufficient to influence the PVR process. In this context, it is notable that a recent uncontrolled study using a stronger antiproliferative agent, mitomycin C at the time of vitrectomy in severe intraocular foreign body cases appeared to reduce the incidence of PVR.[18] Timing of drug delivery will likely have also played a role. Most patients in the ASCOT study had already undergone primary repair of the penetrating injury (69% and 77% of control and adjunct patients) and time of vitrectomy was a median of 28 (control) and 26 (adjunct) days following the primary repair and exceeded 119 days in a quarter of patients (table 1). The use of an adjunctive agent in this subset of patients so long after the original trauma will likely have been too late to alter their outcome or implies that their vitrectomy may not have been directly related their original OGT. Delivery of a therapeutic adjunct at the time of injury, potentially combined with sustained delivery, may produce a greater effect in modifying the PVR process in OGT.

Case selection is an additional factor which may have influenced the results. ASCOT recruited a broad spectrum of open globe trauma cases. Overall, 40% of cases had a globe rupture, 37% penetrating injury, 19% had intraocular foreign bodies and 4% a perforating injury. Cardillo and co-workers[4] documented that these varied injury types have differing incidences of PVR: perforating injuries 43%, globe rupture 21%, penetrating injuries 15% and intraocular foreign bodies 11%. It is likely that the injury subtypes will have differing responses to therapeutic agents and in future studies more focused case selection, potentially limited to only one injury subtype, could result in a positive therapeutic response. Subgroup analysis suggested a possible benefit in eyes in which there was a fovea-involving retinal detachment, although it should be noted that the data was also consistent with no difference and it is well established that subgroup analysis can often be challenging.[19 20] Even so, this subgroup may be of interest in future work.

The results of surgery for PVR have remained unsatisfactory with often poor visual outcomes and a need for multiple procedures. This has led to both preclinical and clinical studies to identify adjunctive agents to modify the disease process and improve surgical results.[21 22] To date, no adjunctive agents have gained widespread acceptance and PVR remains a surgical disease.[14] Intraocular daunomycin[23] and the combination of 5 fluorouracil (5FU) and low-molecular-weight heparin (LMWH)[24–26] have been studied in a series of RCTs. Although these produced promising initial findings—daunomycin reduced re-operations and the 5FU/LMWH combination reduced PVR in high-risk cases—these studies have not resulted in the drugs having widespread use. Likewise, a study of slow-release dexamethasone in established PVR failed to improve anatomical results although macular oedema was reduced and there was a trend to improved VA.[9] A previous study on TA in non-traumatic PVR also failed to show a benefit.[17] The reasons for the failure of these treatments to improve outcomes for PVR surgery is likely multifactorial and appear to relate to a lack of understanding of the PVR disease process and inadequate case selection.

Limitations of the study were its broad inclusion criteria and that it did not specify the indication for vitrectomy. This likely contributed to the observed length of time overall between OGT and vitrectomy in the study (median 27 days (IQR 12–119)). Future PVR trial designs will therefore need to have a clear focus on disease categorisation and the timing of intervention. The use of subconjunctival steroid at the time of the initial primary repair was not recorded as part of the study design, which may have influenced results.

The ASCOT study was designed to investigate TA as an adjunct to vitreoretinal surgery following OGT. It provided a clear answer, in that there was no benefit from TA in a broad mix of OGT cases and adds to the evidence surrounding the treatment of PVR.

**Author affiliations**
[1]Sussex Eye Hospital, Brighton, UK
[2]Ophthalmology, University Hospitals Sussex NHS Foundation Trust, Worthing, UK
[3]Vitreoretinal Department, Moorfields Eye Hospital, London, UK
[4]Imperial Clinical Trials Unit, Imperial College London, London, UK
[5]Ophthalmology, Frimley Health NHS Foundation Trust, Frimley, UK
[6]NIHR Moorfields Biomedical Research Centre, London, UK
[7]Centre for Health Economics & Medicines Evaluation, Bangor University, Bangor, UK
[8]Ophthalmology, William Harvey Hospital, East Kent University Hospitals NHS Trust, UK
[9]RM CTU, Royal Marsden Hospital NHS Trust, London, UK
[10]King's Clinical Trials Unit, King's College London, London, UK

**Twitter** Edward J Casswell @edwardcasswell and Suzie Cro @Suzie_cro

**Collaborators** See Contributor Statement regarding ASCOT Investigator Study Group.

**Contributors** Design of work: SC, VRC, PJB, RTE, VE, CB, JK, CM, ER, DC; acquisition, analysis or interpretation of data for the work: EJC, SC, VRC, PJB, TMZ, RTE, VE, BA, SMS, CB, JK, CM, ER, DC. All authors were involved in the drafting and review of the manuscript as well as final approval. DC is the guarantor of the study and responsible for the overall content. The ASCOT Investigator Study Group served as non-author contributors/collaborators, who collected data and cared for study patients, namely: Mr Arijit Mitra (Birmingham and Midland Eye Centre (BMEC)), Prof Tim Jackson (Kings College Hospital London), Mr Luke Membrey (Maidstone and Tunbridge Wells NHS Trust), Mr Jonathan Smith (Sunderland Eye Infirmary), Ms Arabella Poulson (Addenbrookes Hospital, Cambridge), Prof Ian Pearce (St Pauls Eye Unit, Liverpool), Mr Felipe Dhawahir-Scala (Manchester Royal Eye Hospital), Mr Yash Ramkissoon (Royal Hallamshire Hospital, Sheffield), Mr Alistair Laidlaw (St Thomas' Hospital London), Ms Daniela Vaideanu-Collins (South Tees Hospital NHS Trust), Mr Mark Costen (Hull University Teaching Hospitals), Ms Cordelia McKechnie (Whipps Cross Hospital London), Mr Richard Haynes (University Hospitals Bristol), Dr Jas Singh (Princess Alexandra Eye Pavilion, Edinburgh), Dr David Yorston (Tennent Institute of Ophthalmology, Glasgow), Ms Rahila Zakir (Western Eye Hospital London), Mr Fung Yang (Queen Alexandra Hospital Portsmouth), Prof Robert MacLaren (Oxford Eye Hospital), Mr Fred Frimpong-Ansah (Royal Eye Infirmary Plymouth), Mr Ravikiran Gandhewa (University Hospital, Derby), Mr Aman Chandra (Mid and South Essex NHS Foundation Trust), Mr Kam Balaggan (Royal Wolverhampton NHS Trust), Ms Roxane Hillier (Newcastle Upon Tyne NHS Foundation Trust), Mr David Schultz (East Kent Hospital NHS Foundation Trust), Mr Mandeep Bindra (Stoke Mandeville Hospital).

**Funding** This study was supported by the United Kingdom Clinical Research Collaboration-registered King's Clinical Trials Unit at King's Health Partners, which is in part funded by the NIHR Biomedical Research Centre for Mental Health at South London and Maudsley NHS Foundation Trust and King's College London and the NIHR Evaluation, Trials and Studies Coordinating Centre. EJC was supported by the Royal College of Surgeons in Edinburgh and the Special Trustees of Moorfields Eye Hospital. CB is in part funded/supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at the Royal Marsden NHS Foundation Trust and the Institute of Cancer Research, London. DC is supported by the National Institute for Health Research (NIHR) Biomedical Research Centre based at Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology. These funding organisations had no role in the design or conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

**Disclaimer** The views expressed in this publication are those of the author(s) and not necessarily those of the RCSEd, Special Trustees, NHS, NIHR or Department of Health.

**Competing interests** None declared.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by NRES Committee London Central (14/LO/1428) on 14 September 2014. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** Data are available upon reasonable request. Data requests would need to be assessed by the Moorfields Eye Hospital Research Managers to ensure any data shared complies with Data Protection laws.



**ORCID iDs**
Edward J Casswell http://orcid.org/0000-0002-8837-9910
Suzie Cro http://orcid.org/0000-0002-6113-1173
Syed Mohammed Shahid http://orcid.org/0000-0002-9793-7224
Catey Bunce http://orcid.org/0000-0002-0935-3713

## REFERENCES

1 Négrel AD, Thylefors B. The global impact of eye injuries. *Ophthalmic Epidemiol* 1998;5:143–69.

2 Stryjewski TP, Andreoli CM, Eliott D. Retinal detachment after open globe injury. *Ophthalmology* 2014;121:327–33.
3 Andreoli MT, Andreoli CM. Surgical rehabilitation of the open globe injury patient. *Am J Ophthalmol* 2012;153:856–60.
4 Cardillo JA, Stout JT, LaBree L, *et al*. Post-traumatic proliferative vitreoretinopathy. The epidemiologic profile, onset, risk factors, and visual outcome. *Ophthalmology* 1997;104:1166–73.
5 Tano Y, Chandler DB, McCuen BW, *et al*. Glucocorticosteroid inhibition of intraocular proliferation after injury. *Am J Ophthalmol* 1981;91:184–9.
6 Tano Y, Chandler D, Machemer R. Treatment of intraocular proliferation with intravitreal injection of triamcinolone acetonide. *Am J Ophthalmol* 1980;90:810–6.
7 Rubsamen PE, Cousins SW. Therapeutic effect of periocular corticosteroids in experimental proliferative vitreoretinopathy. *RETINA* 1997;17:44–50.
8 Banerjee PJ, Xing W, Bunce C, *et al*. Triamcinolone during pars plana vitrectomy for open globe trauma: a pilot randomised controlled clinical trial. *Br J Ophthalmol* 2016;100:949–55.
9 Banerjee PJ, Quartilho A, Bunce C, *et al*. Slow-release dexamethasone in proliferative vitreoretinopathy: a prospective, randomized controlled clinical trial. *Ophthalmology* 2017;124:757–67.
10 Koerner F, Koerner-Stiefbold U, Garweg JG. Systemic corticosteroids reduce the risk of cellophane membranes after retinal detachment surgery: a prospective randomized placebo-controlled double-blind clinical trial. *Graefes Arch Clin Exp Ophthalmol* 2012;250:981–7.
11 Banerjee PJ, Cornelius VR, Phillips R, *et al*. Adjunctive intraocular and peri-ocular steroid (triamcinolone acetonide) versus standard treatment in eyes undergoing vitreoretinal surgery for open globe trauma (Ascot): study protocol for a phase III, multi-centre, double-masked randomised controlled trial. *Trials* 2016;17:339.
12 Lo JW, Bunce C, Charteris D, *et al*. A phase III, multi-centre, double-masked randomised controlled trial of adjunctive intraocular and peri-ocular steroid (triamcinolone acetonide) versus standard treatment in eyes undergoing vitreoretinal surgery for open globe trauma (Ascot): statistical analysis plan. *Trials* 2016;17:383.
13 Charteris DG. Proliferative vitreoretinopathy: revised concepts of pathogenesis and adjunctive treatment. *Eye (Lond)* 2020;34:241–5.
14 Esmaeli B, Elner SG, Schork MA, *et al*. Visual outcome and ocular survival after penetrating trauma. A clinicopathologic study. *Ophthalmology* 1995;102:393–400.
15 Munir WM, Pulido JS, Sharma MC, *et al*. Intravitreal triamcinolone for treatment of complicated proliferative diabetic retinopathy and proliferative vitreoretinopathy. *Can J Ophthalmol* 2005;40:598–604.
16 Cheema RA, Peyman GA, Fang T, *et al*. Triamcinolone acetonide as an adjuvant in the surgical treatment of retinal detachment with proliferative vitreoretinopathy. *Ophthalmic Surg Lasers Imaging* 2007;38:365–70.
17 Ahmadieh H, Feghhi M, Tabatabaei H, *et al*. Triamcinolone acetonide in silicone-filled eyes as adjunctive treatment for proliferative vitreoretinopathy: a randomized clinical trial. *Ophthalmology* 2008;115:1938–43.
18 Assi A, Khoueir Z, Helou C, *et al*. Intraocular application of mitomycin C to prevent proliferative vitreoretinopathy in perforating and severe intraocular foreign body injuries. *Eye (Lond)* 2019;33:1261–70.
19 Spears MR, James ND, Sydes MR. Thursday's child has far to go'-interpreting subgroups and the STAMPEDE trial. *Ann Oncol* 2017;28:2327–30.
20 Wang R, Lagakos SW, Ware JH, *et al*. Statistics in medicine -- reporting of subgroup analyses in clinical trials. *N Engl J Med* 2007;357:2189–94.
21 Charteris DG, Sethi CS, Lewis GP, *et al*. Proliferative vitreoretinopathy-developments in adjunctive treatment and retinal pathology. *Eye (Lond)* 2002;16:369–74.
22 Charteris DG. Proliferative vitreoretinopathy: pathobiology, surgical management, and adjunctive treatment. *Br J Ophthalmol* 1995;79:953–60.
23 Wiedemann P, Hilgers RD, Bauer P, *et al*. Adjunctive daunorubicin in the treatment of proliferative vitreoretinopathy: results of a multicenter clinical trial. Daunomycin study group. *Am J Ophthalmol* 1998;126:550–9.
24 Charteris DG, Aylward GW, Wong D, *et al*. A randomized controlled trial of combined 5-fluorouracil and low-molecular-weight heparin in management of established proliferative vitreoretinopathy. *Ophthalmology* 2004;111:2240–5.
25 Wickham L, Bunce C, Wong D, *et al*. Randomized controlled trial of combined 5-fluorouracil and low-molecular-weight heparin in the management of unselected rhegmatogenous retinal detachments undergoing primary vitrectomy. *Ophthalmology* 2007;114:698–704.
26 Asaria RH, Kon CH, Bunce C, *et al*. Adjuvant 5-fluorouracil and heparin prevents proliferative vitreoretinopathy: results from a randomized, double-blind, controlled clinical trial. *Ophthalmology* 2001;108:1179–83.

## Supplementary Material

Contains:

eTable 1: Randomisation of ASCOT trial patients by site and treatment allocation.

eFigure 1: Forest Plot of Subgroup Analyses

eTable 2: Estimand Attributes

eTable 3: Sensitivity analysis exploring the impact of missing data

eTable 4: Sensitivity analysis exploring the impact of visit windows

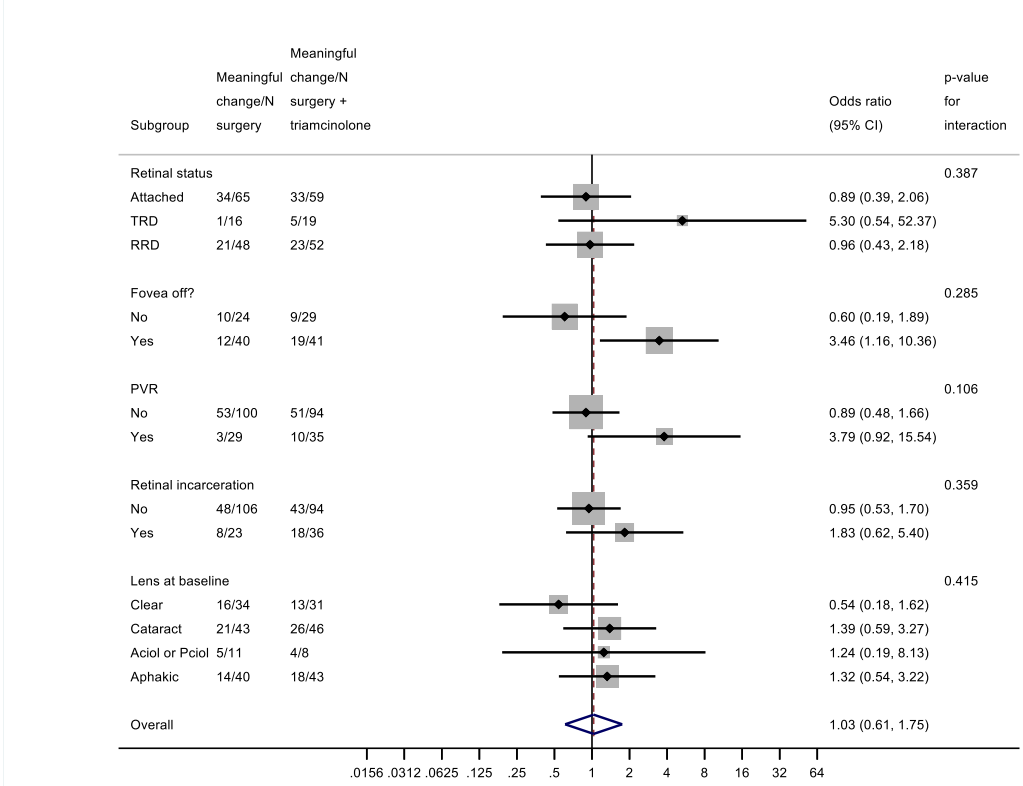
### eTable 1: Randomisation of ASCOT trial patients by site and treatment allocation.

| | Control N (%) | Adjunct N (%) | Total N |
|---|---|---|---|
| Total randomised | 137 | 143 | 280 |
| **Study centre** | | | |
| Birmingham | 5 (4%) | 4 (3%) | 9 (3%) |
| Bristol | 8 (6%) | 7 (5%) | 15 (5%) |
| Cambridge | 1 (1%) | 1 (1%) | 2 (1%) |
| Canterbury William Harvey Hospital | 2 (1%) | 1 (1%) | 3 (1%) |
| Derby | 2 (1%) | 3 (2%) | 5 (2%) |
| Edinburgh | 1 (1%) | 1 (1%) | 2 (1%) |
| Frimley Park | 2 (1%) | 0 (0%) | 2 (1%) |
| Glasgow | 2 (1%) | 3 (2%) | 5 (2%) |
| Hull | 2 (1%) | 2 (1%) | 4 (1%) |
| King's College London | 2 (1%) | 3 (2%) | 5 (2%) |
| Liverpool | 1 (1%) | 0 (0%) | 1 (0%) |
| Maidstone | 7 (5%) | 8 (6%) | 15 (5%) |
| Manchester | 1 (1%) | 2 (1%) | 3 (1%) |
| Moorfields | 56 (41%) | 57 (40%) | 113 (40%) |
| Newcastle | 6 (4%) | 6 (4%) | 12 (4%) |
| Oxford | 0 (0%) | 1 (1%) | 1 (0%) |
| Plymouth | 1 (1%) | 1 (1%) | 2 (1%) |
| Portsmouth | 4 (3%) | 5 (3%) | 9 (3%) |
| Sheffield | 0 (0%) | 1 (1%) | 1 (0%) |
| South Tees | 7 (5%) | 7 (5%) | 14 (5%) |
| Southend | 3 (2%) | 2 (1%) | 5 (2%) |
| St Thomas' London | 2 (1%) | 3 (2%) | 5 (2%) |
| Stoke Mandeville Stoke Mandeville Hospital | 1 (1%) | 2 (1%) | 3 (1%) |
| Sunderland | 5 (4%) | 6 (4%) | 11 (4%) |
| Western Eye London | 12 (9%) | 11 (8%) | 23 (8%) |
| Whipps Cross London | 0 (0%) | 2 (1%) | 2 (1%) |
| Wolverhampton | 4 (3%) | 4 (3%) | 8 (3%) |



Casswell EJ, *et al. Br J Ophthalmol* 2023;0:1–9. doi: 10.1136/bjo-2022-322787

## eFigure 1: Forest Plot of Subgroup Analyses




Forest plot showing the subgroup analyses performed for the primary outcome to explore the uniformity of the treatment effect found overall. Odds Ratio represents the baseline ETDRS adjusted odds of meaningful change for surgery + triamcinolone relative to surgery only for the associated subgroup. (TRD: tractional retinal detachment; RRD: rhegmatogenous retinal detachment; PVR: proliferative vitreoretinopathy)

## Description of primary treatment estimand

An estimand is a clear and unambiguous description of a treatment effect that is targeted by an analysis in a clinical trial, reflecting the clinical question posed by the trial objective. In the following we describe the primary estimand targeted in ASCOT.

The primary clinical question of interest is: What is the difference in the proportion of patients with meaningful change in ETDRS letter score (≥10 letters) at 6 months in adults with full thickness, open- globe ocular trauma undergoing pars plana vitrectomy (as defined by trial inclusion/exclusion criteria), treated with Standard surgery plus triamcinolone given during surgery compared to standard surgery alone, regardless of intervention crossover for any reason or subsequent use of any other intervention post-surgery.

**eTable 2**: **Estimand Attributes**

The estimand is described by the following attributes

| Estimand attribute | Description |
|---|---|
| **Population** | Adults with full thickness, open- globe ocular trauma undergoing pars plana vitrectomy meeting ASCOT eligibility criteria (as fully defined in the ASCOT trial protocol) |
| **Treatment condition** | Standard surgery plus Triamcinolone Acetonide (4mg/0.1ml IVTA and 40mg/1ml subtenons) given during surgery compared to standard surgery alone |
| **Outcome variable** | Change in ETDRS letter score from baseline at 6 months being <10 or ≥10 letters indicating meaningful change. |
| **Strategies used to handle Intercurrent events** | Alternative study treatment given – treatment policy[a]<br>Use of any other intervention post-surgery - treatment policy[a] |
| **Population-level summary measure** | Difference in proportion of patients with meaningful change in ETDRS letter score (≥10 letters) at 6 months |

[a] A treatment policy strategy considers the occurrence of the associated event as irrelevant in defining the treatment effect, and participant data are analysed regardless.
Rationale for estimand: To assess the benefit of surgery plus Triamcinolone Acetonide versus surgery alone, as would be observed in routine practise.

**Additional Statistical Methods**

All regression analyses (primary and secondary) included adjustment for centre. For continuous outcomes the outcome measured at baseline was included in regression analysis.

In the primary analysis model, all missing response values were assumed to be Missing-at-Random (i.e. the probability that the response is missing does not depend on the value of the response after controlling for the observed variables of treatment and baseline vision).

Planned sensitivity analyses for the primary outcome were performed. These included:

Analysis to assess the impact of missing outcome data:

- Use of imputation to explore the optimistic (meaningful change in treatment arm – no change in surgery only arm) or pessimistic (no change in treatment arm – meaningful change in surgery only arm) scenario for participants with missing outcome data. The primary analysis model was retained for use in the sensitivity analysis, following imputation.
- A mean score approach was employed to explore a range of more plausible Missing-not-at-random (MNAR) scenarios. Within this analysis, the primary outcome is analysed under increasing departures from the primary MAR assumption, by assuming a gradual increase in the odds of the outcome (meaningful change in ETDRS) for those with missing data, from 0 (representing MAR) up to 1 for (i) participants in the surgery arm only, (ii) participants in the treatment arm only and (iii) for participants in both arms.

Analysis to assess the impact of out of window outcome data:

- The visit window for the 3 and 6 month follow-up is +/- 4 weeks. In line with the pre-specified SAP data collected outside these recommended periods was included in the primary analysis. A sensitivity analysis was conducted where data collected outside the visit windows was excluded. The analysis model was the same as for the primary analysis.



Casswell EJ, *et al. Br J Ophthalmol* 2023;0:1–9. doi: 10.1136/bjo-2022-322787

- An additional sensitivity analysis where data collected outside the visit windows was included, also using the primary analysis model, but where patients with data outside the visit windows were weighted by ½ was performed. Patients with data within the allowed visit window had a weight of 1. This sensitivity analysis down weighted the data of those with data out of the visit windows such that the data of patients collected outside the allowed windows was considered half as trustworthy.

Pre-planned sub-group analysis investigated whether the treatment effect on the primary outcome differed by,

- retinal detachment: attached;
- retinal detachment: TRD;
- retinal detachment: RRD;
- fovea involvement: yes;
- fovea involvement: no;
- fovea involvement: splitting;
- presence of PVR: yes;
- presence of PVR: no;
- presence of retinal incarceration: yes;
- presence of retinal incarceration: no;
- lens status at baseline: clear (phakic);
- lens status at baseline: cataract (phakic);
- lens status at baseline: ACIOL and PCIOL (pseudophakic)
- lens status at baseline: aphakic.

Each subgroup analysis was performed by adding the relevant treatment-by-subgroup interaction term to the same analysis model as for the primary outcome. P-values for each interaction term are presented. No adjustment for multiple tests was made and the results are hypothesis generating only. The consistency of estimates was depicted visually by means of a forest plot.

**Missing data sensitivity analysis**

Sensitivity analysis initially explored the robustness of the primary analysis results to two extreme missing not at random (MNAR) assumptions (Tabel S1),
Scenario 1: participants in group A have meaningful change, participants in treatment group B do not
Scenario 2: participants in group A do not have meaningful change, participants in treatment group B do have meaningful change
Subsequently further Missing not at random scenarios (MNAR) were explored using a range of plausible assumptions of the odds of clinically meaningful improvement among those with missing data being 0 to 1 times the odds of clinically meaningful



Casswell EJ, *et al. Br J Ophthalmol* 2023;0:1–9. doi: 10.1136/bjo-2022-322787

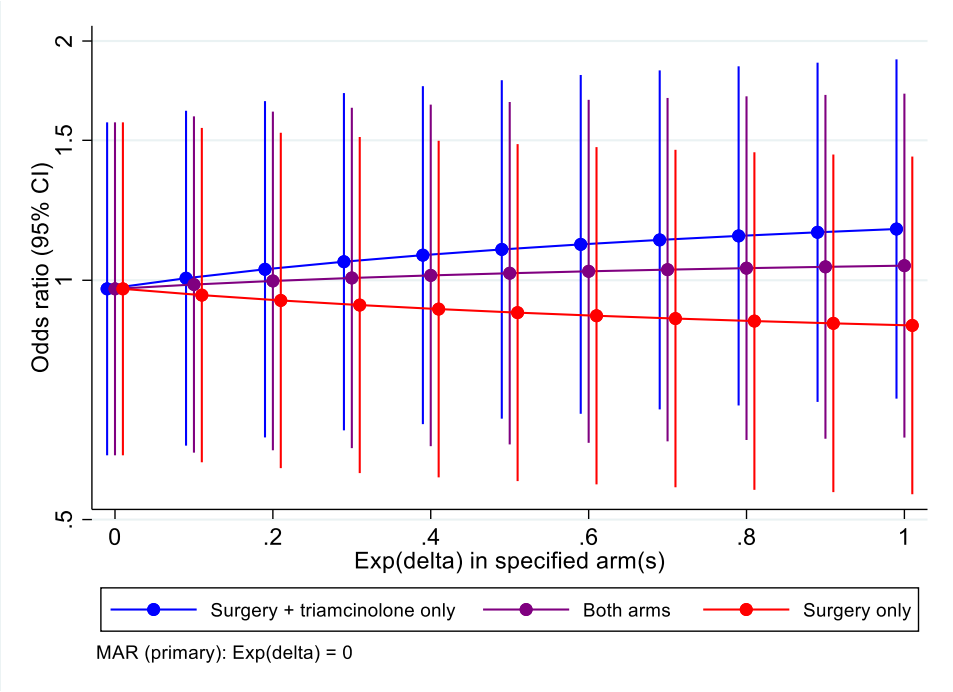
improvement amongst the observed, and viewing these graphically using a mean score approach (eFigure 2).

**eTable 3 Sensitivity analysis exploring the impact of missing data**

| Analysis | Treatment arm OR* [95%CI] | P value |
|---|---|---|
| **Primary analysis (N=259)** | | |
| **MAR** | 1.03 [0.61 to 1.75] | 0.908 |
| **MNAR‡ sensitivity analysis (N=280)** | | |
| Scenario 1 | 0.74 [0.45 to 1.23] | 0.245 |
| Scenario 2 | 1.46 [0.89 to 2.40] | 0.135 |

* OR for surgery plus adjunctive triamcinolone acetonide arm versus standard surgery.

**eFigure 2 Sensitivity analysis exploring the impact of data MNAR**




In comparison to the primary treatment effect (OR=1.03, 95% CI [0.61 to 1.75]), in scenario 1 (participants with missing data in group A have meaningful change, participants in treatment group B do not) the point estimate was more in favour of treatment group A (0.74, 95% CI [0.45 to 1.23]), and in in scenario 2 (participants with missing data in group B have meaningful change, participants in treatment group A do not) the point estimate was more in favour of treatment group B (1.46, 95% CO [0.89 to 2.40]). However, in all sensitivity analyses, inferences were consistent with the primary analysis and did not identify a significant between treatment group difference.

**Out of window sensitivity analysis**

The visit window for the 3 and 6 month follow-up visits was +/- 4 weeks. For primary analysis the ETDRS measurement closest to the 6 month post-surgery time point was taken, regardless of whether this was +/- 4 weeks of the actual 6 month post-surgery time point.

A Sensitivity analysis excluding data collected outside the visit window (6months +/- 4 weeks) was conducted. The analysis model was the same as for the primary analysis. An additional sensitivity analysis where data collected outside the 4 week window was included, but where patients with data outside the 4 week window were weighted by ½ was also be performed (also using the primary analysis model). Participants with data within the allowed visit window had a weight of 1. This second sensitivity analysis down weighted the data of those with data out of the visits window such that the data of participants collected outside the allowed windows was considered half as trustworthy.

In both sensitivity analyses results were consistent with the primary analysis.

**eTable 4 Sensitivity analysis exploring the impact of visit windows**

| Analysis | Treatment arm OR* [95%CI] | P value |
|---|---|---|
| **Primary analysis** | | |
| Including out of window data (N=259) | 1.03 [0.61 to 1.75] | 0.908 |
| **Sensitivity analysis** | | |
| Excluding out of window data (N=176) | 1.07 [0.56 to 2.07] | 0.833 |
| Weighting out of window data (N=259) | 1.06 [0.60 to 1.88] | 0.847 |

* OR for surgery plus adjunctive triamcinolone acetonide arm versus standard surgery.



Casswell EJ, *et al. Br J Ophthalmol* 2023;0:1–9. doi: 10.1136/bjo-2022-322787