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

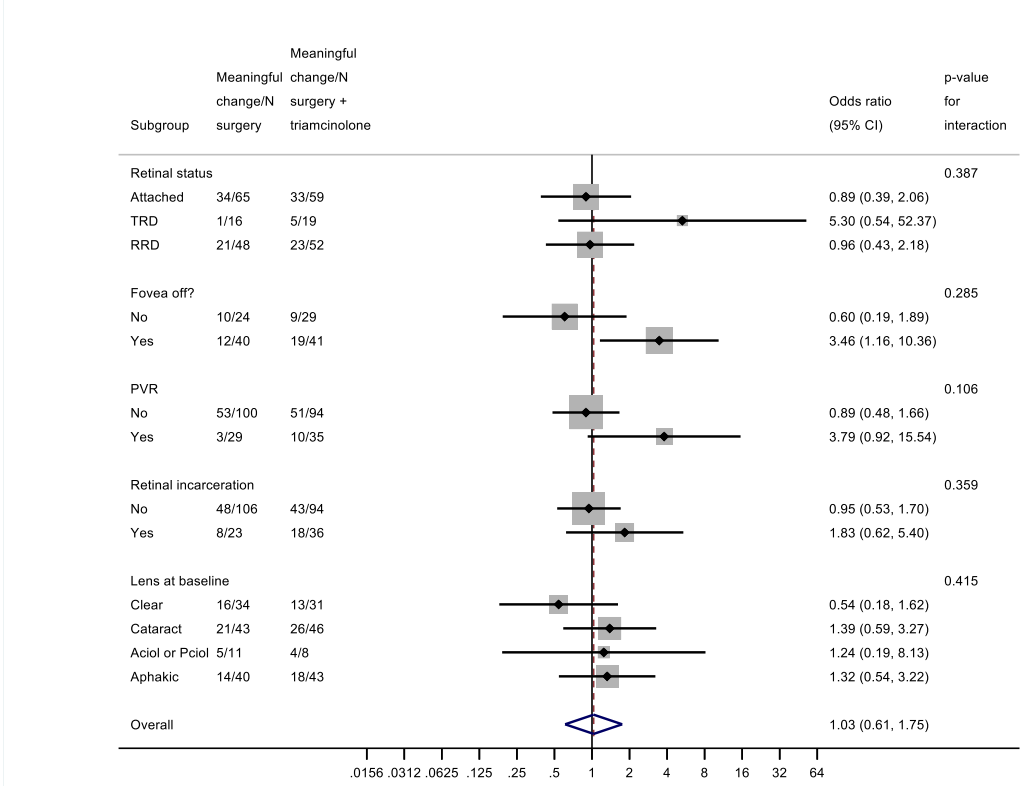
eTable 4: Sensitivity analysis exploring the impact of visit windows

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] 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

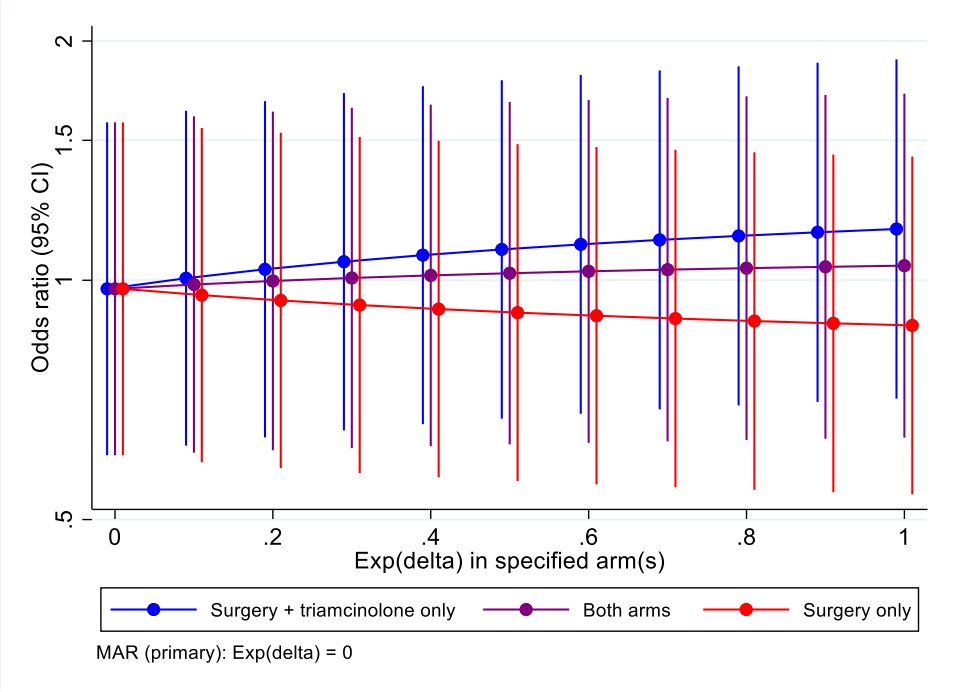
improvement amongst the observed, and viewing these graphically using a mean score approach (eFigure 2).

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