Treatment Allocation in Ophthalmological Randomised-Control Trials (TAO-RCT): A Frequently Uncontrolled and Poorly Reported Parameter

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Introduction

- Randomised-control trials (RCTs) in ophthalmology are complicated by most patients having two eyes.
- Investigators can allocate interventions and controls in many ways; study participants can be randomised to unilateral or bilateral treatment, only a single eye per participant is included and randomised, or the eyes of each participant may be treated differently
- This study appraises a representative sample of ophthalmological RCTs to investigate the relative frequency of 'uncontrolled' treatment allocation: where there is an inconsistent relationship between participant and intervention, where relationships between individuals' eyes may complicate or compromise analysis

Methods

- A systematic review was undertaken to identify ophthalmological RCTs published in 2022
- The Cochrane Library, Embase, and MEDLINE were searched. Quality assessment was carried out using the Joanna Briggs Institute Checklist for Randomised Controlled Trials
- We proposed a nomenclature system to help characterize treatment allocation: 'A' (and subsequent letters) denote treatments (including placebo), 'X' denotes no treatment, '+' between letters corresponding to contralateral eyes within an individual, and '&' used to separate individuals
- Frequency of different treatment allocations was calculated and the relative clarity of reporting for each study was classified as 'explicit', 'implicit' or 'unclear'
- *p-values* for the primary outcome were extracted from each study and a *t*-test was used to determine whether 'uncontrolled' patterns were more likely to yield statistically significant results
- X^2 tests or Fisher's exact tests were used to conduct further analysis to explore potential risk factors for uncontrolled treatment allocation: funding source, country and region of origin, reporting clarity, medical versus surgical intervention, one or two-eye allocation patterns, and ophthalmic subspecialty

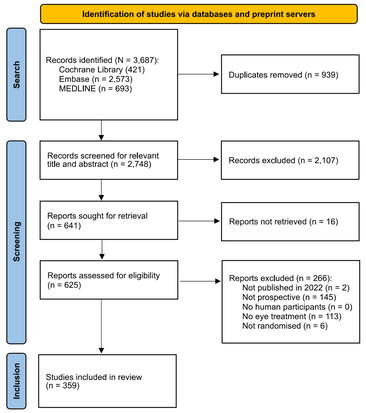


Figure 1: Visualisation of search and screening process using a PRISMA flow chart

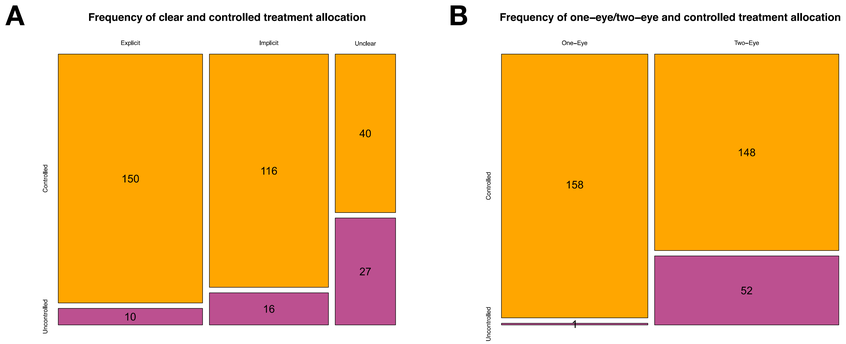


Figure 2: Mosaic plots visualising the relative numbers of 'uncontrolled' vs 'controlled' RCTs and its association with A) clarity of reporting; B) one-eye and two-eye treatment allocation

Results

- 359 out of 3687 RCT reports were ultimately included with 42 different allocation patterns identified
- The most frequent treatment allocation allocation patterns were controlled: A+A & B+B; A+X & B+X; and A+B . The most frequent 'uncontrolled' treatment allocation patterns were A+X & B+X & A+A & B+B; and A+A & B+B & A+X & B+X
- 14.5% of ophthalmological RCTs in 2022 exhibited uncontrolled treatment allocation and was associated with unclear reporting ($\chi^2 = 44.7$, $p < 0.001$).
- Uncontrolled treatment allocation was twice as common in surgical trials relative to medical trials ($\chi^2 = 4.287$, $p = 0.038$), but was not associated with subspecialty (Fisher's exact test, $p = 0.089$).
- Uncontrolled treatment allocation was associated with two-eye allocation patterns (Fisher's exact test, $p < 0.001$)
- Uncontrolled treatment allocation was more common in trials conducted in non-English speaking settings ($\chi^2 = 4.339$, $p = 0.037$)
- Uncontrolled treatment allocation varied significantly with funding source ($\chi^2 = 16.569$, $p = 0.035$), but not specifically with industry funding ($\chi^2 = 2.93$ $p = 0.146$), governmental ($\chi^2 = 0.076$, $p = 0.783$), or academic ($\chi^2 = 1.514$, $p = 0.219$) sources
- Uncontrolled treatment allocation was not associated with world region ($\chi^2 = 2.733$, $p = 0.098$).

Conclusions

- Uncontrolled treatment allocation is a prevalent issue in ophthalmological RCTs and is more common where reporting is unclear, in two-eye allocation patterns, surgical interventions, and non-English speaking settings
- The validity of statistical analysis in uncontrolled RCTs may be compromised by inconsistent relationships between individuals and interventions
- Quality and validity of RCTs can be improved by utilising strategies that support transparent reporting and evaluation of allocation pattern
- Adoption of our nomenclature system in critical appraisal tools or trial registries can help facilitate concise and clearer reporting