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Missed opportunity from randomised controlled trials of medical interventions for open-angle glaucoma

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Abstract

Purpose—To evaluate the extent to which intraocular pressure and visual field have been reported as outcomes in randomised controlled trials (also referred to as ‘trials’) of medical treatments for open-angle glaucoma.

Methods—We identified published reports of trials in a systematic review of medical interventions for open-angle glaucoma our group conducted. We assessed whether intraocular pressure and visual field were reported as trial outcomes and classified them to be either completely or incompletely reported for meta-analysis. We also collected data on the length of time patients were followed and source of funding for the trial.

Results—As of March 2014, we identified 401 trials that had enrolled 76 861 participants. Eighty per cent of 401 trials provided complete information on intraocular pressure and 11% of the 401 trials provided complete information on visual field. Only a minority of trials followed patients for at least 1 year. About half of all reports in our study stated that receiving funding from the industry.

Conclusions—Although the vast majority of trials provided sufficient data for meta-analysis of the effect of medical management of open-angle glaucoma on intraocular pressure, relatively few provided data for analysing the effect on visual field. We considered this as missed opportunity because the data were not available for evidence synthesis. Investigators have an obligation to patients and providers to determine the comparative effectiveness of glaucoma interventions in terms of patient-important outcomes and not to waste data that could have been collected in trials.

INTRODUCTION

A systematic review identifies, appraises and synthesises the existing evidence on a topic. Meta-analysis, done within the framework of a systematic review, combines the quantitative

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results from individual studies statistically.¹ To understand the effectiveness of an intervention in a primary study, two pieces of data are needed for each outcome of interest: the estimate of effect (eg, mean difference, risk ratio) and its precision (eg, SE, CI). The same two pieces of data are required for a meta-analysis in which multiple primary studies are combined. Outcome data that were collected, but not reported or not presented in a way that allows meta-analysis by others, could be considered as research waste.

Evidence to support the management of patients with open-angle glaucoma (OAG) should rely on provider-important outcomes and on patient-important outcomes, for example, how well an intervention improves or stabilises functions that patients value.² The definition of an outcome includes five elements,³ with the outcome ‘domain’ being the name of the outcome being measured. At this time, intraocular pressure (IOP) is an outcome domain for which all glaucoma drugs have been approved by the US Food and Drug Administration⁴ and is the only modifiable risk factor for glaucoma.⁵ IOP, considered a surrogate outcome, might be a reasonable outcome domain for early efficacy trials;⁵ however, IOP is not a direct measure of structural or functional glaucomatous optic neuropathy. Furthermore, the classification of IOP as a surrogate outcome has not been validated.²

It is crucial that we evaluate outcomes that are important to patients and clinicians. Although visual field may be a more patient-important outcome domain than IOP, there are inherent challenges to incorporating visual field as an outcome. For example, there is no accepted definition for visual field progression and visual field progression takes time to develop, requiring at least two visual field tests to detect any change.⁵ Failure to measure patient-important outcomes, and measuring surrogate outcomes alone in study participants, could be considered as missed opportunity.⁶ Our objective was to evaluate the extent to which IOP and visual field have been reported as outcomes domains (henceforth referred to as ‘outcomes’) in randomised controlled trials (RCTs) of medical treatments for OAG.

MATERIALS AND METHODS

For the purpose of conducting a systematic review of medical interventions for OAG, we identified published reports of RCTs (eg, full text, abstracts) that had evaluated medical treatment in participants with OAG. The detailed methodology used was published previously.⁷ In brief, we searched the Cochrane Library, EMBASE and MEDLINE through 11 March 2014. Trials were eligible if they were randomised parallel group trials; if 60% or more of randomised participants had a diagnosis of OAG or ocular hypertension; and evaluated topical medical interventions to reduce IOP or progression of visual field damage. Trials were excluded if they enrolled fewer than 10 participants in each group or were followed for an outcome for fewer than 28 days after randomisation. Two individuals independently screened titles and abstracts for potential eligibility, assessed the full-text reports (‘full reports’) for final eligibility, and extracted the data.

We assessed whether IOP and visual field were reported as trial outcome domains. When there was more than one report associated with a trial we extracted the most ‘complete’ information available, using multiple reports if necessary. For example, for a trial with more than one associated report, if IOP was completely reported in report 1 and not report 2, we

used report 1 for data abstraction. If, however, for the same trial visual field was more completely reported in report 2 compared with report 1, we used report 2. When one or more full reports and one or more short reports (such as conference abstracts) were available for a trial, we used the full report. For both IOP and visual field outcome domains, we evaluated whether sufficient information to estimate the treatment effect and its precision ('complete' information) was reported, or could be calculated to allow inclusion of the data in a meta-analysis (eg, we were able to calculate the SE from the CI or exact p value). We only considered aggregated data. We also collected data on the length of time patients were followed ('follow-up' time) and source of funding for the trial.

RESULTS

As of March 2014, we identified 401 RCTs that had enrolled 76 861 participants. All RCTs were evaluated on full reports. Three hundred and nineteen of the 401 (80%) RCTs provided complete information on IOP and 43/401 (11%) of the RCTs provided complete information on visual field (table 1). Overall, 24 119 (31%) and 69 483 (90%) RCT participants cannot be included in meta-analyses examining the effectiveness of treatment on IOP and visual field outcomes, respectively, because those outcomes were not described in the report or were not completely reported.

Only a minority of RCTs followed patients for at least 1 year (78/401; 19%). Fifty of these 78 (64%) RCTs provided complete information on IOP and 24/78 (31%) provided complete information on visual field (table 2). Consequently, data on 14 886 (54%) and 21 694 (78%) RCT participants were not able to be included in meta-analyses at 1-year follow-up on IOP and visual field outcomes, respectively.

Reports for half of all RCTs in our study stated that funding support had been received from industry (195/401), representing almost 74% of the patients enrolled. Twenty-five out of 401 (6%) trials reported receiving funding supports from nonindustry resources, and the remaining 181/401 (45%) trials did not report funding. Complete information for a meta-analysis of IOP was provided in reports for trials funded by a non-industry source (21/25 trials; 84%) than for trials funded by industry (149/195; 76%), or for unfunded trials or trials that did not report funding (149/181; 82%). Although numbers were very small, the same pattern was found for visual field, with complete information provided in reports for trials funded by a non-industry source (3/25 trials; 12%), than for trials funded by industry (18/195; 9%), or for unfunded trials or trials that did not report funding (22/181; 12%).

The median number of participants reported for the RCTs was 92 (IQR: 43–266; mean: 192). We present the availability of complete information for IOP and visual field respectively in table 3.

DISCUSSION

Although the vast majority of RCTs provided sufficient data for meta-analysis of the effect of medical management of OAG on IOP, relatively few provided sufficient data for analysing the effect on visual field, which has a presumed association with visual function. This is the case among both short-term trials and trials with at least 1 year of follow-up and does not

vary by size of the trials. Furthermore, a large number of RCTs did not present data on visual field in the associated report(s). Thus, we considered data that could have been collected or were collected but not completely reported (we do not know which) from participants enrolled into these RCTs as missed opportunity, for informing policy and patient care.

While not every trial needs to collect visual field data, in general trials should have a good reason for not doing so. Compared with IOP, visual field data are more difficult to collect, analyse and requires longer follow-up time to detect change. Further challenges include that there is no consensus definition of visual field progression and large sample sizes may be necessary to detect differences in progression between treatments.⁵⁸⁹ These challenges can be overcome. Indeed, we identified two RCTs examining change in visual field at 1 and 2 years.⁹¹⁰ We believe that investigators should design RCTs to have a sufficient length of follow-up to measure outcomes that patients value or report directly.

Visual field is one measure of functional glaucomatous optic neuropathy; visual function outcomes such as ability to drive or read fine print as well as population-level outcome such as cost are also important to consider. This is not to say that these outcomes should completely replace biological or surrogate outcomes, including IOP. Investigators have an obligation to patients and providers to determine the comparative effectiveness of glaucoma interventions in terms of patient-important outcomes and not to miss opportunities or even waste data by collecting them in RCTs.

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Table 1

Amount of 'wasted' research by outcome in all trials (n=401)

	<u>Intraocular pressure</u>		<u>Visual field</u>	
	Number of trials (n=401) (%)	Number of participants (n=76 861) (%)	Number of trials (n=401) (%)	Number of participants (n=76 861) (%)
Outcome not described in the report	8 (2)	7969 (10)	319 (79)	61 238 (79)
Outcome described in the report				
Complete information for meta-analysis	319 (80)	52 742 (69)	43 (11)	7378 (10)
Incomplete information for meta-analysis	74 (18)	16 150 (21)	39 (10)	8245 (11)

Table 2

Amount of 'wasted' research by outcome in trials with greater than or equal to 1-year follow-up (n=78)

	<u>Intraocular pressure</u>		<u>Visual field</u>	
	Number of trials (n=78) (%)	Number of participants (n=27 736) (%)	Number of trials (n=78) (%)	Number of participants (n=27 736) (%)
Outcome not described in the report	3 (4)	7093 (26)	42 (54)	18 674 (67)
Outcome described in the report				
Complete information for meta-analysis	50 (64)	12 850 (46)	24 (31)	6100 (22)
Incomplete information for meta-analysis	25 (32)	7793 (28)	12 (15)	2962 (11)

Table 3

Relationship between the size of the RCTs (number of participants) and the completeness of information for a meta-analysis that was reported

Number (%) of RCTs with complete reporting				
	RCTs with 45 participants (n=108) (%)	RCTs with 46–100 participants (n=100) (%)	RCTs with 101–250 participants (n=106) (%)	RCTs with 251 participants (n=87) (%)
IOP	85 (78)	82 (82)	86 (81)	66 (76)
Visual field	11 (10)	17 (17)	9 (8)	6 (7)

IOP, intraocular pressure; RCTs, randomised controlled trials.