Reported outcome measures assessing effectiveness of treatment for amblyopia, strabismus and ocular motility disorders: Protocol for a systematic review

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Contributions

All three authors drafted this protocol and contributed to the development of the selection criteria and data extraction criteria.

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Abstract

This is the protocol for a review and there is no abstract. The objectives are as follows:

The primary objective of this review is to generate an item bank of relevant outcomes previously reported by researchers and clinicians in studies of the treatment of amblyopia, strabismus and ocular motility disorders.

Secondary objectives are to investigate sources of heterogeneity of outcome definitions including:

- Age;
- study design;
- study size;
- variation in method/ instrument of assessment;
- variation in time of assessment;
- type of amblyopia (refractive, strabismic, ametropic, meridional, stimulus deprivation);
- laterality of amblyopia (unilateral, bilateral);
- severity of amblyopia;
- type of strabismus (convergent, divergent, hyper, hypo, cyclo);
- severity of strabismus (constant/intermittent/latent/micro);
- type of motility disorder (nystagmus, horizontal/vertical gaze palsy, cranial nerve palsy, convergence/divergence disorder, skew deviation, patterns of horizontal incomitance, mechanical restrictions, myogenic disorders);
- severity of motility disorder (paresis/palsy);

Keywords: Amblyopia; Strabismus; Ocular motility; Outcome measures; Core outcome set

Introduction:

Amblyopia, strabismus and ocular motility disorders occur in about 10% of the general population (amblyopia 3.6% [1], strabismus 2.3-5% [1-2], ocular motility disorders 2%). Amblyopia and strabismus typically present as childhood conditions and can constitute long-term conditions for children and young adults. Strabismus and ocular motility disorders can develop as acquired conditions in children and adults due to neurological, endocrine and traumatic causes. There are several approaches to the management of these conditions including occlusion, penalisation, exercises, spectacles, prisms, botulinum toxin, drugs, surgery, watchful waiting, or a combination [3]. There are two key issues relating to these management options. First, the inconsistency in the use of outcome measures that report the success or failure of treatment, and second, the lack of use of patient-reported outcome measures (PROMS) [4-7].

Several trials/studies of these interventions underpin clinical practice. Clinical trials should have defined primary and secondary outcomes that answer questions generated by the main hypothesis. Formal trials of treatment options for amblyopia, strabismus and ocular motility disorders have increased in recent years but many with varied outcome measures and several different endpoints for outcomes have been reported [5-7]. This lack of standardisation makes it very difficult to compare the outcomes of these studies and, as a result, renders it challenging to provide clear information on treatment choices which, in turn, makes it difficult to discuss realistically the likely outcomes of treatment with patients in the clinic [8].

One strategy suggested to overcome these issues is the development of core outcome sets which should be measured and reported as a minimum set of outcomes in all randomised controlled trials and cohort studies for these conditions [8]. As a result the risk of outcome reporting bias and heterogeneity can be reduced whilst increasing the potential for carrying out a future meta-analysis for key outcomes [9].

The numerous and diverse outcomes that may be used for amblyopia, strabismus and ocular motility disorders include, amongst others, visual acuity, angle of deviation, range of ocular movements, fixation stability and binocular vision measures. There are a number of Cochrane systematic reviews that consider a range of treatment trials for amblyopia, strabismus and ocular motility disorders. Their recommendations call for clarification of dose/response effect and further investigation of treatment regimens [3, 5, 6]. In particular, the types of outcome measures differ across all reviews with poor validation of measures of severity of conditions and thus criteria for intervention [3, 5, 6]. An attempt to utilise a core outcome set is evident for the National Strabismus Data Set project [4]. This system of deciding a core outcome set is limited as it fails to include all stakeholders and patients and fails to consider a wide variety of domains for outcome measures. It also leads to potential problems including heterogeneity and outcome reporting bias. A recent review recommended four outcome measures for reporting results of surgery for intermittent exotropia [7] but was limited by the extent of literature review and lack of external consensus. A short narrative review of outcome measurements for size of deviation showed considerable variability across the tests available and the recommendations for their use [10].

Therefore, to realistically discuss likely treatment outcomes of amblyopia, strabismus and motility disorders with patients in clinic and to be able to compare interventional trials relevant to these conditions, it is necessary to have a minimum set of standard valid outcomes of treatment for each condition, in other words a core outcome set. The following protocol outlines the proposed methodology for a systematic review in which the primary aim is to generate an item bank of outcomes of treatment for amblyopia, strabismus and ocular motility disorders from existent published literature. The review aims also to determine the heterogeneity of outcome definitions, the number of differing measuring methods used and the specific ways in which they differ. Both clinical and patient–reported outcome measures will be considered. This systematic review will be the first step in the pathway of developing core outcome sets for clinical research and practice in amblyopia, strabismus and ocular motility disorders. It will be followed by an iterative consensus process (group meetings and surveys) of stakeholders including patients, health professionals and methodologists.

Review aim and objectives

The primary aim of this review is to generate an item bank of relevant outcomes previously reported by researchers and clinicians in studies of the treatment of amblyopia, strabismus and ocular motility disorders.

Secondary objectives are to investigate sources of heterogeneity of outcome definitions including:

- Age
- Study design
- Study size
- Variation in method/ instrument of assessment
- Variation in time of assessment
- Type of amblyopia (refractive, strabismic, ametropic, meridional, stimulus deprivation)
- Laterality of amblyopia (unilateral, bilateral)
- Severity of amblyopia
- Type of strabismus (convergent, divergent, hyper, hypo, cyclo)
- Severity of strabismus (constant/intermittent/latent/micro)
- Type of motility disorder (nystagmus, horizontal/vertical gaze palsy, cranial nerve palsy, convergence/divergence disorder, skew deviation, patterns of horizontal incomitance, mechanical restrictions, myogenic disorders)
- Severity of motility disorder (paresis/palsy)

Methods

The systematic review will be carried out by conducting a search of the primary literature.

Subjects of all ages with target conditions will be included.

The target conditions are:

1. Amblyopia (unilateral, bilateral) of any type or severity (refractive, meridional, ametropic, strabismic or stimulus deprivation),
2. Strabismus (latent, manifest, constant, intermittent, micro) of any type and severity (eso, exo, hyper, hypo, cyclo deviation), and
3. Ocular motility disorders of any type and severity (nystagmus, horizontal/vertical gaze palsy, cranial nerve palsy, convergence/divergence disorder, skew deviation, patterns of horizontal incomitance, mechanical restrictions, myogenic disorders)

Definitions of visual conditions

Amblyopia: A condition of diminished form sense in one or both eyes.

Strabismus: Strabismus is the misalignment of the eyes, which can be longstanding from childhood or occur as a result of an insult to the extra-ocular muscles or the cranial nerves supplying them.

Ocular motility conditions: Eye movement palsies or paresis result in the loss of full ability of one or both eyes to move inwards, upwards, downwards or outwards. Nystagmus is a continuous oscillatory movement of the eyes in which both eyes move symmetrically. It may occur in every position of gaze or only be present in certain gaze positions. A further consideration is that patients commonly have multiple defects concurrently.

We will include any reported outcome and outcome measure that was recorded at any point of time from the intervention using any possible instrument or method.

Examples of types of **outcomes** expected to be found from the review for each of the three conditions include:

- Amblyopia: Visual acuity, fixation preference
- Strabismus: Angle of deviation, net change in angle , +/- 8/10 prism dioptres (PD) of orthotropia/phoria
- Ocular motility disorders: Range of ductions and versions -1 to -4, +1 to +4, electro-oculogram (EOG), video recording, oscillatory movements, nystagmography.

Examples of types of **outcome measures** expected to be found from the review include:

- Visual acuity: Snellen's, LogMar, Kay's pictures
- Strabismus: prism cover test (PCT), prism reflection test (PRT), stereo-acuity, fusional amplitude
- Ocular motility: smooth pursuits, saccades, electro-oculography.

Examples of types of **patient-reported outcome measures (PROMS)** expected to be found from the review include:

- Visual function questionnaire VFQ-25
- Diplopia questionnaire
- AS20

Study search

The following types of studies will be included in the review:

- Systematic reviews (with or without meta-analysis) inclusive of diagnostic test accuracy reviews
- Randomised controlled trials
- Controlled clinical trials
- Prospective cohorts
- Retrospective cohorts
- Case series (with more than 10 patients)

Case reports and letters will be excluded.

Search methods for identification of studies

We will search a range of electronic databases including MEDLINE, SCOPUS, Cochrane Library of systematic reviews, AMED and PsycINFO. In an effort to identify further published data, we will search electronic registers in Google Scholar. Additionally, we will perform citation tracking using Web of Science Cited Reference

Search for all included studies and search the reference lists of review articles up to 2016.

We will use the orthoptic search facility web link (http://pcwww.liv.ac.uk/~rowef/index_files/page646.htm) to search in orthoptic journals and conference transactions which are not electronically listed: British and Irish Orthoptic Journal, American Orthoptic Journal, Australian Orthoptic Journal, European Strabismus Association, International Strabismus Association and the International Orthoptic Association. Lastly the reference list of identified reports and articles will be searched for additional studies. Search terms to be used are described in table 1.

All languages will be included and translations will be obtained when necessary. Studies published from January 2006 to 2016 will be considered for inclusion in this review. A 10-year period has been selected given the considerable increase in studies, trials and reviews in recent years and to extract outcome measures that are relevant to current clinical and research practice.

Eligibility of studies

All researchers (SJ, FR & JJK) will independently screen the titles and abstracts identified from the search using a screening proforma based on the eligibility criteria. The full papers of any studies considered potentially relevant will be considered and the selection criteria applied independently by each of the reviewers. We will resolve disagreements by discussion between the review authors. If a disagreement remains, we will seek the opinion of the third reviewer. This process will be undertaken using the Cochrane software for reviews COVIDENCE (https://www.covidence.org).

For the purpose of this study there will be no synthesis of outcome data from the included studies as we seek to create an item bank of all utilised outcomes and outcome measurements. Hence a critique of the methodological quality of the studies is not necessary.

Data extraction

SJ will extract the data using a pre-determined data extraction form (table2) which will be verified by FR or JJK to ensure that all the outcomes have been identified. Disagreement will be resolved through discussion and where resolution is not possible, a third reviewer (JJK or FR) will be consulted.

The following data will be extracted from each study:

Demographics:

1. Study type
2. Author details
3. Year and journal of publication
4. Origin of primary investigator
5. Condition(s) under investigation (amblyopia/strabismus/ocular motility disorder)
6. Age of participants in the study population

Outcomes:

1. The designated primary outcome
2. Designated secondary outcome(s).
3. Methods of measurement(s)
4. The time points at which they were measured.

Data analysis and presentation

For analysis purposes the data will be tabulated so that for each study the outcomes will be listed alongside the measurement instrument. The outcome domains will then be determined following a review of the extracted outcomes by the authors (SJ and FR). The outcomes will be grouped under these domains. We will aim to combine outcomes if they differ in nomenclature across studies but essentially are the same.

End output

We will generate an item bank of relevant outcomes for the treatment of amblyopia, strabismus and ocular motility disorders. We will generate an inventory of measurements for each of these relevant outcomes. We will source time points at

which these outcomes are measured following intervention for amblyopia, strabismus and ocular motility disorders.

Conflicts of interest

The authors report no conflicts in relation to this study.

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