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Title:

Choosing appropriate patient reported outcomes instrument for glaucoma research: *A Systematic Review of Vision Instruments*

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ABSTRACT

Purpose: To identify vision Patient Reported Outcomes instruments relevant to glaucoma and assess their content validity.

Methods: MEDLINE, MEDLINE in Process, EMBASE and SCOPUS (to January 2009) were systematically searched. Observational studies or randomised controlled trials, published in English, reporting use of vision instruments in glaucoma studies involving adults were included. In addition, reference lists were scanned to identify additional studies describing development and/or validation to ascertain the final version of the instruments. Instruments' content was then mapped onto a theoretical framework, the World Health Organization International Classification of Functioning, Disability and Health. Two reviewers independently evaluated studies for inclusion and quality assessed instrument content.

Results: Thirty-three instruments were identified. Instruments were categorised into thirteen vision status, two vision disability, one vision satisfaction, five glaucoma status, one glaucoma medication related to health status, five glaucoma medication side-effects and six glaucoma medication satisfaction measures according to each instruments' content. The National Eye Institute Visual Function Questionnaire-25, Impact of Vision Impairment and Treatment Satisfaction Survey-Intraocular Pressure had the highest number of positive ratings in the content validity assessment.

Conclusion: This study provides a descriptive catalogue of vision-specific PRO instruments, to inform the choice of an appropriate measure of patient reported outcomes in a glaucoma context.

Keywords:

Patient reported outcomes, PROs, Glaucoma, Clinical trials, Quality of life, WHO ICF framework

List of abbreviations:

Activities of Daily Vision Scale	ADVS
Collaborative Initial Glaucoma Treatment Study	CIGTS
Comparison of Ophthalmic Medications for Tolerability	COMTOL
Eye Drop Satisfaction Questionnaire	EDSQ
Glaucoma Disability Index	GDI
Glaucoma Health Perceptions Indices	GHPI
Glaucoma Symptom Scale	GSS
Impact of Vision Impairment	IVI
Indian Visual Function Questionnaire 33	IND-VFQ33
Low Vision Quality Of Life Questionnaire	LVQOL
National Eye Institute Visual Function Questionnaire	NEI-VFQ
Ocular Surface Disease Index	OSDI
Patient Reported Outcomes	PRO
Quality Of Life	QOL
Quality of Life and Vision Function Questionnaire	QLVFQ
Scale of QOL for Disease with Visual Impairment	SQOL DVI

Symptom and Health Problem Checklist	SHPC
Treatment Satisfaction Survey-Intraocular Pressure	TSS-IOP
Vision associated limitations in daily activities	VALDA
Vision Core Measure 1	VCM1
Visual Activities Questionnaire	VAQ
World Health Organization International Classification of Functioning, Disability and Health	WHO ICF

Introduction

Glaucoma is a chronic disease often requiring lifelong treatment. It carries a risk of serious visual impairment and in some cases leads to blindness. The health effects of glaucoma are not only activity limitation due to impaired visual function, but also include side-effects of treatment both in and around the eye, and effects on general health, lifestyle and emotions.

Traditionally, evaluation of outcomes in glaucoma clinical trials has focused on clinical measures of glaucoma status, mainly the extent of visual field loss and level of intraocular pressure. However, such measures do not capture any effects of glaucoma or its treatment on activity limitation and overall wellbeing.

Patient-reported outcomes (PRO) are defined as "outcomes reported by patients" [1]. Aspects that are covered include patients' physical (ability to carry out activities of daily living, such as self care and walking), psychological (emotional and mental well-being) and social functioning (relationships with others and participation in social activities), perception of health status, personal construct (spirituality and stigma) and satisfaction with life or care. PROs of visual functioning and quality of life (QOL) are important as the ultimate goal of therapy is to maintain patients' ability to function in everyday life and should not be considered as surrogates for objective measures of disease as they are measuring different constructs. A large number of instruments have been developed to measure PROs.

Selecting an instrument depends on the objectives of the study and the target population. Generic instruments focus on broad aspects of QOL and health status, and are intended for use in general populations or across a wide range of disease conditions. They are useful for comparing outcomes across conditions. Condition-specific instruments focus on an area of primary interest. They are useful as they include items that reflect issues of importance to a specific population and can be used to detect changes over time. Condition-specific instruments also provide detailed information for clinical practice.

Content is a fundamental consideration when selecting a PRO instrument and should be relevant to the dimensions of health to be measured. Instrument reliability, validity, responsiveness, precision, interpretability, acceptability and feasibility are also important, [2]

however, these properties are not a fixed property of a PRO instrument but dependent upon the population studied [2].

Existing literature reviews of instruments used in glaucoma populations describe or evaluate a range of instrument properties, but none have so far evaluated content validity. Lee and colleagues reviewed the most popular instruments used in patients with cataract and glaucoma [7], whilst three other reviews simply provide instrument descriptions (e.g. number of items and domains) [3, 4, 5]. Others report reliability and construct validity [3, 6] and psychometric properties [5].

Content validity ensures that the instrument items are representative of the construct of health status that is intended to be measured [8]. It is, however, difficult to establish content validity of an instrument because there is no consensus regarding the definition of the important dimension of health [8]. A theoretical framework that is often used to describe health and health related states is the World Health Organization International Classification of Functioning, Disability and Health (WHO ICF) [9]. This framework describes human functioning and restrictions as: functioning and disability; and contextual components. The components of functioning and disability are divided into functioning from the perspective of the body (body systems and structures) and from the individual and society (activities and participation) [9]. The WHO ICF further classifies impairment (I) as 'loss or abnormality in body structure or physiological function', activity limitation (A) as 'difficulties an individual may have to executing activities' and participation restriction (P) as 'problems an individual may experience in involvement in a life situation'. Contextual components comprise of personal and environmental factors which have a dynamic interaction with the health conditions.

The aims of this systematic review are to: i) identify existing vision PRO instruments that have been used in observational or randomised controlled trial studies involving patients with glaucoma; ii) categorise the PRO instruments according to their content using the WHO ICF framework; iii) evaluate their content validity against quality assessment criteria; and iv) provide recommendations on the choice of instrument for a particular clinical study.

METHODS

Search strategy

The following electronic databases were searched: MEDLINE (1950 to January week 3 2009), EMBASE (1980 to 2009 week 1), MEDLINE In Process (1950 to 31th January 2009) and SCOPUS (1960 to January week 1 2009). A sensitive search strategy with both controlled subject headings and text terms relating to glaucoma and quality of life was designed. Details are reported in **Online Resource 1**.

Inclusion and exclusion criteria

All articles, published in English, reporting the use of vision PRO instruments in adult glaucoma participants were included. Once an instrument was identified, any articles relating to its development, and/or validation of the instruments ascertaining to the final version of the instrument were also included. In addition, the content of each instrument had to be fully described in the articles or freely available. Reviews, letters and editorials were excluded.

Data extraction strategy

Two reviewers (JCH, JMB) independently screened the titles and abstracts of all articles identified by the search strategy, assessed the full text copies of all potentially relevant articles and identified vision PRO instruments from primary studies for inclusion. Any disagreements were resolved by discussion or arbitration by a third party (AAB, CR).

A data extraction sheet was developed and piloted on 4 instruments selected from those identified and refined accordingly. For each instrument, two reviewers (JCH, JMB) independently extracted data. Disagreement was resolved by discussion between the two reviewers and if not resolved, involved a panel of reviewers (AAB, CR).

Quality Assessment Strategy

Two reviewers (JCH, JMB) independently assessed the included instruments using a modified version of a published quality assessment tool [10]. The original tool is divided into two parts. The first part assesses the quality of the instruments' development including defining the aim of the instrument and the target population, steps taken in defining the content of the instrument and steps involved in developing the rating scale and scoring

system. The second part assesses the quality of the instruments' performance including validity, reliability, responsiveness and interpretation [10].

Five out of the eight criteria from the first part of the quality assessment tool were relevant for this review. Two additional criteria were added. The first concerned the proportion of participants with glaucoma involved in the focus group during the item identification stage (e.g., if a majority of participants in the focus group had glaucoma, the quality was rated higher than if a small proportion of participants involved in the focus group had the disease). The second criterion concerned instruments that are developed in other languages and were translated into English and whether or not they had subsequently been validated in an English speaking population. The modified quality assessment tool is shown in **Table 1**.

<<**Insert Table 1**>>

Each criterion was evaluated with a positive rating (✓✓), a minimal acceptable rating (✓), or a negative rating (✗). If the criteria were not reported or not applicable, it was evaluated as "NR" or "NA" respectively. Any disagreements were resolved by consensus or arbitration by a third party (AAB, CR). A 'higher quality' study was considered to be one with a high number of positive ratings.

Data synthesis

The vision instruments were categorised into vision-specific, glaucoma-specific and combined instruments. The instruments were further categorised according to the underlying concept of each instrument based on the content mapping to WHO ICF classification [9]. Satisfaction aspects of PROs were given a separate category as WHO ICF only covers health and health related states.

Instruments that contained only body functions and/or body structure components were categorised as *vision or glaucoma impairment measures*. Instruments were classified as *vision or glaucoma status* measures when the content coverage included body functions and/or structures, as well as activity and participation components. When the content only covered activity and participation components, an instrument was classified as a *visual or* a *glaucoma disability* measure. Glaucoma-specific instruments investigating the impact of glaucoma medication on glaucoma patients were divided into *glaucoma medication related to*

health status measures if they contained body functions and/or structures, activity and participation components and *glaucoma medication impairment* measures if they contained only body functions and/or structures components. If the instruments contained satisfaction components, they were classified as *vision* or *glaucoma medication satisfaction* measures. The nature of an instrument classified as a vision status measure is illustrated with the National Eye Institute Visual Function Questionnaire (NEI-VFQ 25) as shown in **Table 2.**

<<Insert Table 2>>

Any combined instrument was treated and evaluated as a whole complete instrument, and then, the vision-specific component was highlighted and evaluated individually within the combined instrument.

A descriptive analysis and rating table was developed to inform selection of the optimal choice of instrument for its intended purpose.

RESULTS

Study selection

Thirty-four instruments were identified from 70 articles (**Figure 1)**. However, one of the identified instruments, the Glaucoma Disability Index (GDI) was excluded because the content of the instrument was not published or freely available for content inspection. Therefore, a total of 33 vision-specific PRO instruments were included in the review.

<<Insert Figure1>>

Description of included PROs instrument

From the 33 instruments reviewed, 16 vision-specific, 16 glaucoma-specific and one combined instrument were identified. The vision-specific instruments comprised instruments measuring vision status (n=13), vision disability (n=2) and vision satisfaction (n=1). The glaucoma-specific instruments measured glaucoma status (n=5), glaucoma medication related to health status (n=1), glaucoma medication impairment (n=4) and glaucoma medication satisfaction (n=6). This categorisation was based on body functions and/or structures, activity and participation component according to the WHO ICF framework. The list of instruments

and content coverage are shown in **Table 3.** The characteristics of the included instruments are shown in **Online Resource 2**.

<<Insert Table 3>>

Identified vision-specific instruments (n=16)

The first vision-specific instrument identified in the review was developed in 1984 [57]. Vision-specific instruments were developed to measure impact of various vision problems on the activities of daily living in people with visual impairment [21, 25-27, 41- 45, 50, 55,57], low vision [50], cataract [13, 15-17, 20, 23], dry eyes [51] and visual field impairment [48-49, 53-54]. However, the Quality of Life and Vision Function Questionnaire (QLVFQ) [59] was the only instrument in this category that assesses visual satisfaction in people with visual impairment. Modes of administration were interview [20], self-administered [21] or both [23]. The number of items in an instrument varied from 4 to 52. Administration time, reported for half of the instruments; varying from 5 to 25 minutes. All the instruments were in English except the Scale of QOL for disease with visual impairment (SQOL DVI [Chinese]) [21], Sumi et al (Japanese) [53-54] and QLVFQ (Italian) [59]. The National Eye Institute Visual Function Questionnaire (NEI-VFQ) and VF-14 have been translated into other languages e.g. French, Greek, Italian, Japanese, Portuguese, Dutch, Turkey, German, Spanish, Bahasa Malaysia and Chinese.

Identified glaucoma-specific instruments (n=16)

The first glaucoma-specific instrument identified in the review was developed in 1986 [60]. Comparison of Ophthalmic Medications for Tolerability (COMTOL) is the only instrument in this category that assesses patients' health status when using glaucoma medications [67-68]. Glaucoma-specific instruments can be administered by interview [60-61, 67-68, 70-72,74-75], self-administered [62-65, 69, 73, 76-79] or both [66]. The number of items in the instruments varied from 4 to 46. Administration time for most of the instruments was not reported. Instruments were in English except for Odberg 2001 (Norwegian) [62-63], Glau QOL 36 (French) [64], Uneishi 2003 [66] and Shibuya 2003 (Japanese) [72]. COMTOL and the Eye Drop Satisfaction Questionnaire (EDSQ) were translated into other languages (e.g. French, Danish, Flemish, Icelandic and German for COMTOL [67-68] and French, Dutch,

Spanish and Italian for EDSQ [80]). The development of the glaucoma medication related measures (related to health status, impairment and satisfaction) were supported by pharmaceutical companies [67-68, 70, 73-80], with the exception of GSS [69] and Shibuya 2003 [72]. Shibuya and colleagues did not report their source of funding for developing their instrument [72].

Combined instrument (n=1)

The Collaborative Initial Glaucoma Treatment Study (CIGTS) was a randomised clinical trial comparing initial medical therapy and initial surgery in the treatment of newly diagnosed glaucoma [81]. The investigators used the CIGTS QOL instrument to compare QOL of participants between two treatment groups and with other diseases [81]. This instrument consists of a combination of generic and disease-specific PRO instruments. The generic components include the Sickness Impact Profile [SIP], Center of Epidemiology Studies and Depression scale (CESD), co-morbidity bothersome scale, generic health perception items and global generic QOL items and disease-specific components include the Visual Activity Questionnaire (VAQ), Symptom and Health Problem Checklist (SHPC), Glaucoma Health Perception Indices (GHPI) and disease-specific QOL items [81]. There are 246 items in this combined instrument which is administered through an interview lasting 45 – 48 minutes. It is available in English or Spanish. For this review, the disease-specific components of the CIGTS QOL instrument are described.

The VAQ instrument [85] was selected from the existing vision-specific instruments available during the planning of CIGTS study because it was the only instrument that contained items addressing peripheral vision. GHPI, SHPC and one global disease-specific QOL item was developed specifically for CIGTS. The VAQ and GHPI are considered vision status measures while SHPC is a glaucoma impairment measure. The item addressing the extent to which glaucoma and its treatment interferes with QOL is considered a QOL measure.

Content validity

Descriptive analyses of the aim, development and content of each instrument are summarised in tables available on **Online Resource 3**. The result of the quality assessment is shown in **Table 4**.

<< Insert Table 4>>

Vision-specific instruments

Overall, the NEI-VFQ and impact of vision impairment (IVI) has the highest number of criteria with positive rating (5/6). Both of the instruments are categorised as vision status measures (n=13). The only low rating received by these instruments was in one criterion; the small proportion of participants with glaucoma involved in the focus group during the item identification phase.

Neither of the instruments in the vision disability category (n=2) performed well in the content validity assessment. The instruments in this category did not achieve any positive ratings.

In the vision satisfaction measures category, the Quality of Life and Vision Function Questionnaire (QLVFQ) was the only instrument identified. As this instrument was in Italian, seven criteria were assessed including the criterion that assessed whether the instrument was translated and validated in an English speaking population. During the development of this instrument, neither the views of glaucoma patients were elicited nor the method of item selection reported. The QLVFQ achieved two positive ratings (2/7).

Most of the vision-specific instruments rated badly for the proportion of glaucoma patients' involved in the development phase (i.e. less than 50% of patients' whose views were considered had glaucoma) (Catquest, OSDI, ADVS, VF14, Turano 1999, Ellwein 1995, LVQOL, SQOL DVI, and QLVFQ) and 18% did not report whether any glaucoma patients' views were considered (Ross 1984, Vision associated limitations in daily activities [VALDA] and Ivers 2000).

Glaucoma-specific instruments

Overall, Treatment Satisfaction Survey-Intraocular Pressure (TSS-IOP) has the highest number of positive rating (5/6). This instrument is categorised as a glaucoma medication satisfaction measure (n=6). TSS-IOP scored a minimal rating in the item selection criteria because the authors only reported the item reduction using factor analysis and internal consistency [76]. The authors did not discuss the removal of items with floor effects or the amount of missing data. Another instrument that has a high number of positive ratings (4/6) in this category is the Eye Drop satisfaction questionnaire (EDSQ). However, this instrument is in item generation phase and validation studies are required to confirm the final items [80].

In the glaucoma status measures category (n=5), the Glau-QOL 36 has the highest number of positive ratings (4/7). However, this instrument is in French and has not been validated in an English speaking population.

COMTOL was the only instrument identified that is categorised in the glaucoma medication related to health status measures. The number of positive ratings was 3/6. Items generated for this instrument were based only on the common side-effects reported by patients in clinical trials of therapy for lowering intraocular pressure (IOP) [68]. The authors did not report on other approaches for item generation e.g. literature review and expert opinion to ensure a good breadth of relevance in the content of instrument.

In the category of glaucoma medication impairment measures (n=4), the Glaucoma Symptom Scale (GSS) has the highest number of positive ratings (2/6). The GSS is a modified version of the Ocular Hypertension Study (OHTS) symptom checklist developed by the investigators of the OHTS [69]. Thus, the process of item identification and selection did not depended on glaucoma patients. Although Haverkamp 2004 has a similar rating, the procedure they used for item generation and selection was not reported.

Combined Instrument

Overall, the CIGTS QOL instrument was given a minimal acceptable rating in all criteria (6/6). In the evaluation of disease-specific components, the SHPC has the highest number of positive rating (5/6). SHPC was categorised as a glaucoma impairment measure. The vision

status measures, the VAQ and GHPI, and the disease-specific QOL item each have two positive ratings.

Discussion

This is the first systematic review evaluating the content validity of existing vision-specific PRO instruments used in a glaucoma context. Thirty-three relevant vision PRO instruments were identified and content validation was undertaken using a modified quality assessment tool [10]. As the items and content varied between the instruments, they were categorised based on the WHO ICF classification [9] to enable comparison between instruments with similar concepts. Thus, informing selection of an appropriate instrument.

Overall, the NEI-VFQ, IVI and TSS-IOP had the highest number of positive ratings (5/6). In individual categories, the number of highest positive rating was given to NEI-VFQ and IVI for the vision status measures, QLVFQ for vision satisfaction measures, Glau-QOL 36 for glaucoma status measures, COMTOL for glaucoma medication related to health status measures, GSS for glaucoma side-effect measures and TSS-IOP for glaucoma medication measures. Vision disability measures did not achieved positive ratings in any of the quality assessment criteria.

The National Eye Institute Vision Function Questionnaire (NEI-VFQ-51 and 25 item was developed to measure vision-targeted functioning and influence of vision problems on health related-QOL (HR-QOL) across several common eye conditions [25-26]. Item generation originated from focus groups involving people with age-related macular degeneration, primary open angle glaucoma, diabetic retinopathy, cataract, cytomegalovirus retinitis and low-vision in general. One-third (82/246) of the participants in the focus group had primary open angle glaucoma with a spectrum of disease severity. The NEI-VFQ has been extensively used and has been shown to be internally consistent [27-28], reproducible [27] and responsive in glaucoma patients [28]. It has been used in glaucoma randomised clinical trials, namely the Early Manifest Glaucoma Study [86] and the Primary Tube Versus Trabeculectomy Study [87]. As the NEI-VFQ-25 is a validated and widely used instrument, it has been used as a benchmark for comparison with glaucoma specific instruments. Re-evaluation of the NEI-VFQ-25 using Rasch analysis in a population of visually impaired working adults demonstrated disordered thresholds for many of the items due to: the number of response

categories; confusing label options; the presence of misfitting items and differential item functioning (DIF) or item bias [34]. However, Rasch analysis on the NEI-VFQ-25 in a glaucoma population has not been evaluated.

The IVI, a vision-specific instrument, was developed to measure the impact of vision impairment on a person's ability to participate in their activities of daily living [40-46]. It is intended to evaluate the effectiveness of low vision rehabilitation programmes. The content of the IVI was based on patient input in focus groups and on existing instruments (i.e. the VQOL) with the core questionnaire (Vision Core Measure 1 [VCM1]) of the VQOL being incorporated into the IVI [88]. As the IVI was intended for use in people who are visually impaired, items relevant to less severe disease, and all stages of glaucoma such as pain and glare were excluded from the content. The IVI has good psychometric properties for its intended use in people with visual impairment [43], but for people with earlier stages of glaucoma, the content and performance of IVI appear inadequate as demonstrated by Rasch analysis [46]. A refinement of the IVI in terms of the addition of items could extend the performance of IVI for use in assessing restriction of participation in daily living for people with all stages of glaucoma.

TSS-IOP is a glaucoma-specific PRO instrument designed to assess patient's satisfaction with various factors associated with topical medications to control IOP. Atkinson and colleagues developed the TSS-IOP using adequate methods [76]. Based on the modified quality criteria, the content area of TSS-IOP is acceptable for it to be considered as a useful measure of patient satisfaction for comparing the effectiveness of IOP lowering medications, but adequate reliability, validity, responsiveness and scoring algorithms for each of the sub-scales are not yet demonstrated [76, 77].

The strength of this review is the usage of systematic methods to identify vision-specific instruments. The presently compiled instrument provides the best available list to guide researchers in choosing the most appropriate vision-specific PRO instrument for their study.

To facilitate content validity in this review, an attempt has been made to categorise instruments by mapping the instruments' content to WHO ICF framework. However, this exercise was crude and loosely follows the recommended linking exercise [11, 89]. Each

instrument was categorised as a status, disability or satisfaction measure depending on whether the content of its items cover: body functions and/or body structures, as well as activity and participation components; only activity and participation components; or satisfaction. This method of categorisation may not reflect the underlying concept of the instrument and whether a required number of items in each component are needed to define the underlying concept of an instrument. Further research may be needed to examine the content of each instrument by classifying their items according to their health domains.

Bias in assessment of content validity of the instruments was minimised by using a quality assessment tool with objective criteria. The actual content criterion was the only subjective criterion as it needed the judgement of the reviewers. Both reviewers were ophthalmologists who made their decision based on clinical experience. To reduce the inter-observer variability, the instruments were reviewed independently and any disagreement was resolved by consensus between the observers or with a third party. Inadequate reporting of item identification [57] and selection [59, 66, 60-63, 75] in the development of the instruments by the developers may affect the results of the review.

Content validity provides investigators with overall information on how well the construct under measurement is represented by an instrument. However, an investigator will need to examine the individual item content to determine its appropriateness for a particular trial [8]. Once an investigator has selected the appropriate instrument for their trial, the next step is evaluating the performance and practicality of the instruments. Practicality is another important aspect to ensure high participation and motivation from the patients and staff involved in the trial. If an instrument is content validated and psychometrically sound but unacceptable to patients, poor response rates and difficult administration will affect the instrument's performance in the trial.

In this review, the identified vision-specific PRO instruments can be used as a catalogue for choosing the appropriate instrument for glaucoma trials. The modified quality assessment criteria may be useful to guide content development of new instruments or content assessment of existing instruments for use in glaucoma trials. Classifying the instruments according to their underlying concepts will aid investigators in interpreting their trial results. The review also highlights the need to develop glaucoma-specific instruments which measure

both the impact of glaucoma and glaucoma medication to people with glaucoma. Further research is needed on content examination using the WHO ICF classification.

In summary, this review informs the first stage of choosing appropriate content validated vision-specific PRO instruments. Only then does the performance of the content relevant measure need to be considered to determine if any of the existing instruments are sufficiently valid and reliable to measure PROs.

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