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Adverse effects and Safety in Glaucoma Patients - Agreement on Clinical Trial Outcomes for Reports on Eye Drops (ASGARD) - A Delphi Consensus Statement

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Adverse effects and Safety in Glaucoma Patients - Agreement on Clinical Trial Outcomes for Reports on Eye Drops (ASGARD) - A Delphi Consensus Statement

Short title: Reporting AEs in anti-glaucomatous eye drops: a Delphi study

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Abstract

Purpose: The purpose of this study is to establish consensus among experts on outcomes and methods to be used in clinical trials to assess adverse effects of anti-glaucomatous eye drops.

Design: Modified Delphi method.

Methods: Clinical experts from Europe, North America, South America, the Middle East, and Asia were invited to participate in two sequential web-based surveys administered from June 27 to August 29, 2021. A total of 91 clinical experts were invited to participate. Of these, 71 (78%) experts from 23 different countries accepted the invitation and answered the first questionnaire. The importance of items was ranked using a 10-point scale (1 as not important, 10 as very important).

Results: A total of 84 items were rated in round one by 71 participants. Of these, 68 (81%) reached consensus. In round two, 19 items, including three additional items, were rated by 53 (75%) participants. Consensus was reached in 98% of investigated items. Eight outcomes were agreed as important to assess when conducting future trials: ocular surface, dryness, epithelial damage, local adverse effects related to eye drops as reported by patients, periocular surroundings and eyelids, quality of life questionnaires, hyperemia, visual acuity, tear film, and anterior chamber inflammation.

Conclusion: We propose a consensus-based series of outcomes and assessment methods to be used in clinical trials assessing adverse effects of anti-glaucomatous eye drops. This will hopefully improve the comparability of results from future trials and thus facilitate meta-analyses and progress in this field.

Table of Contents Statement

AJO-22-108 "Adverse effects and Safety in Glaucoma Patients - Agreement on Clinical Trial Outcomes for Reports on Eye Drops (ASGARD)"

There are large variations in how clinical trials report adverse effects, safety, and tolerability related to anti-glaucomatous eye drops. The study proposes a consensus-based series of outcomes and assessment methods to be used in future clinical trials. This will make it easier for the results of studies to be compared and combined in reviews and meta-analyses, which facilitates decision-making for clinicians and ultimately benefits the patients.

Implications

There are large variations in how clinical trials report adverse effects (AEs), safety, and tolerability related to anti-glaucomatous eye drops. Inconsistencies and discrepancies in outcomes and methods lead to missed opportunities when comparing studies and combining results in meta-analyses, making it difficult to synthetize evidence. The purpose of this study is to establish consensus among experts on outcomes to be assessed and methods to be used in future clinical trials.

Introduction

Glaucoma is the leading cause of irreversible blindness worldwide, affecting approximately 80 million people. With a growing elderly population, this number is estimated to increase to 111 million by 2040.[1] The only current treatment is lowering the intraocular pressure (IOP), which is most often done with eye drops.[2] For most patients, treatment is lifelong and the chronic use of topical ocular medications can be associated with AEs such as redness, irritation, feeling of dryness, burning and stinging, discomfort, tearing, itching, and foreign body sensation as seen in dry eye disease (DED).[3] The prevalence of DED in the general elderly population is approximately 15% compared to 60% in patients with glaucoma.[4] The severity of local AEs has been shown to affect adherence and thus potentially the efficacy of anti-glaucomatous eye drops.[5,6] It is therefore important to take AEs into account when treating patients with glaucoma.

Clinical trials studying topical treatment for glaucoma show diverse reporting of safety measures which makes comparisons between treatments challenging and prevents indirect comparisons which, ultimately, leads to missed opportunities for potentially synthetizing evidence and informed decision-making. Examples include the study by Hedengran *et al.* evaluating the efficacy and safety of benzalkonium chloride (BAK)-preserved eye drops compared to alternatively preserved and preservative-free eye drops in the treatment of glaucoma and the study by Steensberg *et al.* evaluating the efficacy and safety of generic vs original prostaglandin analogues in the treatment of glaucoma.[5,7] Inconsistency in outcomes and methods prevented the studies from synthesizing evidence to address current concerns on the safety profiles of preserved eye drops and generic substitutions. Furthermore, inconsistencies hindered detailed AE comparisons that are essential for optimal and individualized patient care. In the current study, we wanted to establish consensus on outcomes and methods that could be recommended for future trials evaluating the safety of anti-glaucomatous eye drops.

Method

We used the Delphi method, an iterative process to establish consensus on a given subject. The Delphi method is characterized by a controlled feedback cycle where participants are presented with the median responses of the collected group compared to their own previous responses and are hereby encouraged to re-evaluate their initial responses[8].

A core group of leading clinical experts in the fields of glaucoma and ocular surface was established. Core members included researchers experienced in DED, glaucoma management, and the pathology and biology of ocular surface damage associated with glaucoma medications. Core group members

were identified through previous work in the mentioned fields. Members were required to have clinical trial experience, preferably as chief investigators, and to hold a faculty position equivalent to associate professor or higher. Each core member recommended 8-10 international glaucoma or ocular surface experts who were invited to participate in the Delphi process. The study aimed for a majority of clinicians with clinical trial experience but also accepted scientists with relevant expertise in the participant group. Delphi participants were required to hold a medical degree with clinical experience in relevant fields and preferably had clinical trial experience. Participants without direct clinical trial experience were recommended by core group members based on relevant experience demonstrated through previous collaborations.

Domains and methods were initially extracted from clinical trials included in the systematic review and meta-analysis performed by Hedengran *et al*. All mentioned domains and methods in the studies were included.[5,7,9-30] Quality of life questionnaires were extracted from a literature review by Okumura *et al*.[31] Items were then augmented and altered by the core group. Items were translated into survey-format questions and organized into outcome domains, e.g. visual acuity, with subgroups concerning measurement method, e.g. Snellen chart.

Participants were asked to rank outcomes and methods on a scale from 1-10 based on importance (1 as not important and 10 as very important). Consensus on an outcome being important was achieved when the mean value of an item was 7 or higher and the interquartile

range (IQR) of scores was 3 or lower. Consensus in 90% of the investigated domains was considered a valid status for conclusion. Items marked "no preference or unfamiliar with method" or not answered by more than 50% of the experts were concluded as "no preference".

Invitations were sent to potential participants via email with an individual link to the REDCap questionnaire. Each survey round was conducted over 2-4 weeks. The study aimed for 2-4 Delphi rounds. In the first round, participants were asked to rank items on a scale from 1-10 and were given the opportunity to comment and suggest additional outcomes or methods. The mean, median, and IQR of each item were calculated. Items with interquartile range (IQR) of scores greater than 3 (i.e. lack of consensus) were included in the following round. Items were then presented with the median response from the collected group and the individual's own response from the previous round. Experts were also asked to rate new items suggested by participants in the previous round.

Results

The Delphi study was conducted from June 27 to August 29, 2021, using Research Electronic Data Capture (REDCap) hosted by the University of Copenhagen. Only two rounds were required to reach consensus.

A total of 91 clinical experts were invited to participate. Of these, 71 (78%) experts from 23 different countries (Figure 2) accepted the invitation and answered the first questionnaire. Only participants who completed round one were invited to participate in round two. Of the invited participants, 53 (75%) answered the second questionnaire. Participants were evenly distributed in the fields of

glaucoma (55%) and ocular surface (45%). The vast majority of participants were clinical experts of which 56 (79%) had been directly involved in clinical trials. For geographical distribution, see Figure 2.

In the first round, participants were asked to rate 84 items, of which 81% reached consensus. In the second round, participants were asked to rate 19 items, three of which were new items suggested by the participants in the first round, and the remaining 16 items that did not reach consensus in the first round. Of the investigated domains, 98% had reached consensus after round two, and the study was concluded (Figure 1).

Experts agreed that the following outcomes were important when assessing AEs in clinical trials studying topical treatment for glaucoma (from highest to lowest mean score): ocular surface, dryness, epithelial damage, local AEs related to eye drops as reported by patients, periocular surroundings and eyelids, quality of life (QoL), hyperemia, visual acuity, tear film, and anterior chamber inflammation. One or more methods were recommended for each outcome except hyperemia, where there was no preference for any of the presented methods. The full results of all examined domains and methods are available in Table 1.

Participants also commented on the importance of time standardization for domains and methods. After the first round, three questions regarding time standardization were identified through participants' answers: 1) the duration of clinical trials, 2) the optimal time of measurement before/after instillation of eye drops, and 3) the optimal time of day for measurements. Experts agreed that the duration of clinical trials should be 3 months or longer as 96% of participants marked optimal clinical trial duration as either "3-6 months" or "12 months and longer". Experts also agreed that the time before/after instillation of eye drops was important for clinical evaluations (0% marked "not important") and assessment of patient reported outcomes (8% marked "not important"). However, there was no agreement on the optimal time.

Discussion

We conducted a Delphi study to establish a consensus on what outcomes and methods to use when assessing AEs of anti-glaucomatous eye drops in clinical trials. Eight domains were identified as important (Table 1).

The Delphi method provides a practical and beneficial way of gathering opinions among a larger group of individuals. The online format mitigated the challenge of gathering individuals from different countries, and the individual questionnaire format reduced the effect of dominating individuals in group dynamics. While presenting consensus among experts, outputs and recommendations from the Delphi process were based on clinical opinions and clinical trial experiences of the participants and did not include other stakeholder groups such as patients. The guidance presented in this study therefore only seeks to summarize the opinion of clinical experts. The presented recommendations mainly reflect European practice, as 80% of participants practiced in Europe. However, the rated items represent global practice as they were based on clinical trials distributed in Asia, Africa, North America, South America, Europe, and Australia/Oceania.

Methods for assessing each outcome were also ranked, although for a significant percentage (21%) there was “no preference”. This can be interpreted as meaning that experts have no preference for the method or that they are unfamiliar with the suggested methods. Particularly when rating scales, e.g. for “ocular surface, dryness, epithelial damage” and “hyperemia”, experts commented in the comment box that they were not familiar with one or more of the suggested scales. Experts also highlighted in the comments that cost-benefit should be considered and their preferred method would be the one with minimal time consumption and data collection.

The study explored consensus on time standardization for clinical trials assessing AEs in IOP-lowering eye drops. In the first round, experts commented on the importance of time standardization in trials. In the second round, experts were asked to choose specific durations and time points of measurements. Despite agreement on a minimal trial duration of 3 months, a more precise agreement on duration and time points was not achieved. This could be due to unclear questions or disagreement on the topic. A standardization of trial duration and optimal timing to measure AEs should be further explored with qualitative research conducted with patients, clinicians, and researchers.

Our study has some limitations. The study did not include any assessment of the validity of instruments and further studies are needed for such validation. Delphi participants were solely identified based on core group member recommendations, clinical experience, and field of expertise. More well-defined criteria such as years of practice, clinical trial experience, or faculty position could have provided more detailed demographics of the participant group. Extraction of domains and methods included in the first questionnaire was based on few systematic reviews and meta-analysis. More comprehensive search criteria might have identified additional outcomes to be included. The addition of a physical or virtual meet-up to conclude the Delphi process might have elucidated experts’ comments and preferences to provide a more concise set of method recommendations.

In conclusion, we propose a consensus-based series of outcomes and assessment methods to be used in clinical trials assessing AEs of anti-glaucomatous eye drops. Eight outcomes were agreed as important to assess when conducting future trials: ocular surface, dryness, epithelial damage, local AEs related to eye drops as reported by patients, periocular surroundings and eyelids, quality of life questionnaires, hyperemia, visual acuity, tear film, and anterior chamber inflammation. Using consensus-based outcomes makes it easier for the results of studies to be compared and combined in reviews and meta-analyses, which facilitates decision-making for clinicians and ultimately benefits the patients.

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RA holds patents on the infrared meibography technique (Japanese patent registration no. 5281846; U.S. patent publication no. 2011-0273550A1; European patent publication no. 2189108A1), is a consultant for Topcon Company (Tokyo, Japan) and Technopia Japan (Tokyo, Japan). RA has received lecture fees from Santen, Senju, Lumenis, Inami, J&J, Alcon and Novartis. GG has received grants from Thea and Santen, consulting fees from Allergan,

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Tables legends

Table 1.

Title: Delphi results for evaluation of outcomes for adverse effects in anti-glaucomatous eye drops in clinical trials

Legend: Items were concluded “important” (bolded) when the mean value was 7 or higher and “not important” when the mean value was lower. Consensus required that the IQR (not shown) was 3 or lower. Items marked “no preference or unfamiliar with method”, or with no answer, by more than 50% of the experts were concluded as “no preference”.

Figure legends

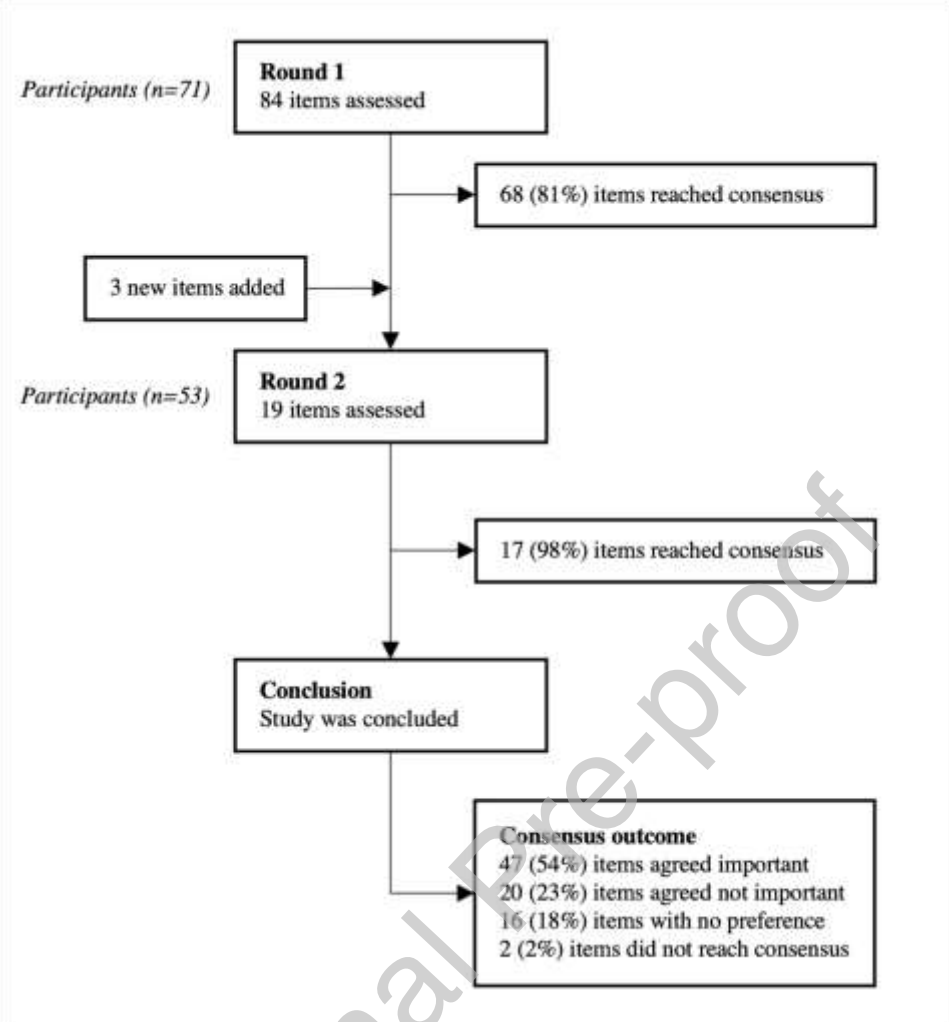

Figure 1.

Title: Delphi process flow

Legend: Flow of participants and items through the Delphi process. Items include domains and methods.

Figure 2:

Title: Geographical distribution

Legend: Geographical distribution of Delphi participants.

Tables

Table 1: Delphi results for evaluation of outcomes for adverse effects in anti-glaucomatous eye drops in clinical trials

Domain / method	Conclusion	Mean	% of participants with no preference*
Visual acuity	Important	7.7	25%
ETDRS	Important	8.4	38%
Snellen	Important	7.9	38%
Landolt C	No preference	7.4	55%
Periocular surroundings and eyelids	Important	7.9	0%
Hyperpigmentation	Important	8.0	16%
Orbital atrophy	Important	7.9	17%
Erythema	Important	8.7	16%
Meibomian gland dysfunction			
Eyelash contamination	Important	7.2	24%
Meibum quantity and quality	Important	7.8	17%
Lid margin foam	Not important	6.6	26%
Abnormal lid margin findings of vascularity	Important	7.5	25%

Plugging of gland orifices	Important	7.6	14%
Lid margin irregularity	Important	7.1	25%
Lid margin thickening	Important	7.4	17%
Partial glands	Not important	6.4	28%
Gland dropout	Important	7.2	24%
Morphology of meibomian glands by non-invasive meibography, "Meiboscore"	Important	7.0	32%
Photo documentation	Important	7.7	9%
Tear film	Important	7.5	0%
2% fluorescein staining	Important	8.7	14%
Non-invasive TBUT with keratometry	Important	7.0	32%
Non-invasive TBUT with tearscope	Not important	6.7	39%
Interferometry	Not important	6.0	45%
Infrared thermography	Not important	5.2	48%
Blink rate (blink/minute)	Important	7.0	23%
Tear film production			
Schirmer 1 (without anesthetics)	Important	7.0	23%
Schirmer 2 (Schirmer 1 but with	Inconclusive (IQR	3.5	32%

nasal provocation)	higher than 3)		
Basic secretion (with anesthetics)	Not important	5.2	26%
Tear film clearance test	Not important	5.8	23%
Height of tear film meniscus in µm	Not important	6.3	28%
Tear film quality			
Tear film osmolality	Not important	6.5	27%
Tear film component: Inflammatory markers e.g. cytokines	Important	7.2	27%
Tear film component: Mucins	Not important	6.9	31%
Tear film component: Lipids	Important	7.0	28%
Tear film component: Microbiome	Not important	6.3	34%
Ocular surface, dryness, epithelial damage	Important	8.3	0%
Efron system	No preference	6.5	53%
Annunziato system	No preference	5.4	78%
Cornea and Contact Lens Research Unit (CCLRU) grading scales	No preference	6.4	65%
Vistakon system	No preference	5.7	79%
Oxford grading scale	Important	7.7	34%

National Eye Institute grading system (NEI)	Important	7.5	44%
Lissamine green, van Bijsterveld score	Not important	6.3	38%
Lissamine green, SICCA Ocular Staining Score (OSS)	Not important	6.6	28%
Fluorophotometry	Inconclusive (IQR higher than 3)	4.2	49%
Hyperemia	Important	7.7	0%
McMonnie and Chapman-Davies (MC-D) scale	No preference	6.6	69%
The Institute for Eye Research (IER) scale for bulbar redness	No preference	7.1	65%
The Validated Bulbar Redness (VBR 5) scale	No preference	6.9	68%
Japan Ocular Allergy Society (JOAS) conjunctival hyperaemia severity grading	No preference	6.3	78%
Cornea and Contact Lens Research Unit (CCLRU) grading scales	No preference	6.0	68%
Efron scale	No preference	7.2	65%
Annunziato pictorial	No preference	6.4	79%

Vistakon-Synoptik photographic grades	No preference	6.0	79%
Jenvis grading scale, bulbar redness	No preference	6.4	78%
Jenvis grading scale, limbal redness	No preference	6.4	78%
Cell density	Not important	6.0	7%
Modified Nelson's grading system (goblet cells)	Not important (as domain is not important)	7.2	24%
Staging of conjunctival squamous metaplasia	Not important (as domain is not important)	6.1	23%
In vivo confocal microscopy, conjunctival	Not important (as domain is not important)	6.6	18%
In vivo confocal microscopy, corneal	Not important (as domain is not important)	7.1	16%
Anterior chamber inflammation	Important	7.2	26%
Laser-flare meter	Not important	6.2	42%
Slit lamp, Standardization of Uveitis Nomenclature (SUN) grading	Important	7.8	32%
Patient reported local adverse events	Important	8.0	3%

related to eye drops			
Red eye	Important	8.8	17%
Foreign body sensation	Important	8.6	16%
Miscolouring / hyperpigmentation	Important	7.9	17%
Eyelash growth	Important	7.6	16%
Pain	Important	8.7	14%
Irritation, burning, stinging	Important	9.0	14%
Itching	Important	8.8	16%
Dryness	Important	8.4	14%
Blurred vision	Important	8.6	14%
Tearing	Important	8.1	14%
Light sensitivity	Important	8.3	16%
Symptoms associated with orbital fat atrophy	Not important	6.8	23%
Quality of Life Questionnaires	Important	7.8	3%
Ocular Surface Disease Index (OSDI)	Important	8.6	24%
Impact of Dry Eye in Everyday Life (IDEEL)	No preference	6.8	62%
Dry Eye-Related Quality-of-life	Important	7.8	45%

Score (DEQS)			
University of North Carolina Dry Eye Management Scale (UNC DEMS)	No preference	6.1	80%
Chinese version of DEQS	No preference	4.8	85%
25-Item National Eye Institute Visual Function Questionnaire (NEI VFQ-25)	Important	7.3	42%
The Glaucoma Symptom Scale (GSS)	Important	7.8	48%
Standard Patient Evaluation of Eye Dryness Questionnaire (SPEED)	Important	7.4	34%

Table 1: Items were concluded “important” (bolded) when the mean value was 7 or higher and “not important” when the mean value was lower. Consensus required that the IQR (not shown) was 3 or lower. Items marked “no preference or unfamiliar with method”, or with no answer, by more than 50% of the experts were concluded as “no preference”.