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Development of a Core Outcome Set for Clinical Trials in Non-infectious Uveitis of the Posterior Segment

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Abstract

Purpose

To develop an agreed set of outcomes known as a core outcome set (COS) for Non-Infectious Uveitis of the Posterior Segment (NIU-PS) clinical trials.

Design

Mixed-methods study design comprising a systematic review and qualitative study followed by a two round Delphi exercise and face-to-face consensus meeting.

Participants

Key stakeholders including: patients diagnosed with NIU-PS; their caregivers; healthcare professionals involved in decision-making for patients with NIU-PS including ophthalmologists, nurse practitioners and policymakers/commissioners.

Methods

A long list of outcomes was developed based on the results of (1) a systematic review of clinical trials of NIU-PS and (2) a qualitative study of key stakeholders including focus groups and interviews. The long list was used to generate a two-round Delphi exercise of stakeholders rating the importance of outcomes on a nine-point Likert scale. The proportion of respondents rating each item was calculated, leading to recommendations of 'include', 'exclude' or 'for discussion' that were taken forward to a face-to-face consensus meeting of key stakeholders at which the final COS was agreed.

Main outcome measure

Items recommended for inclusion in the COS for NIU-PS

Results

A total of 57 outcomes grouped in 11 outcome domains were presented for evaluation in the Delphi exercise, resulting in 9 outcomes directly qualifying for inclusion and 15 outcomes being carried forward to the consensus meeting of which 7/15 were agreed for inclusion. The final COS contained

16 outcomes organized into 4 outcome domains comprising visual function, Health Related Quality of Life (HRQoL), treatment side effects and disease control.

Conclusion

This study builds on international work across the clinical trials community and our qualitative research to construct the world's first COS for NIU-PS. The COS provide a list of outcomes that represent the priorities of key stakeholders and provides a minimum set of outcomes for use in all future NIU-PS clinical trials. Adoption of this COS can improve the value of future uveitis clinical trials and reduce non-informative research. Some of the outcomes identified do not yet have internationally agreed methods for measurement and should be the subject of future international consensus development.

Trial Registration

The study was registered with COMET (http://comet-initiative.org/studies/details/640)

Key words

Uveitis, outcomes, core outcome set, macular oedema/edema, domain, Delphi technique/exercise, consensus method, clinical trials, key stakeholders.

Precis

This study presents the development of a core outcome set (COS) for non-infectious uveitis of the posterior segment (comprising intermediate, posterior and panuveitis) to ensure outcomes represent the priorities of all stakeholders, to enhance evidence synthesis and reduce research waste.

1. Background

Uveitis describes a group of diseases characterized by intraocular inflammation (1-6), responsible for 10–15% of total blindness in Europe and North America (7) and up to 25% of blindness in the developing world (1-5, 7). Intermediate, posterior and panuveitis are the most sight-threatening forms of uveitis that often share a number of common features including their higher risk of sight-threatening complications (e.g. uveitic macular edema, UME) and their requirement for systemic or local injection-based therapy. Those forms affect the more posterior structures of the eye and are often grouped together as non-infectious uveitis of the posterior segment (NIU-PS) (8, 9). Uveitis may be due to (a) an infectious agent or (b) non-infectious inflammation, either as a part of an underlying systemic disease or purely confined to the eye (10). Non-infectious uveitis is the most common type observed (11) and is the focus of this study.

A clinical trial is conducted to evaluate the safety and efficacy of a new or existing medical treatment, drug, or device (12) with a view to providing the evidence that will enhance decision making across individual patient care, clinical guidelines and health policy (13). The information gained from such trials may however be limited if key stakeholders do not regard the outcomes measured as being relevant, or if trials all measure different outcomes or the same outcomes are being reported/measured in different ways such that findings cannot be compared or evaluated across studies such as through a meta-analysis (14). Within NIU-PS, there is marked inconsistency and heterogeneity in reporting and measuring outcomes (15), with a systematic review noting that across 104 clinical trials identified, 14 different outcomes were used as a primary outcome, most commonly ‘visual acuity’, ‘vitreous haze’ or ‘macular edema’. Even where the same outcome was used there was often variation in the way it was measured, analyzed and reported (16). Additionally some trials failed to report the outcome and its measurement sufficiently well for comparison or replicability further limiting the contribution of such trials to evidence synthesis (17, 18).

The standardization of a core outcome set (COS) for use in effectiveness trials is one way to address inconsistent use and inappropriate reporting of outcomes (19). A COS is an agreed minimum set of

outcomes for use in clinical trials for a specific health condition using a systematic, standardized approach for outcomes selection and reporting. COS are not restrictive since other outcomes can be collected in addition to the COS, but rather this approach ensures that certain key outcomes are always collected in a standardized way, reducing reporting bias and facilitating study comparison and meta-analysis (19, 20). COS methodology is designed to ensure that the views of all key stakeholders are elicited for consideration during COS development to ensure that the final COS includes outcomes that matter to patients, clinicians and policy-makers/commissioners (20).

To date COSs have been developed for a number of areas in ophthalmology including dry eyes (21), cataract (22), macular degeneration (23), glaucoma (24), thyroid eye disease (25), strabismus and ocular motility disorders (26), with ongoing work in cerebral visual impairment (27) and Behcet's syndrome (28).

The development of a COS for NIU-PS has the potential to profoundly enhance the value of trials in this condition, through avoiding inappropriate outcome measures and providing the standardization needed to enable comparison and meta-analysis of outcomes across trials (even where they may have selected different primary outcomes) (20, 29). In this study we aimed to develop a COS for NIU-PS according to robust methodology that represents the priorities of all groups of stakeholders and supported by international consensus, with a view to supporting the uveitis community to enhance research pertinence and provide long-term value for every future clinical trial into this sight-threatening condition (30).

2. Methods

2.1 Study design

The study was registered with the Core Outcome Measures in Effectiveness Trials (COMET) initiative (published online at http://www.comet-initiative.org/Studies/Details/640) (19), and the full protocol was published prior to study commencement.(31) In brief, a three-phase approach was used to develop the COS (**Error! Reference source not found.**). First, a comprehensive list of outcomes was identified through a review of outcomes reported in existing trials (systematic review) and focus groups and semi-structured interviews with stakeholders (qualitative study). Second, a Delphi

exercise was conducted with key stakeholder groups to prioritize outcomes for inclusion through sequential online surveys. Third, a consensus meeting was held with key stakeholders (patients, caregivers, health care professionals) to discuss the Delphi results and agree on the final outcomes in the COS (31).

Methods from Phase 1: Identifying a comprehensive list of potential outcomes for consideration

A) Outcomes identified through systematic review of trials in NIU-PS

A systematic review was conducted on the effectiveness of pharmacological agents for NIU-PS (including NIU-PS with UME) to identify candidate outcomes for inclusion in the core outcome set (32, 33).

Standard systematic review methodology (34, 35) was employed to identify, select and extract data from comparative studies of pharmacological interventions in patients with NIU-PS and associated macular edema. Searches were conducted (February 2017) through bibliographic databases (Cochrane Library, MEDLINE, EMBASE and CINAHL) and clinical trials registers e.g. clinicaltrials.gov, International Standard Randomized Controlled Trials, WHO International Clinical Trials Registry Platform and UK Clinical Research Network. No restriction was placed on either language or year of publication. Translation of non-English language articles was undertaken to minimize selection bias. Data extraction included the following: basic trial information and name; investigator names; year of study; primary outcome and secondary outcomes; method of measurement and analysis for all outcomes (33).

B) Outcomes identified through qualitative research with key stakeholders

- **Focus groups**

Four focus group discussions were conducted with patients who had NIU-PS. Participants were grouped according to whether or not their uveitis was complicated by the sight-threatening condition uveitic macular edema (UME). Macular edema is the most common cause of vision loss in uveitis and is a frequent outcome measure in major clinical trials in the field (6, 16, 36) . This part of the study is described in full in our previous report (37).

- **Telephone interviews**

Twelve one-to-one telephone interviews were conducted with UK healthcare professionals (ophthalmologists, nurse practitioners and policy-makers/commissioners) who are involved in decision-making for patients with NIU-PS either directly or through policy.

Focus group discussions and interviews were audio recorded, professionally transcribed and analyzed using a framework analytical approach (38). Initially, the transcripts were read repeatedly to allow familiarization with the data and help the generation of the preliminary codes supported by the qualitative data analysis software NVivo version 12 (QSR International- Pty Ltd, Australia). A coding framework was developed iteratively (4-6 times) by two researchers in consultation with the broader research team. During this process our definition of an outcome was broad, including any consequence of NIU-PS or its treatment that clearly had significance to NIU-PS patients. Once we had finalized our coding framework it was then applied to the whole dataset from interviews and focus groups (indexing).

Compiling the 'long list' for evaluation

The outcomes identified through the systematic review and qualitative research were aggregated and evaluated by two researchers (MOT and JMM) for removal of any duplicates, and refinement to ensure their meanings were clear, with any disagreement being adjudicated by (PIM and AD). Outcomes were then grouped into broader *outcome domains*. For example, the domain '*Functional ability'* was created to group the following items: work/employment, educational participation; driving; activities of daily living and self-care; participation in social and leisure activities (37).

All outcome domains were then converted into questionnaire items which asked participants to rate the importance of including each outcome in future research trials. To ensure the questionnaire was easy to read and understood by all stakeholder groups, definitions of outcomes including the type of language used was informed by the qualitative research findings, NHS choices and patient facing

183 medical information. The questionnaire was piloted with patients and caregivers to examine
184 understanding, usability and highlight any potential practical issues prior to the next phase.

185 ## Methods from Phase 2: Delphi Methodology

186 ### 2.2 Delphi participants' eligibility criteria

187 Participants were recruited from all key stakeholder groups. Inclusion criteria were as follows:
188 *Patient participants*: confirmed diagnosis of NIU-PS (intermediate uveitis, posterior uveitis or
189 panuveitis) with or without macular edema; were under active follow-up for the disease; were at
190 least 18 years of age; had a capacity to read and write in English.
191 *Caregiver participants:* adult caregiver for someone with NIU-PS. A caregiver was defined as a person
192 who was at least 18 years of age (e.g. friend, family member or spouse) and providing unpaid care to
193 the patient during his/her illness.
194 *Healthcare professional participants:* ophthalmologists or nurse practitioners directly involved in
195 caring for patients with NIU-PS.
196 *Healthcare policy-makers and commissioner participants:* individuals who may have influence on
197 uveitis care at the health system level e.g. through defining or implementing policy, regulatory
198 approvals related to NIU-PS.

199 ### 2.3 Recruitment

200 Recruitment was as follows:
201 *Patient and caregiver participants:*
202 All eligible patients meeting the inclusion criteria attending the specialist uveitis clinics (Birmingham
203 and Midland Eye Centre, Sandwell and West Birmingham Hospitals NHS Trust, UK; and Queen
204 Elizabeth Hospital, University Hospitals Birmingham NHS Foundation Trust, UK) from July-September
205 2018 were invited to take part in the study. Clinicians distributed the recruitment packs to the eligible
206 participants. A recruitment pack included an invitation letter and a participant information sheet.
207 Patients/caregivers were asked if they had any questions and whether they would be happy to be
208 contacted regarding taking part in the research study. The clinical doctoral research fellow (MOT)

contacted potential participants 3-5 working days later asking if they were still interested in taking part the study. Agreement was confirmed with those who wished to participate, and details of the focus group discussions were sent at a later stage.

Participation in this study was voluntary, and therefore represents the views of those who were willing to engage with research. This may result in bias due to under-representation of certain groups. For patients and caregivers. We tried to attain sample diversity by purposively sampling with respect to age, ethnicity and gender. We did not undertake purposive sampling for all under-represented groups (e.g. higher levels of social deprivation). Focus groups were however continued until saturation of views was reached

Healthcare professional participants:

Ophthalmologists, health policy-makers and health commissioners were recruited via UK and international clinical, research and health service networks, such as the Uveitis National Clinical Study Group (UK) and the International Uveitis Study Group (IUSG), with purposive sampling to ensure a broad representation of geography and setting, supported by the COSUMO (Core Outcome Set in patients with posterior segment involving uveitis with and without Uveitic Macular Oedema) international advisory board; nurse practitioners involved in uveitis care were invited via an International Ophthalmic Nurses Group

Healthcare policy-makers and commissioner participants were identified through UK and international health service networks purposively sampling people in those roles who had been most involved in uveitis policy decisions (e.g. regulators who had overseen policy on interventions in uveitis). For policy-makers we invited to ensure that at a minimum the major US and European regulators were included (FDA, EMA and MHRA). We recognize that there may be international variation in policy maker views that were not captured by this sampling.

Eligible participants were identified by consultant ophthalmologists (PIM and AD) and eligible participants were identified by consultant ophthalmologists (PIM and AD) and contacted via email, including a recruitment pack with an invitation letter and a participant information sheet. The clinical

doctoral research fellow (MOT) contacted all potential participants who had agreed to participate in the study, provided further information about the research and answered their enquiries prior to arranging an interview date. Participants were asked to provide their preferred method of contact and their telephone number for the interview. A convenient time and date were agreed and a reminder was sent two days prior. Verbal consent was obtained from each participant prior to commencing the interview.

Furthermore, for the Delphi study participants were given a unique ID number to gain access to the online Delphi survey. Informed consent was obtained prior to the study commencement. If a potential participant was no longer interested in taking part they were thanked for their time and interest in the study. All participants were asked to identify the key stakeholder group they belong to. Health professionals and health policy-makers were asked to provide their professional role and years of experience

2.4 Sampling of participants and sample size

We attempted to achieve a diverse sample with purposive criteria including patients of varying age, ethnicity and gender; with and without UME; with active and inactive disease: and with uveitis of different etiologies. For healthcare professionals, level of experience in ophthalmology/ uveitis and geographical area of work were considered. There is no consensus on the sample size used in Delphi methodology, however, the chosen sample size for both the Delphi exercise and the consensus group is based upon previous Delphi studies (39, 40). Given the complexity of the topic, it was however considered that approximately 80 participants would be necessary for the Delphi exercise. In addition, approximately 25 participants would be approached for consensus meeting. A good representation from the key stakeholders (patients/ caregivers (54%), and healthcare professionals (46%) was considered which is generally regarded as good practice in terms of a COS being generalizable to future patients and in convincing other stakeholders of its value.

2.5 Ethical approval

Ethical approval for the study was granted by the UK National Research Ethics Service (NRES) West Midlands –South Birmingham Research Ethics Committee (Reference number 17-WM-0111).

Design and delivery of the Delphi Survey

The Delphi process was conducted in line with COMET recommendations (41). Participants' opinions were sought through two sequential rounds, with feedback from round 1 being provided anonymously to all participants prior to them completing round 2 (39). The Delphi was administered via an online survey (*Delphi Manager* Version 4.0, University of Liverpool, UK). Participants were asked to prioritize each outcome for inclusion in clinical trials of NIU-PS based on their level of importance using a nine-point Likert scale from 1 (no importance) to 9 (critically important). If a participant did not wish to complete the survey electronically, then a paper copy was provided; if participants had visual impairment, then the survey could be completed with assistance either via accessibility software (such as a 'screen reader') or from a cargiver or other individual who would read and record the responses without influencing them.

Delphi Rounds

Two Delphi rounds were conducted with all the stakeholder groups.

- **Delphi Round 1:**

Participants were asked to identify the stakeholder group that they belonged to and relevant additional features such as duration of uveitis (patients only); duration of caring for someone with uveitis (caregivers only); and country of work, duration of experience in ophthalmology and uveitis (healthcare professionals and policy-makers/commissioners).

Participants were presented with a list of outcomes and were asked to rate the importance of each for inclusion in clinical trials for NIU-PS based on the nine-point Likert scale (1 = no importance; 9 = critically important). Participants were then also invited to answer the following questions in free text: (1) "Do you think there are any other outcomes relating to posterior segment involving uveitis that should be measured in research studies" and (2) "Any other comments?".

All new listed additional outcomes were reviewed by two researchers (MOT, PIM) with a view to including in round 2 provided that they represented new outcomes. New outcomes were organized under appropriate existing outcome domains. All item scores in round 1 were summarized and retained for round 2.

- **Delphi Round 2:**

All participants from round 1 were invited to participate in round 2. All outcomes were again presented (including new outcomes from round 1) but accompanied by the results from round 1 including the number of responses and distributions of scores for each outcome, presented for both their own stakeholder and other stakeholder groups. Participants were asked to review their score and either keep it or amend if they wished to do.

2.6 Analysis of Delphi exercise

A statistical analysis using SPSS software 26 (IBM Corporation, Armonk, N.Y., USA) was conducted calculating total number of registrations; total number of participants in each stakeholder group; the response rate in each of the stakeholder groups and the proportion of respondents rating each outcome on the nine-point Likert scale. Partially completed questionnaires were excluded from the analysis process.

At the end of round 2, responses were analyzed to determine whether each outcome should be included in the final COS. The 9-point Likert scoring system where outcomes are graded in accordance to their level of importance is a common method used in COS. Typically, 1 to 3 signifies an outcome is of limited importance, 4 to 6 important but not critical, and 7 to 9 critical (20, 42)This framework is recommended by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group for assessing the level of importance about research evidence and has been widely adopted in other core outcome development research groups using Delphi methods (43).

All outcomes defined as ‘consensus in’ (an outcome was scored 7-9 by more than 70% of participants) were accepted and all outcomes defined as ‘consensus out’ (an outcome scored 1-3 by

more than 70% of participants) were rejected. If discrepancy was noted among stakeholder groups about importance of outcome; further discussion was held at the consensus meeting. Attrition level following the closure of round 2 was assessed. Data analysis was summarized by the stakeholder group.

Phase 3: Consensus meeting

The consensus process concluded with a face-to-face meeting of key stakeholders and the research team. The meeting was led by an independent facilitator whose role was to lead, promote and mediate the discussion among the key stakeholders. Purposive sampling was used to ensure that there was appropriate balance of representation of the different stakeholder groups (patients, caregivers, ophthalmologists, nurse practitioners, health policy-makers and commissioners).

A list of outcomes were sent to all participants in advance of the meeting to make them aware of outcomes to be discussed in the meeting and enable them think independently what sort of outcomes they feel important to be included in the COS. The meeting included a summary of the work to date, discussion and voting on outcomes that have not achieved consensus through the Delphi exercise. The meeting then considered the outcomes as follows: (1) outcomes scored critically important (7-9) by over 90% of both patients/caregivers and professionals; (2) outcomes scored highly important (7-9) by over 70% overall, but where there was some disagreement between patients/caregivers and healthcare professionals (i.e. less than 60% of either patients/caregivers or professionals rated it critically important (7-9); (3) discussion and voting on outcomes that have some degree of disagreement considering whether which of those outcomes should be included in COS when a clear rationale for inclusion is provided; (4) outcomes excluded during the Delphi process, and their rationale for exclusion.

Discussions were taken iteratively among the stakeholder groups before the final voting took place. All participants were asked to vote anonymously on those outcomes using an electronic voting software (Turning Technologies, Youngstown, Ohio, USA) highlighting the importance of each

outcome on a nine-point Likert scale (1 =no importance; 9 = critically important). Outcomes were classified as 'Consensus In' if >70% of whole group voted 7-9 to retain in COS.

After voting was completed, all members including patients, caregivers and health professionals were then asked to ratify the final list of outcomes. Finally, all participants discussed and agreed the final categorization (outcome domains) for these retained outcomes in the final COS.

3. Results

Phase 1: Identification of long list of outcomes and development of survey questionnaire

A long list of items (n=142) was identified through systematic review, focus groups, and interviews. Items were reviewed, refined and amalgamated to form a single comprehensive list of 52 outcomes organized in 11 outcome domains comprising: (1) visual function, (2) symptoms, (3) functional ability, (4) impact on relationships, (5) financial impact, (6) psychological morbidity and emotional well-being (7) psychosocial adjustment to uveitis, (8) doctor/patient/interprofessional relationships and access to health care, (9) treatment burden, (10) treatment side effects, (11) disease control. Each domain was translated to generate a questionnaire item in the Delphi survey.

Phase 2: Prioritization of outcomes

Delphi Round 1:

A total of 116 participants were invited to participate in round 1; of those 80 (69%) responded, and 36 (31%) declined. A total of 33 patient/caregiver participants (41% of the total group) completed round 1 of the survey (28 patients; 5 caregivers). Participants in this group had a median age of 55 years (range 35-75 years); patients reported that they had uveitis for a mean of 14 years (range 5-28); caregivers reported that their duration of care was a mean of 11 years (range 5-25).

A total of 47 health professionals (59% of the total group) completed round 1 of the survey; of those 40 ophthalmologists (85%), 2 nurse practitioners (4%), 5 policy-makers (11%). Fifteen different countries from across the world were represented including: Australia (n=3), Austria (n=1), Belgium (n=1), Brazil (n=1), Canada (n=1), Germany (n=2), India (n=2), Italy (n=2), Japan (n=1), Singapore (n=1), South Africa (n=2), Switzerland (n=2), Tunisia (n=1), United States of America (n=6) and United

Kingdom (n=22). Participants' demographic data for patients, caregivers and health professionals were similar between round 1 and round 2. All members (n=7) of the advisory group completed the Delphi exercise (Round 1 and 2). A more detailed profile on the socio-demographic details are reported in **Error! Reference source not found.**

Delphi Round 2:

A total of 74 participants completed round 2, comprising 26 patients (35%), 5 caregivers (7%), 36 ophthalmologists (49%), 2 nurse practitioner (3%) and 4 policy-makers (6%). Round 2 evaluated all 52 original items and five additional outcomes proposed during round 1 (**Error! Reference source not found.**). Nine outcomes were rated as critically important by over 90% of the participants and were recommended for inclusion in the COS; 33 outcomes were excluded based on the pre-specified thresholds; and 15 items were carried forward for discussion in consensus meeting. Summary of items scores and outcomes decision are reported in **Error! Reference source not found.**.

Phase 3: Consensus meeting

Of the 80 stakeholders who participated in the Delphi exercise, 24 participants attended the face-to-face consensus meeting that was held at the University of Birmingham on 23rd January 2020. These voting participants comprised 9 patients, 4 caregivers, 9 ophthalmologists, 1 nurse practitioner and 1 policy-maker; the ophthalmologists attending included members of the international advisory board (n=4) and represent current NIU-PS practice from around the world [including in Australia, Switzerland, Brazil, Germany and the UK].

The final COS of 16 outcomes was a conclusion of combined agreement across patients/caregivers and health professionals (is shown in **Error! Reference source not found.**. The meeting summarized the following

1. *Ratification of 'consensus in' items:* After review, the consensus group ratified all 9 items that had exceeded 90% of 7-9 scores by both patients/caregivers and professionals during the Delphi exercise.

2. *Discussion and voting of items that exceeded over 70% that had some degree of discordance between stakeholder groups during Delphi exercise:* After discussion the consensus group voted in 7 items from this category for inclusion into the COS. The consensus group advised that a number of items that were voted for inclusion should be incorporated into other items, notably:
    a. The outcome of continuing/maintaining education as a part of the outcome of work-related impact;
    b. The outcome of social and leisure activities as a part of day-to-day usual activities;
    c. The outcome of distortion of vision as part of visual disturbance.
3. *Review of any new items identified during Delphi round 2 or consensus meeting:* no new items were identified for evaluation or inclusion.
4. *Confirmation of 'consensus out' items:* The consensus group confirmed exclusion of all 33 items that had merited 'consensus out' on the prespecified threshold.
5. *Refining descriptions of items:* The consensus group advised a number of refinements including:
    a. The outcome 'retinitis' should be extended to include choroiditis and chorioretinitis in line with recent trial outcome definitions and the similarity of how these conditions would be experienced by a patient.
    b. The outcome 'structural changes' should be extended to include retinal scarring, optic nerve damage (including glaucoma), formation or progression of band keratopathy, formation or progression of epiretinal membrane.
    c. The definition of the outcome 'intraocular pressure' should be extended to include change in the pressure inside the eye above or below the normal range rather than raised intraocular pressure.
6. *Refining relations of items to domains and domain definitions:* The consensus group advised that:

a. The term ‘Health Related Quality of Life (HRQoL)’ was adopted as a domain title to include the following core outcomes: depression and mental well-being; work-/ education-related impact, driving/commuting related impact, and day-to-day usual activities including social and leisure activities.
b. The domain ‘Disease Control’ should include clinical activity, structural changes and flare/relapse/recurrence.
c. The domain ‘visual function’ should include distance vision, near vision and visual disturbance

Discussion

This COS represents the culmination of a five-year program dedicated to discovering and defining the outcomes that are most important to patients with non-infectious NIU-PS, their caregivers and the healthcare professionals who are engaged with their medical care and the policies that support this care. COSs are increasingly recognized as a powerful tool for increasing relevance of studies and maximizing the value of clinical trials, both over the short and long term. In a health area such as uveitis where the number of clinical trials are few (44), there is perhaps an even greater ethical imperative to ensure that results from each trial counts and we measure the most relevant outcomes important to all stakeholders – is a key part of this.

A defining key feature of this first COS for NIU-PS, is the strong representation of different stakeholder groups. Empirically we recognize that there may be a diversity in the value that different stakeholders place on outcomes. We expect that for a patient or caregiver these outcomes are likely to reflect the lived experience of uveitis; for a clinician, the priority outcomes might be the measured visual acuity or the physical signs seen directly or on imaging; and for the policy-maker or commissioner, it may be the longer term functional impact or cost of care. In fact, it was striking that in our study there was relatively good concordance between stakeholder groups, although differences were noted in round 2 of the Delphi exercise. For example, near vision was voted critically important by 93.5% of patients and caregivers while only 58% of healthcare professionals considered this important. A detailed discussion therefore concluded an agreement of inclusion by the vast majority of the key stakeholders. Furthermore, disagreement among the stakeholders was also noted for the item of formation of band keratopathy by which patients/caregivers were guided by the last part of the definition (that cause pain and a reduction in vision) and scored this as critically important (84%) compared to healthcare professionals (67%). However, following a detailed iterative discussion, both patients and caregivers developed a better understanding of the

item and all agreed to exclude this item from the COS and keep it as a part of structural changes outcome.

Although systemic co-morbidities were scored highly by patients/cares (83.9%) and healthcare professionals (90.7%) in Delphi round 2, at the consensus meeting the vast majority of the stakeholders (90%) voted consensus out. This may have an impact on disease progression and could be linked to the uveitis etiology; however, this is not an outcome to be measured for clinical effectiveness of uveitis. A similar scenario was noted with the item "other ocular co-morbidities" that was scored highly by patients/caregivers (83.9%) and health professionals (93.0%) after Delphi round 2. However, when comorbidities were discussed in the consensus meeting the group considered that comorbidities were most relevant as an important parameter to record as an attribute of a patient going into a study (similar to demographic profile) rather than as an outcome. The group recognized that some comorbidities may arise as a consequence of an intervention, but advised that these would be captured by *Treatment Side Effects*. There was therefore consensus not to include comorbidities in the COS**.**

Although this is the first COS for NIU-PS, there have been previous initiatives with relevance to this area. For example, the Multinational Interdisciplinary Working Group for Uveitis in Childhood proposed an outcome set for JIA-associated uveitis (45), that has been registered on COMET database, although it is not explicitly described as a COS (41). This initiative has some similarities to our study in that a long list of items were identified from a literature review, and that this underwent refinement through a Delphi process followed by a consensus meeting. Although of value, we would suggest that it has a number of limitations compared to our study, namely that the participants were all clinical experts without wider stakeholder representation, and there were no qualitative research elements to the study which might have generated outcomes that different stakeholders might deem important. However, it must be acknowledged that this study was conducted over a decade ago, and that even today the COS methodology and the incorporation of other voices (particularly the patient and caregiver) is still a relatively new phenomenon.

In this regard it is worth noting that the key Standardization of Uveitis Nomenclature (SUN) classification system was also based on clinical experts alone, however the lack of patient voice is less problematic here since SUN did not aim to be a comprehensive list of outcomes but rather an agreed set of definitions and its scope primarily covers the clinician's assessment of inflammatory activity within the eye (the SUN grading systems) (46).

Another strength was the study employed widely used consensus methods using a diverse sample including patients, caregivers, healthcare professionals and policy-makers from varied socio-demographic and clinical backgrounds. Furthermore, healthcare professional stakeholders were recruited from a wide geographical area including UK and other international countries. A robust consensus process therefore was achieved with a broad range of the key stakeholder representatives. Participants were actively involved in the consensus meeting discussion and the voting process.

There are some limitations to our study. We recognize that one could extend the systematic review stage of the study to include other types of studies of NIU-PS (including non-interventional), however our review focused on those studies where there is most intense research within uveitis, and where the adoption of a COS is likely to have maximal impact. Additionally, the qualitative stage within the COS process provided an opportunity for any outcomes not captured by the Systematic Review stage to be added.

Participation in this study was voluntary, and therefore represents the views of those who were willing to engage with research. This may result in bias due to under-representation of certain groups. For patients and caregivers we tried to address this by undertaking purposive sampling with respect to age, ethnicity and gender. We did not undertake purposive sampling for all under-represented groups (e.g. higher levels of social deprivation). Focus groups were continued until no new insights emerged for discussion at the final focus group and no new outcomes or relevant concepts were being identified with further data collection i.e. a point of code saturation had been reached. We therefore believe that our domain structure provides a comprehensive picture of the

issues of importance to patients and their care givers and healthcare professionals. Although the clinical experts were gathered from the international community, patients and caregivers were only recruited from the UK. Since this is a single state-funded health care system it is possible that this might limit the wider generalizability of the results. On the other hand, the ophthalmologists engaged throughout the whole process of the COS development are a good representation of the international community from all types of health systems; early subgroup analysis suggested no difference between UK and international ophthalmologists. Although we have used a standard and recommended approach by COMET initiatives for gaining consensus, we also recognize that the results may be skewed by the mix of participant stakeholders. Therefore, we tried to balance levels of stakeholders across the whole consensus process to avoid one group being over-represented. We emphasize that results were consistent across stakeholders. Furthermore, running a heterogeneous consensus group meeting among all stakeholders is becoming more widely used in COS methodology, thus generalizability of results is improved based on the overall agreement rather than by specific stakeholder group (47, 48).

Implementation is critical to realizing the potential of a COS. This depends on a number of factors, including feasibility, methods of measurement and adoption. The COS provides standardization about 'what' to measure but not 'how' or 'when' to measure. The 'how' and 'when' to measure are usually a later stage in the process which is usually determined through a similar consensus process; this will form the next phase of work. In terms of feasibility, a COS will only be widely adopted if the burden of measurement is considered acceptable by all users, both patients and trial staff. In terms of methods of measurement, it is a limitation of many COS – ours included – that outcomes may be identified as important for which no reliable measure exists, or at least for which there is no agreed measure. Our COS includes 16 outcomes, many of which are routinely measured during clinical trials either as stand-alone clinical measures or investigations, or as part of a quality of life/visual function assessment such as the National Eye Institute Visual Function Questionnaire – 25 Item (NEI-VFQ25) questionnaire (49).

In our COS, most outcomes identified do have a standard method of measurement, but these measures are often imperfect, for example our subjective measures of inflammation based on clinician-estimate (46, 50) or the widespread use of the NEI-VFQ25 as a way to evaluate a number of the HRQoL elements, despite the limitations of that questionnaire (51). Additionally, there are some outcomes identified in our COS for which there is no agreement on the best way of measurement (for example the measurement of near vision), and our COS does not resolve this issue. It is however recognized that identification of unmet measurement needs is one of the values of COS development and can be used to focus new research efforts on such areas.

In terms of adoption, any COS depends on the relevant community recognizing its value and committing to incorporate into their trial design and reporting. It helps that the advantages of COS are becoming more widely recognized, and indeed within ophthalmology, no COS has so far been used in clinical trials for non-infectious uveitis of the posterior Segment. It is not clear, however, the extent to which these COS have been adopted in areas with significant trial activity. In part this may be for reasons of feasibility (overly burdensome numbers of outcomes) or availability of agreed measurement methods, but in some cases it may also be a lack of engagement with the expert community and a failure to communicate the value and importance of COS adoption
Building a COS is an investment by the community. This has been five years in the making and the participation of the international community and active engagement of all groups of stakeholders has been critical. For it to benefit patients we, as a community, now need to implement and start using it. It will however be a vital part of our next steps to communicate the COS more widely, and to provide resources that help the community adopt and implement it as a universal standard.

Conclusion

To our knowledge, this is the first published work worldwide that focused on developing a COS for NIU-PS clinical trials. The consensus process representing patients, caregivers and healthcare professionals identified a list of 16 outcomes of sufficient importance to be included in the COS, and

thereby recommended for measurement in all future studies of NIU-PS. The COS is not restrictive since other data can be collected and does not constitute a single composite outcome measure but rather ensures that certain key outcomes are always collected in a standardized way. The development of a COS for NIU-PS provides for the first time a standardized set of outcomes that has value to all stakeholders (patients, caregivers, ophthalmologists, nurse practitioners, health policy-makers and commissioners) maximizing the value of each clinical trial since key outcomes are measured and reported in all relevant trials; ensuring that outcomes measured include those that are most important to each group of stakeholders, rather than just to one group. The adoption of the COS would lead to a richer, more consistent collection and reporting of data across clinical studies in NIU-PS. It is suitable across all settings regardless of whether the primary area of interest is reduction in flares of disease, long-term medication reduction, quality of life or some other aspect of the condition. By collecting the COS alongside the primary outcome of interest, it means that a study that was designed to address one outcome (e.g. effectiveness in reduction of flares defined by vitreous haze) can still contribute to evidence synthesis related to other outcomes (e.g. treatment side effects) due to their collection within the COS. The use of COS also helps to reduce outcome-selection bias and outcome-reporting bias since the whole COS is measured and reported, improving evidence synthesis and meta-analysis (20, 30). The next step will be to determine and validate the optimal measurement tool for each included outcome in the COS. COS will move us towards greater consistency in outcome measurement for clinical trials in NIU-PS, and advance the care of patients with this sight-threatening disease.

Abbreviations

BMEC	Birmingham and Midland Eye Centre
BUS	Birdshot Uveitis Society
CINAHL	Cumulative Index to Nursing and Allied Health Literature.
COMET	Core Outcome Measurement in Effectiveness Trials
COS	Core Outcome Set

COSUMO	Core Outcome Set in patients with posterior segment involving uveitis with and without Uveitic Macular Oedema
CPROR	Centre for Patient Reported Outcome Research
Embase	Excerpta Medica database
HRQoL	Health-Related Quality of Life
IRAS	Integrated Research Application System.
MEDLINE	Medical Literature analysis and Retrieval System Online
NIU-PS	Non-infectious uveitis of the posterior segment
PInGU	Patient Involvement Group in Uveitis
UIG	Uveitis Information Group
UME	Uveitic Macular Edema
RCT	Randomized Controlled Trials

Ethical approval

Ethical approval for the study has been granted by the National Research Ethics Service (NRES) West Midlands –South Birmingham Research Ethics Committee (Reference number 17-WM-0111).

Competing interests

All named authors declare that they have no competing interests relating to this manuscript. MC receives funding from the National Institute for Health Research (NIHR) Birmingham Biomedical Research Centre, the NIHR Surgical Reconstruction and Microbiology Research Centre and NIHR ARC West Midlands at the at the University of Birmingham and University Hospitals Birmingham NHS Foundation Trust, Health Data Research UK, Innovate UK (part of UK Research and Innovation), Macmillan Cancer Support, UCB Pharma . MC has received personal fees from Astellas, Takeda, Merck, Daiichi Sankyo, Glaukos, GSK and the Patient-Centered Outcomes Research Institute (PCORI) outside the submitted work.

Authors' contributions

All authors contributed to the study design. MOT is the clinical research fellow and he is involved in all stages of the study design, data collection, and analysis of the focus group discussions and interviews. MOT led the first draft of the manuscript. MOT organized and conducted the Delphi exercise with supervision from AKD, PIM, and MJC. MOT conducted the focus group discussions with facilitation from JMM. MOT ran the telephone interviews. MOT, JMM, PIM and AKD were involved in identifying the list of outcomes and outcome domains and established definitions of outcomes and outcome domains. MOT, PM and AKD led the participant recruitment process. MOT analyzed the Delphi exercise. MOT chaired the consensus meeting and Sara Brookes facilitated the consensus meeting. All authors have read and approved the final manuscript.

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COSUMO Working Group

The COSUMO Working Group comprises the International uveitis Advisory Board and additional consensus group members.

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Prof Manfred Zierhut	Department of Ophthalmology, University of Tuebingen, Germany
Prof Marc D. de Smet	Leiden University, the Netherlands; MIOS, Lausanne, Switzerland

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625 *Additional consensus group members of the COSUMO Working Group*

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Mrs Gaynor M Hollis	Patient, UK
Mr Graham Roberts	Patient, UK
Mrs Joanna Emerson	Patient, UK
Mr Joseph Quigley	Patient, UK
Miss Katie Cave	Patient, UK
Mr Kenneth Twigge	Patient, UK
Miss Maxine McCarthy	Patient, Olivia's Vision, UK
Ms Ruth Davis	Patient, UK
Mrs Eileen Twigge	Caregiver, UK
Mrs Helen Roberts	Caregiver, UK
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Figure 1: Flow diagram illustrating the three-phase approach used to develop the core outcome set (COS) for non-infectious uveitis of the posterior segment (NIU-PS)

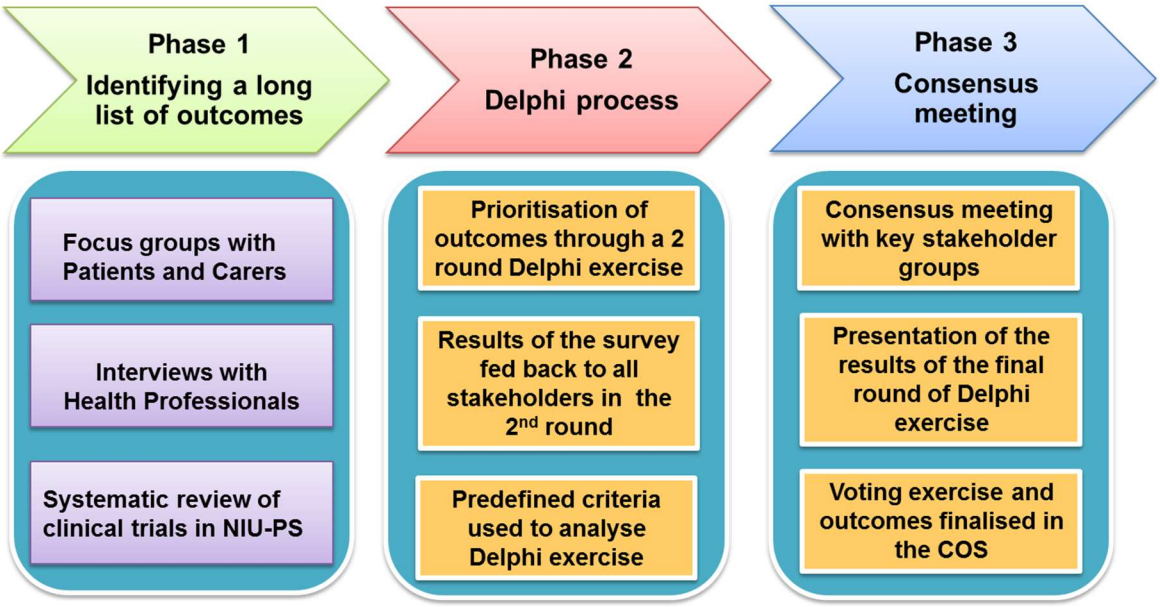
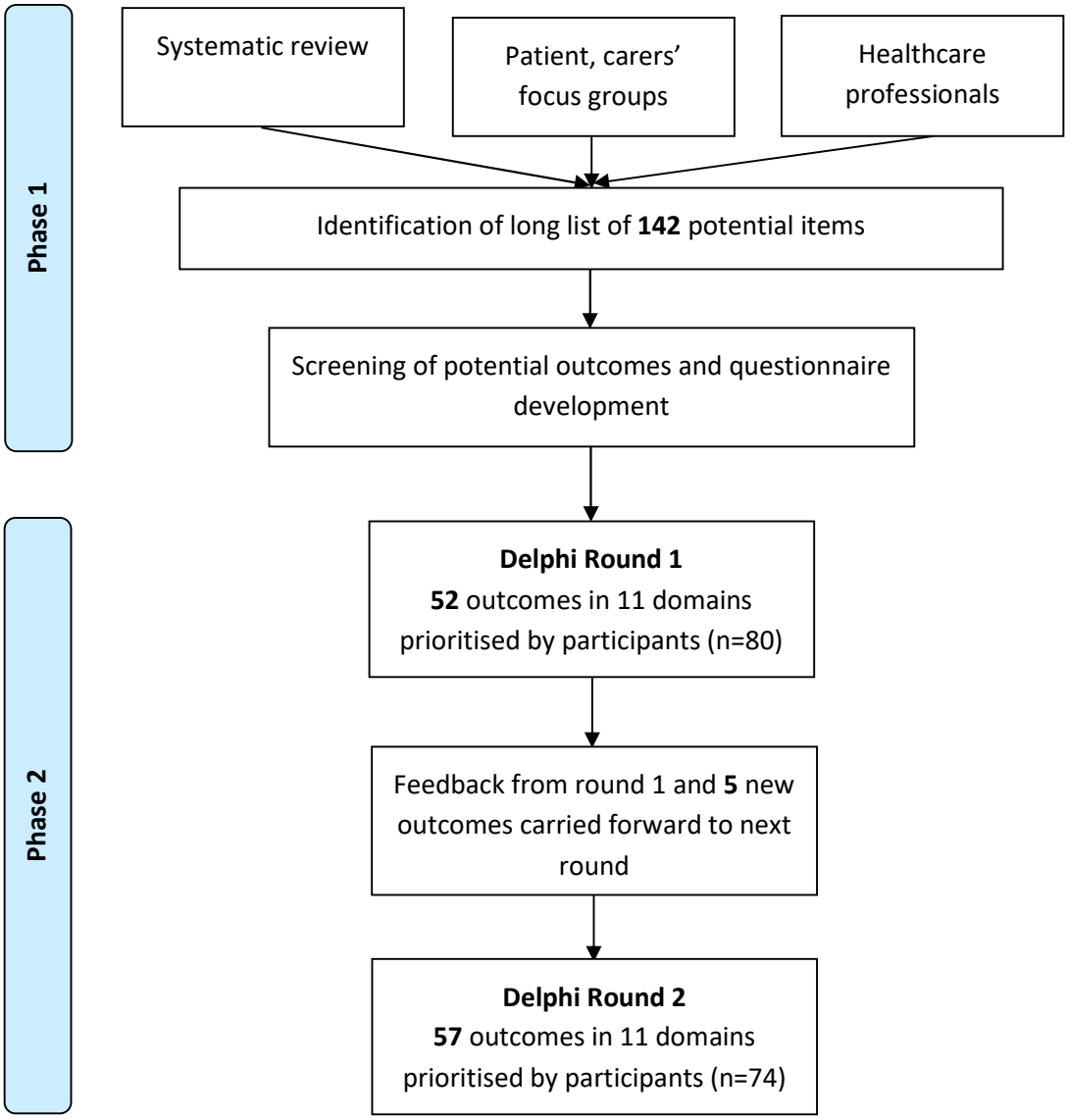


Figure 2: Summary of development of a Core Outcome Set for Effectiveness and Efficacy Trials in non-infectious uveitis of the posterior segment (NIU-PS)



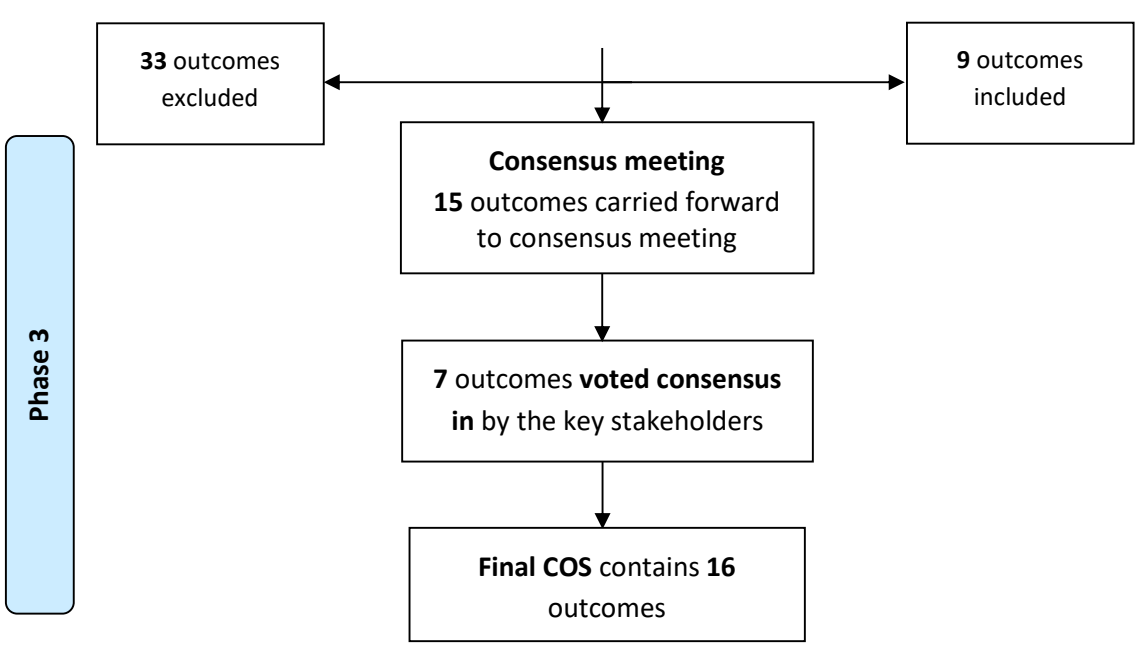


Table 1: Demographics characteristics of participants in the Delphi survey

Patients and carers		Healthcare professionals	
Gender	**n (%)**	**Gender**	**n (%)**
Male	9 (27%)	Male	28 (60%)
Female	24 (73%)	Female	19 (40%)
Age		**Age**	
18-24 years	-	18-24 years	-
25-34 years	-	25-34 years	2
35-44 years	1	35-44 years	19
45-54 years	22	45-54 years	25
55-64 years	9	55-64 years	2
65-74 years	1	65-74 years	-
Duration of uveitis for patient		**Length of experience in uveitis**	
Less than 5 years	2	Less than 5 years	4
5-10 years	8	5-10 years	2
11-15 years	7	11-15 years	10
16-20 years	4	16-20 years	11
More than 20 years	12	More than 20 years	20
Duration of being a carer		**Job role**	
Less than 5 years	-	Ophthalmologist	40
5-10 years	2	Nurse practitioner	2
11-15 years	1	Policy maker/commissioner	5

16-20 years	1
More than 20 years	1
Role	
Patient	28
Carer	5

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673 **Table 2: Importance of outcome as indicated by percentage of stakeholder group rating the**
674 **outcome as 'critically important' (7 to 9) during the Delphi process (round 2) and the consensus**
675 **meeting**

Outcomes	Percentage Scoring Outcome as 7-9			Items (In or carried forward to consensus meeting)	Consensus meeting voted in or incorporated into other item
	Patients/carers (n=33)	HCPs (n=74)	All participants (n=107)		
Distance vision	96.8%	93.0%	94.6%	Yes	In
Near vision	93.5%	58.1%	73.0%	Yes	In
Distortion of vision	87.1%	88.4%	87.8%	Yes	Part of visual disturbance
Visual disturbance	90.3%	86.0%	87.8%	Yes	In
Color vision	48.4%%	20.9%	32.4%	No	-
Contrast sensitivity	74.2%	23.3%	44.6%	No	-
Depth perception	71.0%	4.7%	32.4%	No	-
Peripheral vision	80.6%	55.8%	59.5%	No	-
Fatigue	61.3%	20.9%	37.8%	No	-
Floaters	54.8%	79.1%	68.9%	No	-
Headache	74.2%	30.2%	48.6%	No	-
Photosensitivity	83.9%	39.5%	58.1%	No	-
Redness	48.4%	18.6%	31.1%	No	-
An uncomfortable or painful eye/s	74.2%	48.8%	59.5%	No	-
Watery eye	48.4%	7.0%	24.3%	No	-
Day to day usual activities	90.3%	88.4%	89.2%	Yes	In
Driving/commuting	96.8%	86.0%	90.5%	Yes	In
Education related impact	67.7%	76.7%	73.0%	Yes	Part of work related impact
Social and Leisure activities	74.2%	74.4%	74.3%	Yes	Out
Work related impact	93.5%	90.7%	91.9%	Yes	In

Financial impact due to early retirement; the need to take a part-time job or redundancy	74.2%	69.8%	71.6%	No	-
Financial impact of treatments	67.7%	74.4%	71.6%	No	-
Desire to have children; able to conceive and lactate	54.8%	55.8%	55.4%	No	-
Relationships with family and/or friends	71.0%	41.9%	54.1%	No	-
Depression and mental illness	77.4%	79.1%	78.4%	Yes	In
Frustration and Anger	74.2%	37.2%	52.7%	No	-
Stress	74.2%	62.8%	67.6%	No	-
Anxiety	67.7%	67.4%	67.6%	No	-
Access to uveitis clinic and/ facilities	80.6%	74.4%	77.0%	No	-
Access to counselling and psychotherapy services	51.6%	27.9%	37.8%	No	-
Access to physical aids and other resources	61.3%	25.6%	40.5%	No	-
Doctors-patient relationship/communication	83.9%	46.5%	62.2%	No	-
Inter-professional relationships	61.3%	39.5%	48.6%	No	-
Shared decision-making	67.7%	53.5%	59.5%	No	-
Overall wellbeing	64.5%	67.4%	66.2%	No	-
Coping	64.5%	37.2%	48.6%	No	-
Identity	51.6%	32.6%	40.5%	No	-
Normality	54.8%	37.2%	44.6%	No	-
Overall psychosocial adjustment	61.3%	41.9%	50.0%	No	-
Sense of self	64.5%	34.9%	47.3%	No	-
Adherence	67.7%	95.3%	83.8%	No	-
Amount of medications	61.3%	86.0%	75.7%	No	-
Number of hospital visits	45.2%	79.1%	64.9%	No	-
Treatment side effects	96.8%	97.7%	97.3%	Yes	In
Formation of band keratopathy	83.9%	67.4%	74.3%	Yes	Part of structural changes
Formation of Epiretinal membrane	90.3%	72.1%	79.7%	Yes	
Systemic co-morbidities	83.9%	90.7%	87.8%	Yes	Out
Anterior segment inflammation	87.1%	97.7%	93.2%	Yes	In
Cataract	80.6%	88.4%	85.1%	Yes	Out
Flare/relapse/ recurrence	100.0%	97.7%	98.6%	Yes	In
Other ocular co-morbidities	83.9%	93.0%	89.2%	Yes	Out
Raised intraocular pressure	83.9%	95.3%	90.5%	Yes	In
Retinal vasculitis	96.8%	100.0%	98.6%	Yes	In
Retinitis	96.8%	100.0%	98.6%	Yes	In
Structural changes	93.5%	97.7%	95.9%	Yes	In
Uveitic macular edema	93.5%	100.0%	97.3%	Yes	In
Vitreous inflammation/haze	96.8%	100.0%	98.6%	Yes	In

Table 3: Final Core Outcome Set (COS) for clinical trials in non-infectious uveitis of the posterior segment (NIU-PS)

Outcome	Definition
Issues relating to visual function	
Distance vision	*A person's ability to see objects/people clearly from distance (beyond arm's length) (e.g. road signs, TV, cinema)*
Near vision	*A person's ability to see near objects (e.g. reading, seeing prices on a menu, seeing phone numbers and other close-up tasks)*
Visual disturbance	*A person complains of seeing blurred, hazy, foggy, grainy vision, double vision, flashing/shimmering lights or that straight lines may appear bent, crooked or wavy*
Issues relating to Health related Quality of Life (HRQoL)	
Work/education related impact	*A person's performance and ability to maintain or continue work/employment or education*
Driving/commuting related impact	*A person's ability to maintain or continue driving a vehicle or commuting for example bicycle, train, bus, tram*
Day to day usual activities related impact	*A person's ability to maintain and continue engagement in day-to-day activities (e.g. care for own self, shaving beard, washing face, gardening, shopping, cooking and doing the washing etc.) including social and leisure activities*
Depression and mental wellbeing	*Feelings of severe sadness or feeling depressed with loss of interest or lack of enjoyment.*
Issues relating to treatment side effects	
Treatment side effects	*Describes undesired or unintended treatment effects that patients may experience*
Issues relating to disease control	
Anterior segment inflammation	*Inflammation in the front of the eye between the cornea and the iris*

Vitreous inflammation/haze	*Inflammation/haze/cloudiness of vitreous jelly located between the lens and the retina*
Retinal vasculitis	*Inflammation of the blood vessels of the retina (the light sensitive layer at the back of the eye)*
Retinitis/choroiditis/ chorioretinitis	*Inflammation of the retina and/or choroid layers (the light sensitive layer and the supporting blood vessel layer at the back of the eye)*
Flare/relapse/recurrence	*Recurrence or increase of inflammation in the front or back of the eye that may be associated with effects on vision*
Intraocular pressure	*Change in the pressure inside the eye above or below the normal range and if left untreated may permanently damage the sight*
Uveitic macular edema	*Fluid that builds up in the central part of the retina causing swelling of the macula. The macula is responsible for detailed central vision*
Structural changes	*Changes to the structure of the eye including:* *retinal scarring,* *optic nerve damage (including glaucoma),* *formation or progression of band keratopathy - white, chalky deposits on the surface of the cornea (the 'window' of the eye) that may cause pain and a reduction in vision,* *formation or progression of epiretinal membrane – a thin layer of scar tissue that forms on the surface of the retina usually at the macula (the sensitive central part of the retina) that may reduce vision*

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