

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

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27 **Abstract**

28 **Purpose**

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

31 **Design**

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

34 **Participants**

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

38 **Methods**

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

45 **Main outcome measure**

46 Items recommended for inclusion in the COS for NIU-PS

47 **Results**

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

51 16 outcomes organized into 4 outcome domains comprising visual function, Health Related Quality of
52 Life (HRQoL), treatment side effects and disease control.

53 **Conclusion**

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

61 **Trial Registration**

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

63 **Key words**

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

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67 **Precis**

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

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78 **1. Background**

79 Uveitis describes a group of diseases characterized by intraocular inflammation (1-6), responsible for
80 10–15% of total blindness in Europe and North America (7) and up to 25% of blindness in the
81 developing world (1-5, 7). Intermediate, posterior and panuveitis are the most sight-threatening
82 forms of uveitis that often share a number of common features including their higher risk of sight-
83 threatening complications (e.g. uveitic macular edema, UME) and their requirement for systemic or
84 local injection-based therapy. Those forms affect the more posterior structures of the eye and are
85 often grouped together as non-infectious uveitis of the posterior segment (NIU-PS) (8, 9). Uveitis
86 may be due to (a) an infectious agent or (b) non-infectious inflammation, either as a part of an
87 underlying systemic disease or purely confined to the eye (10). Non-infectious uveitis is the most
88 common type observed (11) and is the focus of this study.

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

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

104 outcomes for use in clinical trials for a specific health condition using a systematic, standardized
105 approach for outcomes selection and reporting. COS are not restrictive since other outcomes can be
106 collected in addition to the COS, but rather this approach ensures that certain key outcomes are
107 always collected in a standardized way, reducing reporting bias and facilitating study comparison
108 and meta-analysis (19, 20). COS methodology is designed to ensure that the views of all key
109 stakeholders are elicited for consideration during COS development to ensure that the final COS
110 includes outcomes that matter to patients, clinicians and policy-makers/commissioners (20).
111 To date COSs have been developed for a number of areas in ophthalmology including dry eyes (21),
112 cataract (22), macular degeneration (23), glaucoma (24), thyroid eye disease (25), strabismus and
113 ocular motility disorders (26), with ongoing work in cerebral visual impairment (27) and Behcet's
114 syndrome (28).
115 The development of a COS for NIU-PS has the potential to profoundly enhance the value of trials in
116 this condition, through avoiding inappropriate outcome measures and providing the standardization
117 needed to enable comparison and meta-analysis of outcomes across trials (even where they may
118 have selected different primary outcomes) (20, 29). In this study we aimed to develop a COS for NIU-
119 PS according to robust methodology that represents the priorities of all groups of stakeholders and
120 supported by international consensus, with a view to supporting the uveitis community to enhance
121 research pertinence and provide long-term value for every future clinical trial into this sight-
122 threatening condition (30).

123 **2. Methods**

124 **2.1 Study design**

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

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

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

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

138 A systematic review was conducted on the effectiveness of pharmacological agents for NIU-PS
139 (including NIU-PS with UME) to identify candidate outcomes for inclusion in the core outcome set
140 (32, 33).

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

151 ***B) Outcomes identified through qualitative research with key stakeholders***

152 • **Focus groups**

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

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159 • **Telephone interviews**

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

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

172 **Compiling the 'long list' for evaluation**

173 The outcomes identified through the systematic review and qualitative research were aggregated
174 and evaluated by two researchers (MOT and JMM) for removal of any duplicates, and refinement to
175 ensure their meanings were clear, with any disagreement being adjudicated by (PIM and AD).

176 Outcomes were then grouped into broader *outcome domains*. For example, the domain '*Functional
177 ability*' was created to group the following items: work/employment, educational participation;
178 driving; activities of daily living and self-care; participation in social and leisure activities (37).

179 All outcome domains were then converted into questionnaire items which asked participants to rate
180 the importance of including each outcome in future research trials. To ensure the questionnaire was
181 easy to read and understood by all stakeholder groups, definitions of outcomes including the type of
182 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)

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

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

218 *Healthcare professional participants:*

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

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

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

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

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

247 **2.4 Sampling of participants and sample size**

248 We attempted to achieve a diverse sample with purposive criteria including patients of varying age,
249 ethnicity and gender; with and without UME; with active and inactive disease: and with uveitis of
250 different etiologies. For healthcare professionals, level of experience in ophthalmology/ uveitis and
251 geographical area of work were considered. There is no consensus on the sample size used in Delphi
252 methodology, however, the chosen sample size for both the Delphi exercise and the consensus
253 group is based upon previous Delphi studies (39, 40). Given the complexity of the topic, it was
254 however considered that approximately 80 participants would be necessary for the Delphi exercise.
255 In addition, approximately 25 participants would be approached for consensus meeting. A good
256 representation from the key stakeholders (patients/ caregivers (54%), and healthcare professionals
257 (46%) was considered which is generally regarded as good practice in terms of a COS being
258 generalizable to future patients and in convincing other stakeholders of its value.

259 **2.5 Ethical approval**

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

262 **Design and delivery of the Delphi Survey**

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

273 **Delphi Rounds**

274 Two Delphi rounds were conducted with all the stakeholder groups.

- 275 • **Delphi Round 1:**

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

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

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

289 • **Delphi Round 2:**

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

295 **2.6 Analysis of Delphi exercise**

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

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

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

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

315 **Phase 3: Consensus meeting**

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

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

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

336 outcome on a nine-point Likert scale (1 =no importance; 9 = critically important). Outcomes were
337 classified as 'Consensus In' if >70% of whole group voted 7-9 to retain in COS.
338 After voting was completed, all members including patients, caregivers and health professionals
339 were then asked to ratify the final list of outcomes. Finally, all participants discussed and agreed the
340 final categorization (outcome domains) for these retained outcomes in the final COS.

341 **3. Results**

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

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

350 **Phase 2: Prioritization of outcomes**

351 **Delphi Round 1:**

352 A total of 116 participants were invited to participate in round 1; of those 80 (69%) responded, and
353 36 (31%) declined. A total of 33 patient/caregiver participants (41% of the total group) completed
354 round 1 of the survey (28 patients; 5 caregivers). Participants in this group had a median age of 55
355 years (range 35-75 years); patients reported that they had uveitis for a mean of 14 years (range 5-
356 28); caregivers reported that their duration of care was a mean of 11 years (range 5-25).
357 A total of 47 health professionals (59% of the total group) completed round 1 of the survey; of those
358 40 ophthalmologists (85%), 2 nurse practitioners (4%), 5 policy-makers (11%). Fifteen different
359 countries from across the world were represented including: Australia (n=3), Austria (n=1), Belgium
360 (n=1), Brazil (n=1), Canada (n=1), Germany (n=2), India (n=2), Italy (n=2), Japan (n=1), Singapore
361 (n=1), South Africa (n=2), Switzerland (n=2), Tunisia (n=1), United States of America (n=6) and United

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

366 **Delphi Round 2:**

367 A total of 74 participants completed round 2, comprising 26 patients (35%), 5 caregivers (7%), 36
368 ophthalmologists (49%), 2 nurse practitioner (3%) and 4 policy-makers (6%). Round 2 evaluated all
369 52 original items and five additional outcomes proposed during round 1 (**Error! Reference source
370 not found.**). Nine outcomes were rated as critically important by over 90% of the participants and
371 were recommended for inclusion in the COS; 33 outcomes were excluded based on the pre-specified
372 thresholds; and 15 items were carried forward for discussion in consensus meeting. Summary of
373 items scores and outcomes decision are reported in **Error! Reference source not found..**

374 **Phase 3: Consensus meeting**

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

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

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

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

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

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441 **Discussion**

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

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

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

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

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

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

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

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

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

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

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

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

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

564

565 **Conclusion**

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

569 thereby recommended for measurement in all future studies of NIU-PS. The COS is not restrictive since
570 other data can be collected and does not constitute a single composite outcome measure but rather
571 ensures that certain key outcomes are always collected in a standardized way. The development of a
572 COS for NIU-PS provides for the first time a standardized set of outcomes that has value to all
573 stakeholders (patients, caregivers, ophthalmologists, nurse practitioners, health policy-makers and
574 commissioners) maximizing the value of each clinical trial since key outcomes are measured and
575 reported in all relevant trials; ensuring that outcomes measured include those that are most important
576 to each group of stakeholders, rather than just to one group. The adoption of the COS would lead to
577 a richer, more consistent collection and reporting of data across clinical studies in NIU-PS. It is suitable
578 across all settings regardless of whether the primary area of interest is reduction in flares of disease,
579 long-term medication reduction, quality of life or some other aspect of the condition. By collecting the
580 COS alongside the primary outcome of interest, it means that a study that was designed to address
581 one outcome (e.g. effectiveness in reduction of flares defined by vitreous haze) can still contribute to
582 evidence synthesis related to other outcomes (e.g. treatment side effects) due to their collection
583 within the COS. The use of COS also helps to reduce outcome-selection bias and outcome-reporting
584 bias since the whole COS is measured and reported, improving evidence synthesis and meta-analysis
585 (20, 30). The next step will be to determine and validate the optimal measurement tool for each
586 included outcome in the COS. COS will move us towards greater consistency in outcome measurement
587 for clinical trials in NIU-PS, and advance the care of patients with this sight-threatening disease.

588 **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

589 **Ethical approval**

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

592 **Competing interests**

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

601 **Authors' contributions**

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

611 **Acknowledgements**

612 We would like to thank all patients, caregivers and health care professionals who kindly participated
613 in the study and helped the development of the core outcome set through the Delphi process. We
614 thank Sara Brookes for her role as the independent chair of the consensus meeting. We would also
615 like to thank the UK uveitis charity *Olivia's Vision* for their generous support for the consensus
616 meeting.

617 In addition, we thank the health care professionals, patients and caregivers who attended our
618 consensus meeting and/or contributed as members of the International Advisory Board.

619

620 ***COSUMO Working Group***

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

623 *Uveitis International Advisory Board*

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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
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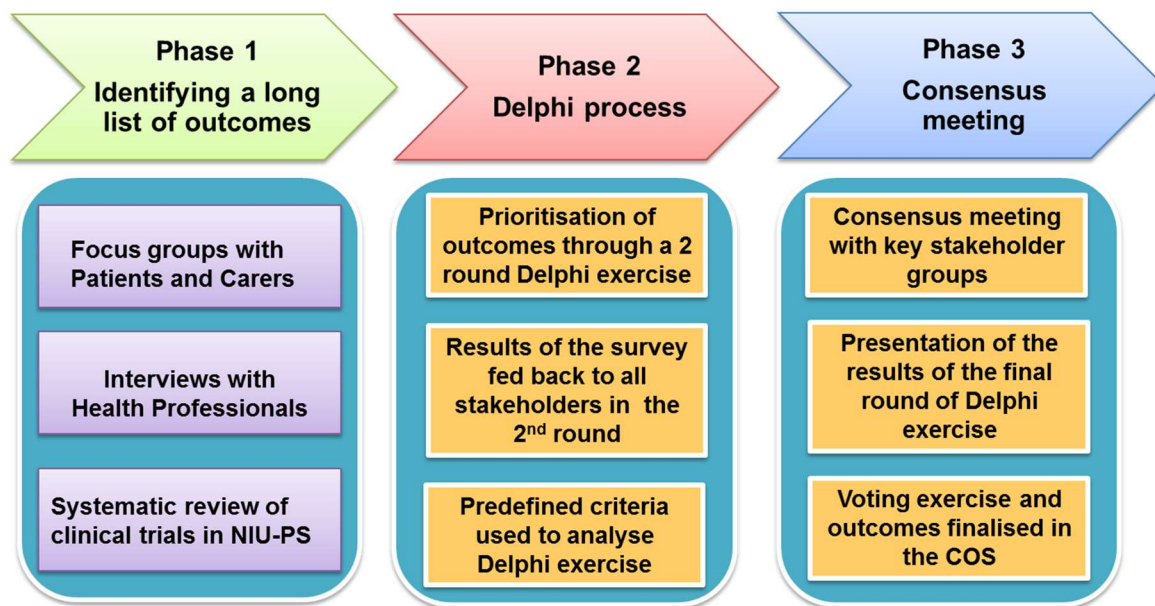
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627 **Funding**

628 This article represents an independent research project funded by the National Institute for Health
629 Research (NIHR) under the Program Clinical Doctoral Research Fellowship Scheme at the University
630 of Birmingham. The views and opinions expressed by authors in this publication are those of the
631 authors and not necessarily those of the NHS, the NIHR or the Department of Health.

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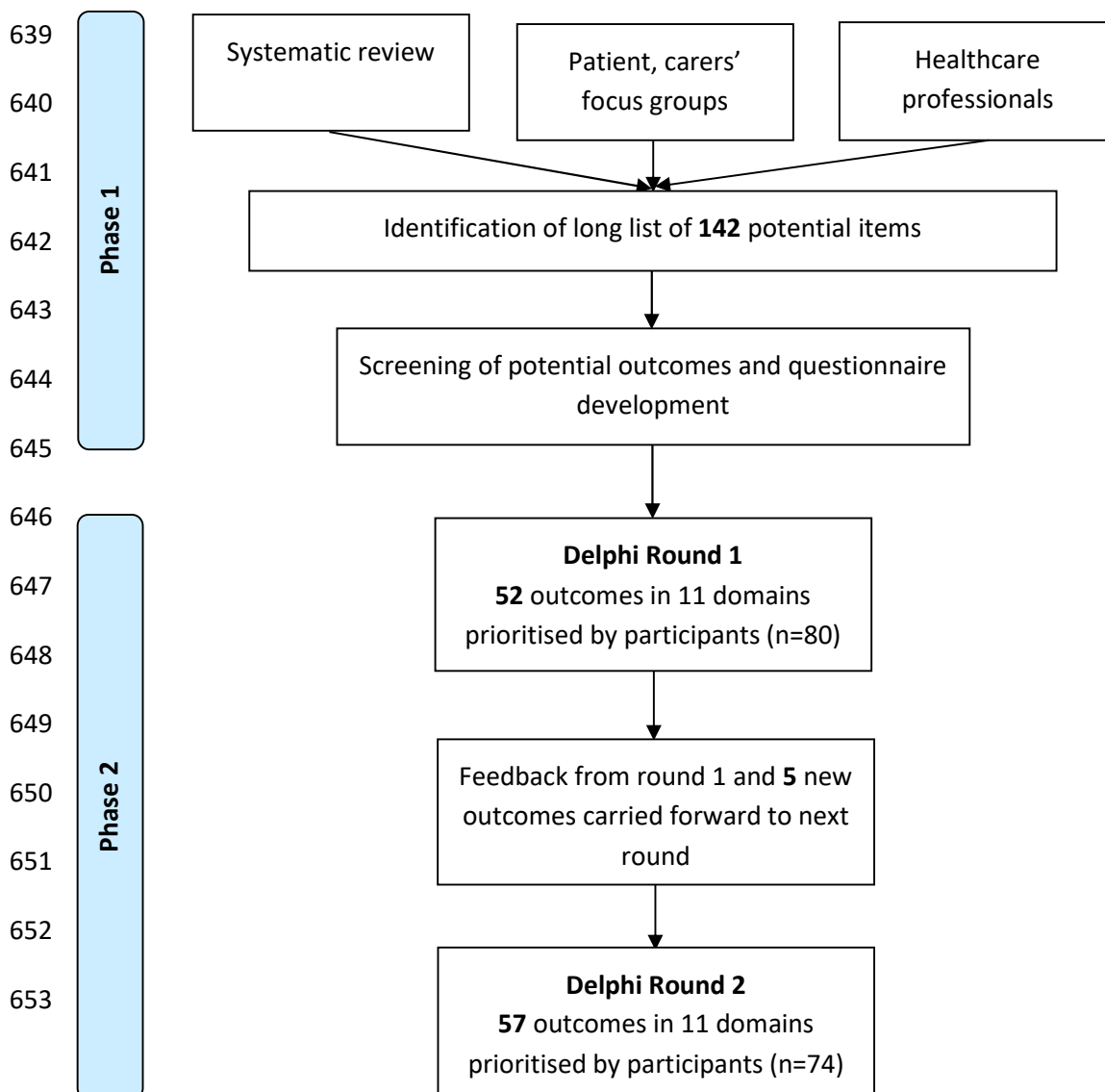
633 **Figure 1: Flow diagram illustrating the three-phase approach used to develop the core outcome**
634 **set (COS) for non-infectious uveitis of the posterior segment (NIU-PS)**



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



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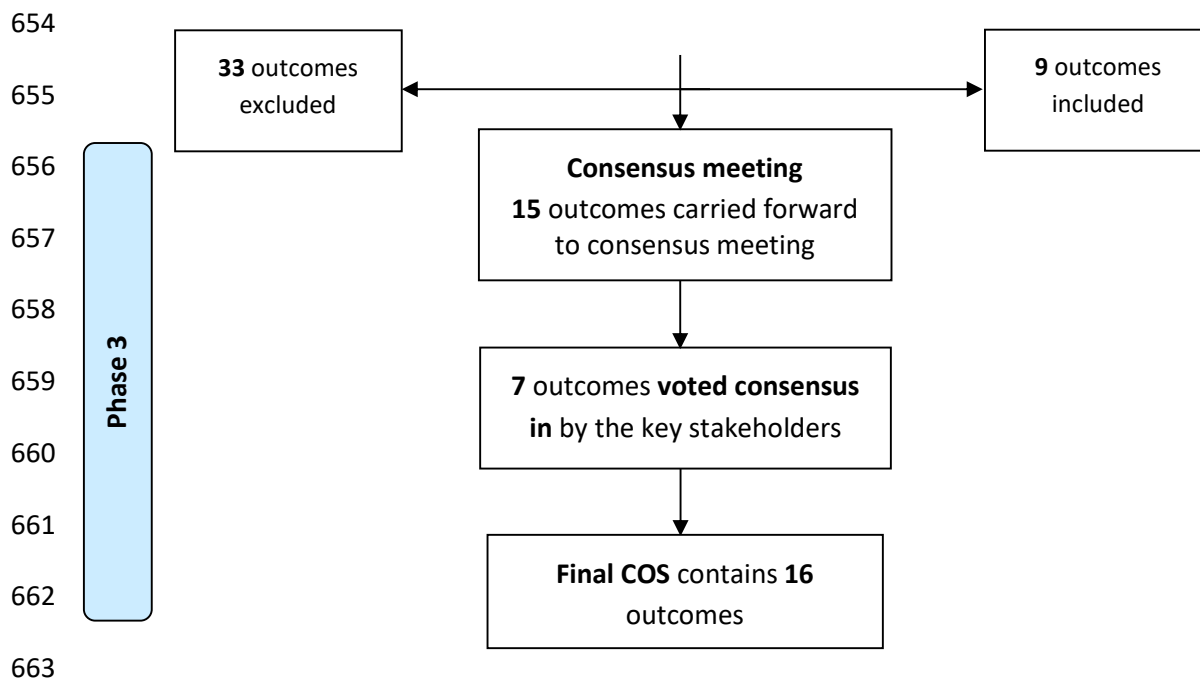
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664 **Table 1: Demographics characteristics of participants in the Delphi survey**

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	Part of structural changes
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

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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	<i>A person's ability to see objects/people clearly from distance (beyond arm's length) (e.g. road signs, TV, cinema)</i>
Near vision	<i>A person's ability to see near objects (e.g. reading, seeing prices on a menu, seeing phone numbers and other close-up tasks)</i>
Visual disturbance	<i>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</i>
Issues relating to Health related Quality of Life (HRQoL)	
Work/education related impact	<i>A person's performance and ability to maintain or continue work/employment or education</i>
Driving/commuting related impact	<i>A person's ability to maintain or continue driving a vehicle or commuting for example bicycle, train, bus, tram</i>
Day to day usual activities related impact	<i>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</i>
Depression and mental wellbeing	<i>Feelings of severe sadness or feeling depressed with loss of interest or lack of enjoyment.</i>
Issues relating to treatment side effects	
Treatment side effects	<i>Describes undesired or unintended treatment effects that patients may experience</i>
Issues relating to disease control	
Anterior segment inflammation	<i>Inflammation in the front of the eye between the cornea and the iris</i>

Vitreous inflammation/haze	<i>Inflammation/haze/cloudiness of vitreous jelly located between the lens and the retina</i>
Retinal vasculitis	<i>Inflammation of the blood vessels of the retina (the light sensitive layer at the back of the eye)</i>
Retinitis/choroiditis/ chorioretinitis	<i>Inflammation of the retina and/or choroid layers (the light sensitive layer and the supporting blood vessel layer at the back of the eye)</i>
Flare/relapse/recurrence	<i>Recurrence or increase of inflammation in the front or back of the eye that may be associated with effects on vision</i>
Intraocular pressure	<i>Change in the pressure inside the eye above or below the normal range and if left untreated may permanently damage the sight</i>
Uveitic macular edema	<i>Fluid that builds up in the central part of the retina causing swelling of the macula. The macula is responsible for detailed central vision</i>
Structural changes	<i>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</i>

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706 **References**

707 1. Williams GJ, Brannan S, Forrester JV, Gavin MP, Paterson-Brown SP, Purdie A, Viridi M,
708 Olson JA. The Prevalence of Sight-Threatening Uveitis in Scotland. British journal of ophthalmology.
709 2007;91(1):33-6.

710 2. Gritz DC, Wong IG. Incidence and Prevalence of Uveitis in Northern California: The
711 Northern California Epidemiology of Uveitis Study. Ophthalmology. 2004;111(3):491-500.

712 3. Suhler EB, Lloyd MJ, Choi D, Rosenbaum JT, Austin DF. Incidence and Prevalence of Uveitis
713 in Veterans Affairs Medical Centers of the Pacific Northwest. American journal of ophthalmology.
714 2008;146(6):890-6. e8.

715 4. Rao NA. Uveitis in Developing Countries. Indian journal of ophthalmology. 2013;61(6):253-
716 4.

717 5. de Smet MD, Taylor SR, Bodaghi B, Miserocchi E, Murray PI, Pleyer U, Zierhut M, Barisani-
718 Asenbauer T, LeHoang P, Lightman S. Understanding Uveitis: The Impact of Research on Visual
719 Outcomes. Progress in retinal and eye research. 2011;30(6):452-70.

720 6. Durrani O, Meads C, Murray P. Uveitis: A Potentially Blinding Disease. Ophthalmologica.
721 2004;218(4):223-36.

722 7. Suttorp-Schulten M, Rothova A. The Possible Impact of Uveitis in Blindness: A Literature
723 Survey. The British journal of ophthalmology. 1996;80(9):844.

- 724 8. Mikhail M, Sallam A. Novel Intraocular Therapy in Non-Infectious Uveitis of the Posterior
725 Segment of the Eye. Medical Hypothesis, Discovery and Innovation in Ophthalmology.
726 2013;2(4):113.
- 727 9. Merrill PT, Clark WL, Banker AS, Fardeau C, Franco P, LeHoang P, Ohno S, Rathinam SR, Ali
728 Y, Mudumba S. Efficacy and Safety of Intravitreal Sirolimus for Non-Infectious Uveitis of the Posterior
729 Segment: Results from the Sakura Program. Ophthalmology. 2020.
- 730 10. Nussenblatt RB, Whitcup SM, Palestine A. Uveitis: Fundamentals and Clinical Practice:
731 Mosby Philadelphia; 2004.
- 732 11. Thorne JE, Suhler E, Skup M, Tari S, Macaulay D, Chao J, Ganguli A. Prevalence of
733 Noninfectious Uveitis in the United States: A Claims-Based Analysis. JAMA ophthalmology.
734 2016;134(11):1237-45.
- 735 12. WHO. World Health Organisation- Clinical Trails- Health Topics 2016, Available From:
736 [Http://Www.Who.Int/Topics/Clinical_Trials/En/](http://www.who.int/topics/clinical_trials/en/)- Access Date: 08.02.2020 2016 [
- 737 13. NHS-. Nhs Choices 2015. Available From:[Http://Www.Nhs.Uk/Conditions/Clinical-](http://www.nhs.uk/conditions/clinical-trials/pages/introduction.aspx)
738 [Trials/Pages/Introduction.aspx](http://www.nhs.uk/conditions/clinical-trials/pages/introduction.aspx). Access Date:10.01.2020 [
- 739 14. Clarke M. Standardising Outcomes for Clinical Trials and Systematic Reviews. Trials.
740 2007;8(1):1.
- 741 15. Barry RJ, Denniston AK. Controversies in the Pharmacological Treatment of Uveitis. Current
742 pharmaceutical design. 2015;21(32):4682-7.
- 743 16. Denniston AK, Holland GN, Kidess A, Nussenblatt RB, Okada AA, Rosenbaum JT, Dick AD.
744 Heterogeneity of Primary Outcome Measures Used in Clinical Trials of Treatments for Intermediate,
745 Posterior, and Panuveitis. Orphanet journal of rare diseases. 2015;10(1):97.
- 746 17. Kirkham JJ, Dwan KM, Altman DG, Gamble C, Dodd S, Smyth R, Williamson PR. The Impact
747 of Outcome Reporting Bias in Randomised Controlled Trials on a Cohort of Systematic Reviews. Bmj.
748 2010;340:c365.
- 749 18. Denniston AK, Dick AD. Systemic Therapies for Inflammatory Eye Disease: Past, Present and
750 Future. BMC ophthalmology. 2013;13(1):1.
- 751 19. COMET Initiatives. Defining a Core Outcome Set for Efficacy Trials in Adult Patients with
752 Posterior Segment-Involving Uveitis 2015. Available From: [Http://Www.Comet-](http://www.comet-initiative.org/studies/details/640)
753 [Initiative.Org/Studies/Details/640](http://www.comet-initiative.org/studies/details/640). Access Date: 17.09.2019 2015 [
- 754 20. Williamson PR, Altman DG, Blazeby JM, Clarke M, Devane D, Gargon E, Tugwell P.
755 Developing Core Outcome Sets for Clinical Trials: Issues to Consider. Trials. 2012;13(1):1.
- 756 21. Wang MT, Craig JP. Core Outcome Sets for Clinical Trials in Dry Eye Disease. JAMA
757 ophthalmology. 2018;136(10):1180-1.

- 758 22. Mahmud I, Kelley T, Stowell C, Haripriya A, Boman A, Kossler I, Morlet N, Pershing S,
759 Pesudovs K, Goh PP. A Proposed Minimum Standard Set of Outcome Measures for Cataract Surgery.
760 JAMA ophthalmology. 2015;133(11):1247-52.
- 761 23. Rodrigues IA, Sprinkhuizen SM, Barthelmes D, Blumenkranz M, Cheung G, Haller J,
762 Johnston R, Kim R, Klaver C, McKibbin M. Defining a Minimum Set of Standardized Patient-Centered
763 Outcome Measures for Macular Degeneration. American journal of ophthalmology. 2016;168:1-12.
- 764 24. Ismail R, Azuara-Blanco A, Ramsay CR. Consensus on Outcome Measures for Glaucoma
765 Effectiveness Trials: Results from a Delphi and Nominal Group Technique Approaches. Journal of
766 glaucoma. 2016;25(6):539-46.
- 767 25. Douglas RS, Tsirbas A, Gordon M, Lee D, Khadavi N, Garneau HC, Goldberg RA, Cahill K,
768 Dolman PJ, Elner V. Development of Criteria for Evaluating Clinical Response in Thyroid Eye Disease
769 Using a Modified Delphi Technique. Archives of ophthalmology. 2009;127(9):1155-60.
- 770 26. Al Jabri S, Kirkham J, Rowe FJ. Development of a Core Outcome Set for Amblyopia,
771 Strabismus and Ocular Motility Disorders: A Review to Identify Outcome Measures. BMC
772 ophthalmology. 2019;19(1):47.
- 773 27. COMET. Development of a Core Outcome Set for Clinical Research and Practice in
774 Amblyopia, Strabismus and Ocular Motility Disorders 2016. Available From: [Http://Www.Comet-](http://www.comet-initiative.org/studies/details/900)
775 [Initiative.Org/Studies/Details/900](http://www.comet-initiative.org/studies/details/900). Access Date: 28.03.2020.
- 776 28. Hatemi G, Merkel PA, Hamuryudan V, Boers M, Direskeneli H, Aydin SZ, Yazici H. Outcome
777 Measures Used in Clinical Trials for Behçet Syndrome: A Systematic Review. The Journal of
778 rheumatology. 2014;41(3):599-612.
- 779 29. Ward-Smith P. Developing Core Outcome Sets for Clinical Trials: Issues to Consider.
780 Urologic Nursing. 2014;34(4):204-6.
- 781 30. Kirkham JJ, Boers M, Tugwell P, Clarke M, Williamson PR. Outcome Measures in
782 Rheumatoid Arthritis Randomised Trials over the Last 50 Years. Trials. 2013;14(1):1.
- 783 31. Tallouzi MO, Mathers JM, Moore DJ, Murray PI, Bucknall N, Blazeby JM, Calvert M,
784 Denniston AK. Cosumo: Study Protocol for the Development of a Core Outcome Set for Efficacy and
785 Effectiveness Trials in Posterior Segment-Involving Uveitis. Trials. 2017;18(1):576.
- 786 32. Tallouzi MO, Moore DJ, Barry RJ, Calvert M, Mathers J, Murray PI, Denniston AK. The
787 Effectiveness of Pharmacological Agents for the Treatment of Uveitic Macular Edema (Umo): A
788 Systematic Review. Ocular immunology and inflammation. 2019:1-23.
- 789 33. Tallouzi MO, Moore DJ, Calvert M, Murray PI, Bucknall N, Denniston AK. The Effectiveness
790 of Pharmacological Agents for the Treatment of Uveitic Macular Oedema (Umo): A Systematic
791 Review Protocol. Systematic reviews. 2016;5(1):29.
- 792 34. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, Lee K, Boersma C,
793 Annemans L, Cappelleri JC. Interpreting Indirect Treatment Comparisons and Network Meta-Analysis

- 794 for Health-Care Decision Making: Report of the Ispor Task Force on Indirect Treatment Comparisons
795 Good Research Practices: Part 1. Value in health : the journal of the International Society for
796 Pharmacoeconomics and Outcomes Research. 2011;14(4):417-28.
- 797 35. Song F, Loke YK, Walsh T, Glenny A-M, Eastwood AJ, Altman DG. Methodological Problems
798 in the Use of Indirect Comparisons for Evaluating Healthcare Interventions: Survey of Published
799 Systematic Reviews. *Bmj*. 2009;338(7700):932-5.
- 800 36. Lardenoye CW, van Kooij B, Rothova A. Impact of Macular Edema on Visual Acuity in
801 Uveitis. *Ophthalmology*. 2006;113(8):1446-9.
- 802 37. Tallouzi MO, Moore DJ, Bucknall N, Murray PI, Calvert MJ, Denniston AK, Mathers JM.
803 Outcomes Important to Patients with Non-Infectious Posterior Segment-Involving Uveitis: A
804 Qualitative Study. *BMJ Open Ophthalmology*. 2020;5(1):e000481.
- 805 38. Ritchie J, Lewis J, Nicholls CM, Ormston R. *Qualitative Research Practice: A Guide for Social
806 Science Students and Researchers*. 12 ed: Sage; 2013.
- 807 39. Sinha IP, Smyth RL, Williamson PR. Using the Delphi Technique to Determine Which
808 Outcomes to Measure in Clinical Trials: Recommendations for the Future Based on a Systematic
809 Review of Existing Studies. *PLoS Med*. 2011;8(1):e1000393.
- 810 40. Payne K, Nicholls SG, McAllister M, MacLeod R, Ellis I, Donnai D, Davies LM. Outcome
811 Measures for Clinical Genetics Services: A Comparison of Genetics Healthcare Professionals and
812 Patients' Views. *Health Policy*. 2007;84(1):112-22.
- 813 41. COMET. Proposed Outcome Measures for Prospective Clinical Trials in Juvenile Idiopathic
814 Arthritis-Associated Uveitis: A Consensus Effort from the Multinational Interdisciplinary Working
815 Group for Uveitis in Childhood 2012. Available From: [Http://Www.Comet-
816 Initiative.Org/Studies/Details/272](http://www.comet-initiative.org/studies/details/272). Access Date: 11.02.2020.
- 817 42. GRADE. Grade Working Group, Grading of Recommendations Assessment, Development
818 and Evaluation (Grade) 2012. Available From: [Http://Www.Gradeworkinggroup.Org](http://www.gradeworkinggroup.org). Access Date:
819 10.12.2019. [
- 820 43. Harman NL, Bruce IA, Callery P, Tierney S, Sharif MO, O'Brien K, Williamson PR. Moment-
821 Management of Otitis Media with Effusion in Cleft Palate: Protocol for a Systematic Review of the
822 Literature and Identification of a Core Outcome Set Using a Delphi Survey. *Trials*. 2013;14(1):1.
- 823 44. Lin P, Suhler EB, Rosenbaum JT. The Future of Uveitis Treatment. *Ophthalmology*.
824 2014;121(1):365-76.
- 825 45. Heiligenhaus A, Foeldvari I, Edelsten C, Smith JR, Saurenmann RK, Bodaghi B, de Boer J,
826 Graham E, Anton J, Kotaniemi K. Proposed Outcome Measures for Prospective Clinical Trials in
827 Juvenile Idiopathic Arthritis-Associated Uveitis: A Consensus Effort from the Multinational
828 Interdisciplinary Working Group for Uveitis in Childhood. *Arthritis care & research*. 2012;64(9):1365-
829 72.

- 830 46. Group SoUNW. Standardization of Uveitis Nomenclature for Reporting Clinical Data.
831 Results of the First International Workshop. American journal of ophthalmology. 2005;140(3):509-
832 16.
- 833 47. Kea B, Sun BC-A. Consensus Development for Healthcare Professionals. Internal and
834 Emergency Medicine. 2015;10(3):373-83.
- 835 48. Williamson PR, Altman DG, Bagley H, Barnes KL, Blazeby JM, Brookes ST, Clarke M, Gargon
836 E, Gorst S, Harman N. The Comet Handbook: Version 1.0. *Trails*. 2017;18(3):280.
- 837 49. Scott IU. Visual Functioning and General Health Status in Patients with Uveitis. Evidence-
838 Based Ophthalmology. 2002;3(2):92-3.
- 839 50. Denniston AK, Keane PA, Srivastava SK. Biomarkers and Surrogate Endpoints in Uveitis: The
840 Impact of Quantitative Imaging. *Investigative ophthalmology & visual science*. 2017;58(6):BIO131-
841 BIO40.
- 842 51. Braithwaite T, Calvert M, Gray A, Pesudovs K, Denniston AK. The Use of Patient-Reported
843 Outcome Research in Modern Ophthalmology: Impact on Clinical Trials and Routine Clinical Practice.
844 Patient related outcome measures. 2019;10:9.
- 845