Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Steps of Our Study Identifying and Prioritizing Research Questions and Outcomes for Dry Eye From the Patient Perspective

Step 1: Selecting research questions to be prioritized by patients
In a prior study,* we translated all clinical recommendations from the 2013 American Academy of Ophthalmology (AAO) Preferred Practice Patterns (PPP) on dry eye** into answerable questions. We then conducted a two-round survey of clinicians managing patients with dry eye, identifying 24 important questions. We selected the 12 most important questions for rating by patients in the current study.

Step 2: Selecting outcomes to be prioritized by patients
We identified the 109 unique outcomes examined in the 20 systematic reviews, 134 published clinical trials, and four National Eye Institute (NEI)-funded trials registered on ClinicalTrials.gov addressing dry eye. We determined whether each outcome was "popular" (i.e., ≥10% of studies examined it; n=18 outcomes) or "unpopular" (i.e., <10% of studies examined it; 91 outcomes) in existing research.

Step 3: Identifying survey participants (patients with dry eye)
We identified subscribers to *KeratoScoop* (R.P.'s weekly newsletter) as appropriate recipients of the two-round Delphi survey. We restricted participation in this study to subscribers who were current or former patients or caregivers of patients with dry eye.

Step 4: Delphi Round 1
We asked patients to assign the 12 research questions and 18 popular outcomes an importance rating of 0 (low) to 10 (high) in Round 1. We also asked patients to indicate whether they considered any of the 91 unpopular outcomes was important. Round 1 of the survey was completed by 622 patients.

Step 5: Delphi Round 2
We asked patients to re-rate the importance of each of the 18 popular outcomes, this time after reviewing the distribution of ratings and anonymized comments by their peers from Round 1. We also asked for specific ratings of importance of the top-10 unpopular outcomes. Round 2 of the survey was completed by 420 patients.

Step 6: Designating and ranking important research questions and outcomes
We considered a given question/outcome to be "important" if ≥75% of all patients assigned a rating of 6 or greater. We considered a given question/outcome to be "moderately important" if ≥75% of all patients assigned a rating of 5 or greater. For questions, we analyzed the Round 1 ratings as final, and for outcomes, we analyzed the Round 2 ratings as final.

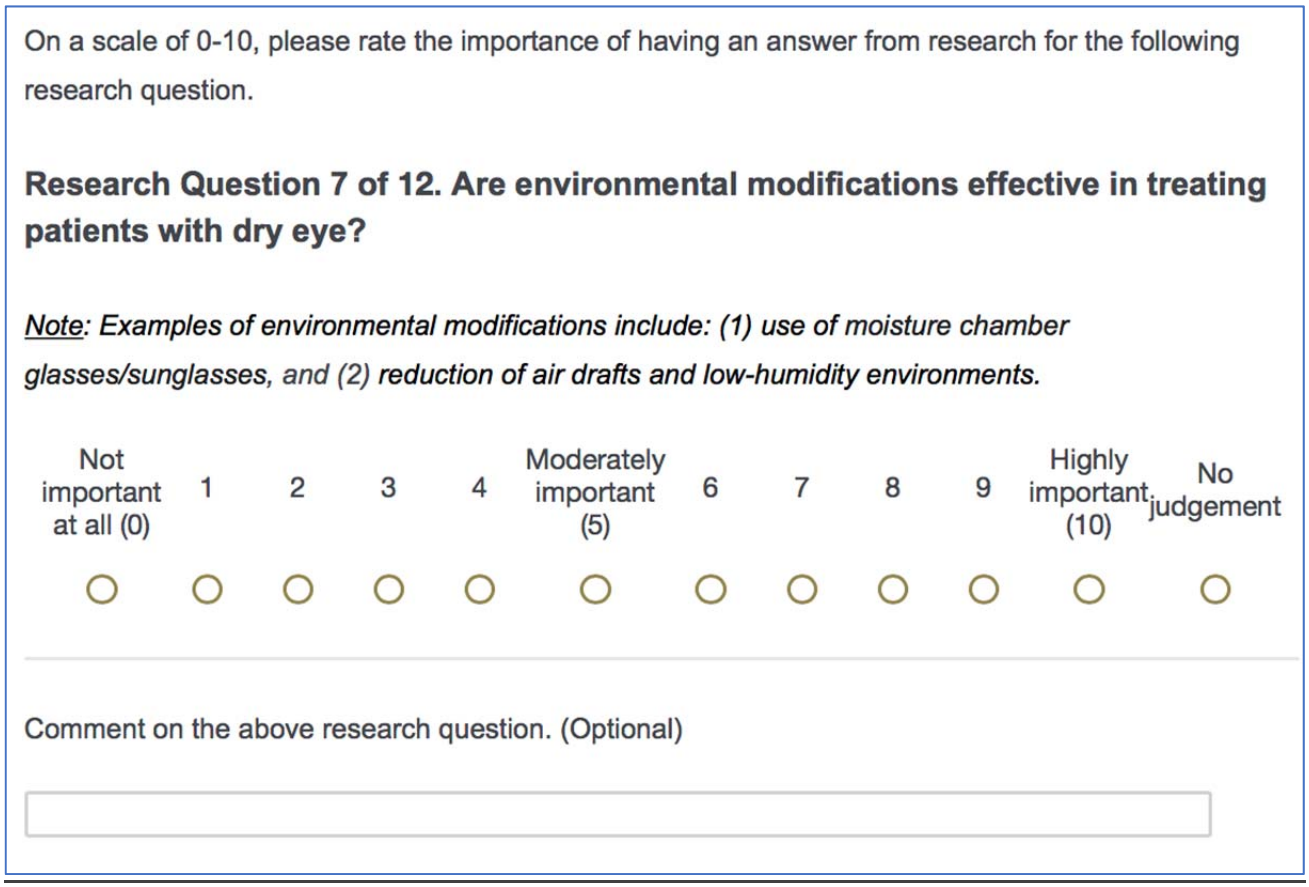
We identified eight questions and 26 outcomes as important to patients with dry eye.

* Saldanha IJ, Dickersin K, Hutfless ST, Akpek EK. Gaps in current knowledge and priorities for future research in dry eye. *Cornea* 2017;36(12):1584-1591.

** American Academy of Ophthalmology Cornea/External Disease Panel. Preferred Practice Pattern® Guidelines. Dry Eye Syndrome. San Francisco, CA: American Academy of Ophthalmology; 2013. Available at: www.aao.org/ppp. Last accessed May 9, 2018.

eAppendix 2. Sample View of Survey Portion Pertaining to 1 of the 12 Research Questions Presented to Patients for Rating in Round 1 of the Delphi Survey in Qualtrics

For each of the 12 questions, we asked patients to "rate the importance of having an answer from research" for that question. Responses were analyzed using an 11-point Likert-type scale from 0 ("Not important at all") to 10 ("Highly important"). For each question, patients could elect to not provide a rating by selecting "No judgement".


On a scale of 0-10, please rate the importance of having an answer from research for the following research question.

Research Question 7 of 12. Are environmental modifications effective in treating patients with dry eye?

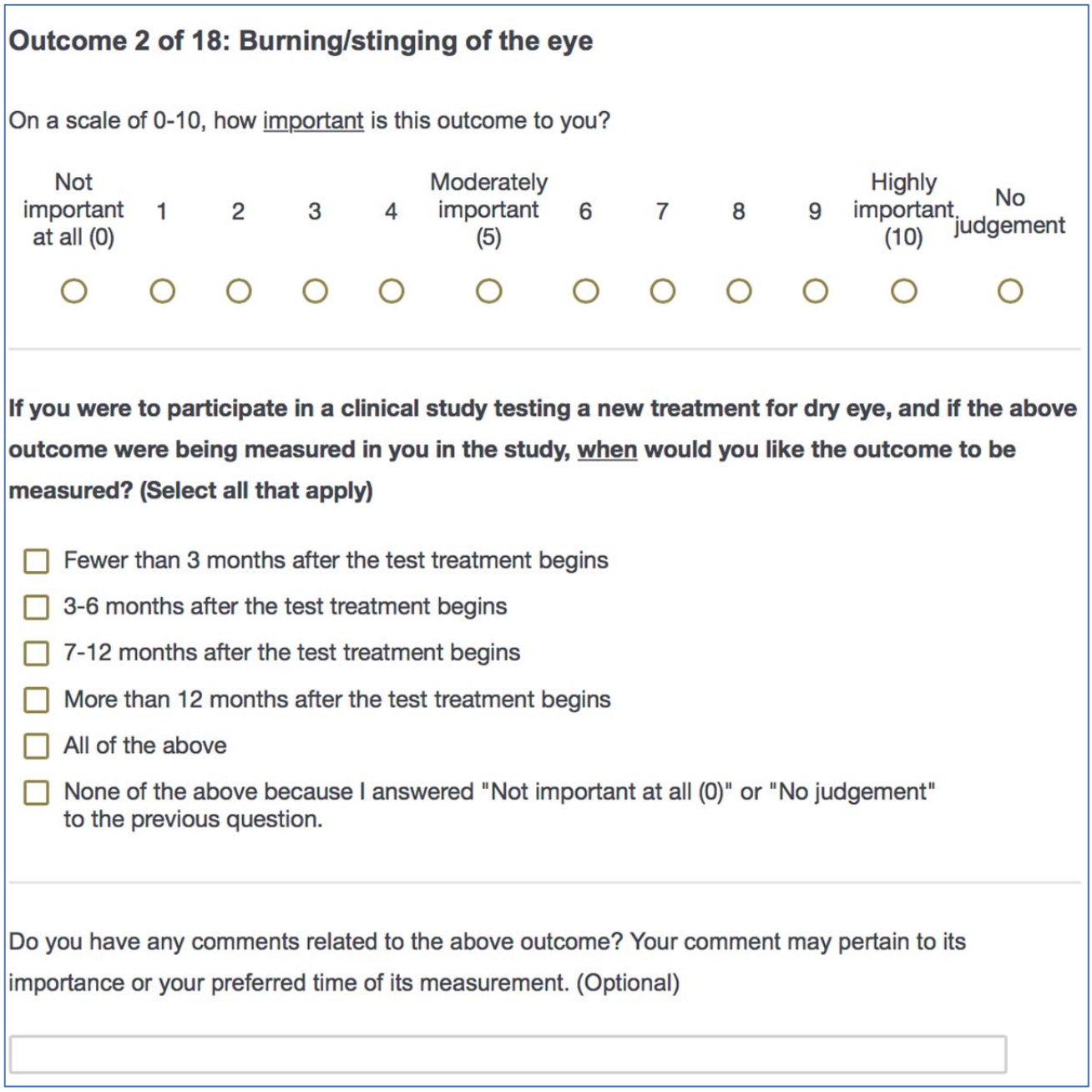
Note: Examples of environmental modifications include: (1) use of moisture chamber glasses/sunglasses, and (2) reduction of air drafts and low-humidity environments.

Not important at all (0)	1	2	3	4	Moderately important (5)	6	7	8	9	Highly important (10)	No judgement
○	○	○	○	○	○	○	○	○	○	○	○

Comment on the above research question. (Optional)

Appendix 3. Sample View of Survey Portion Pertaining to 1 of the 18 Outcomes Presented to Patients for Rating in Round 1 of the Delphi Survey in Qualtrics

For each of the 18 outcomes, we asked patients how "important" the outcome was to them. Responses were analyzed using an 11-point Likert-type scale from 0 ("Not important at all") to 10 ("Highly important"). For each question, patients could elect to not provide a rating by selecting "No judgement". We also asked patients about when they would like the outcome to be measured if they were participating in a hypothetical clinical trial for a new treatment for dry eye.



Outcome 2 of 18: Burning/stinging of the eye

On a scale of 0-10, how important is this outcome to you?

Not important at all (0)	1	2	3	4	Moderately important (5)	6	7	8	9	Highly important (10)	No judgement
○	○	○	○	○	○	○	○	○	○	○	○

If you were to participate in a clinical study testing a new treatment for dry eye, and if the above outcome were being measured in you in the study, when would you like the outcome to be measured? (Select all that apply)

- ☐ Fewer than 3 months after the test treatment begins
- ☐ 3-6 months after the test treatment begins
- ☐ 7-12 months after the test treatment begins
- ☐ More than 12 months after the test treatment begins
- ☐ All of the above
- ☐ None of the above because I answered "Not important at all (0)" or "No judgement" to the previous question.

Do you have any comments related to the above outcome? Your comment may pertain to its importance or your preferred time of its measurement. (Optional)

eAppendix 4. References to All 158 studies Identified as Existing Research for Dry Eye (ie, Systematic Reviews, Published Clinical Trials, and Trials Registered on ClinicalTrials.gov)

Systematic reviews (N=20)

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Published clinical trials (N=134)

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Clinical trials registered on ClinicalTrials.gov (N=4)

1. rhDNase eye drops in patients with ocular graft-vs.- host disease (NCT02702518)
2. Dry Eye Assessment and Management Study (DREAM) (NCT02128763)
3. Dry Eye Assessment and Management: Feasibility Study (DREAM) (NCT01102257)
4. Dry eye disease in the vitamin D and omega-3 trial (VITAL) (NCT01880463)

eAppendix 5. All 109 Unique Outcome Domains Examined in Existing Research Addressing Interventions for Dry Eye (ie, Systematic Reviews, Clinical Trials Included in the Systematic Reviews, and National Eye Institute [NEI]-Funded Trials Registered on ClinicalTrials.gov)

Serial Number	Category of Outcome	Subcategories and Outcome Domains
1	Symptoms	Patient's overall assessment of ocular surface symptoms
2		Ocular itching
3		Ocular burning/stinging
4		Ocular foreign body sensation
5		Ocular gritty/sandy sensation
6		Ocular dryness
7		Ocular tiredness/fatigue
8		Ocular discomfort
9		Ocular pain
10		Photosensitivity/photophobia
11		Intolerance to air drafts
12		Intolerance to smoke
13		Eyelid/eyelash crusting
14		Eyes stuck shut
15		Inability/difficulty with opening eyes in light/after sleeping
16		Inability/difficulty with sleeping
17		Watery eyes/tearing/mucus
-*		Patient's overall assessment of visual symptoms
18		Fluctuating vision
19		Blurred vision
20		Difficulty with reading
21		Patient's overall assessment of dryness
22		Dryness of the mouth/Xerostomia
23		Dryness of the tongue
24		Reduced feeling/sensation of the mouth
25		Inability/difficulty with speaking
26		Inability/difficulty with swallowing
27		Mouth discomfort/comfort
28		Dryness of the skin
29		Dryness of the vagina
30		Dryness of the nose/nasal passage
-*		General symptoms
31		General body fatigue
32		General body pain
33		Muscle pain or myalgia
34		Joint pain or arthralgia
35		Depressive mood
-*	Signs/Clinical testing	Ocular surface- and tear film-related signs/clinical testing
36		Ocular surface staining
-*		Conjunctiva-related signs/clinical testing
37		Conjunctival hyperemia/erythema/injection/redness

38		Conjunctival staining
39		Conjunctival swelling/edema/chemosis
40		Conjunctival discharge/foam
41		Conjunctival wetting
42		Lid parallel conjunctival fold (LIPCOF)
-*		Cornea-related signs/clinical testing
43		Corneal punctate erosions/superficial keratitis
44		Corneal staining
45		Corneal sensitivity
46		Corneal surface topography/corneal fluorophotometry
47		Corneal epithelial permeability
48		Corneal filaments
-*		Tear film-related signs/clinical testing
49		Tear film lipid layer structure/thickness
50		Tear film lipid layer spread time
51		Tear production/volume/secretion (Schirmer Test/Fluorophotometry
52		Tear osmolarity
53		Tear film meniscus height /volume
54		Tear film stability (Tear Film Break Up Time/ Tear film thinning time)
55		Tear interference
56		Tear evaporation
57		Tear drainage/clearance/flow
-*		Eyelid-related signs/clinical testing
58		Eyelid edema
59		Eyelid/eyelid margin erythema/injection/inflammation
60		Meibomian gland plugging
-*		Vision-related signs/clinical testing
61		Visual acuity
62		Contrast sensitivity
63		Mean refractive spherical equivalent (MSE)
-*	Laboratory measurements	Ocular surface- and tear film-related laboratory measurements
64		Corneal epithelial cell nucleus/cytoplasm ratio
65		Tear lysozyme
66		Tear lactoferrin
67		Tear matrix metalloprotein-9 **(**MMP-9)
68		Tear extracellular DNA (eDNA)
69		Tear cell count
70		Tear cytokine
71		Tear mucin 5a (MUC 5a)
72		Tear prostaglandin E
73		Goblet cell density
74		Conjunctival impression cytology
75		Conjunctival human leukocyte antigen D-related (HLA-DR)
76		Conjunctival epithelial cell morphology
77		Conjunctival CD11a- and CD3-positive lymphocytes (i.e., activated lymphocytes)
-*		Saliva/salivary gland measurements
78		Salivary production
79		Salivary flow/drainage/clearance
80		Salivary pH

81		Salivary gland biopsy
-*		Serum/blood measurements
82		Serum immunoglobulin G (IgG)
83		Serum immunoglobulin A (IgA)
84		Serum immunoglobulin M (IgM)
85		Serum erythrocyte sedimentation rate (ESR)
86		Serum rheumatoid factor (RF)
87		Serum hemoglobin
88		Serum B lymphocytes
89		Serum C-reactive protein (CRP)
90		Serum Apo 2.7+ cells
91		Serum Periodic Acid-Schiff (PAS) cells
92		Red blood cell (RBC) membrane fatty acid
93	Safety outcomes	Adverse events (type unspecified)
94		Adverse events (ocular)
95		Adverse events (non-ocular)
96		Intraocular pressure
97	Quality-of-life-related outcomes	General quality-of-life
98		Vision-related quality-of-life
99		Patient treatment acceptability/satisfaction with treatment
100		Overall assessment of treatment effectiveness assessed by patients
101		Overall assessment of treatment effectiveness assessed by provider/researcher
102		Impact of disease on patient's work
103		Impact of disease on patient's daily life
-*	Other outcomes	Economic outcomes
104		Costs of treatment for the patient
-*		Treatment-related outcomes
105		Artificial tear use
106		Need for additional medications, e.g., analgesics
107		Adherence/compliance with treatment
108		Response rate
109		Patient preference

*Rows that include a "-" in the Serial Number column pertain to subcategories that were added for organizational purposes only; these are not outcome domains examined in existing research.

eAppendix 6. Number of Studies in Existing Research Addressing Interventions for Dry Eye (ie, Systematic Reviews, Clinical Trials Included in the Systematic Reviews, and National Eye Institute (NEI)-Funded Trials Registered on ClinicalTrials.gov) That Examined Each of the 28 Outcomes Rated by 420 Patients in Round 2 of the Delphi Survey

Serial Number	Category of outcome	Outcome	Number of studies in existing research examining the outcome		
			Systematic reviews (N=20) n %	Clinical trials (N=138) n %	Total (N=158) n %
Outcomes classified as "important" (i.e., ≥75% of all patients assigned a rating of 6 or higher)					
1	Symptoms	Ocular burning/stinging	3 (15)	28 (20)	31 (20)
2	Symptoms	Ocular discomfort	3 (15)	23 (17)	26 (17)
3	Symptoms	Ocular pain*	1 (5)	10 (7)	11 (7)
4	Symptoms	Ocular dryness	7 (35)	38 (28)	45 (29)
5	Signs/Clinical testing	Visual acuity	4 (20)	14 (10)	18 (11)
6	Quality-of-life-related	Impact of dry eye disease on patient's daily life*	1 (5)	2 (1)	3 (2)
7	Quality-of-life-related	Vision-related quality-of-life*	3 (15)	2 (1)	5 (3)
8	Quality-of-life-related	Patient's acceptability/satisfaction with treatment*	8 (40)	1 (1)	9 (6)
9	Symptoms	Patient's overall assessment of ocular surface symptoms	13 (65)	47 (34)	60 (38)
10	Symptoms	Ocular foreign body sensation	2 (10)	21 (15)	23 (15)
11	Symptoms	Ocular gritty/sandy sensation*	1 (5)	12 (9)	13 (8)
12	Signs/Clinical testing	Tear film stability	18 (90)	87 (63)	105 (67)
13	Quality-of-life-related	Overall assessment of treatment effectiveness assessed by patients*	6 (30)	1 (1)	7 (4)
14	Safety-related	Adverse events (ocular)	7 (35)	33 (24)	40 (25)
15	Other	Artificial tear use	7 (35)	15 (11)	22 (14)
16	Symptoms	Ocular tiredness/fatigue*	4 (20)	2 (1)	6 (4)
17	Symptoms	Photosensitivity/photophobia*	13 (65)	1 (1)	14 (9)
18	Symptoms	Intolerance to air drafts*	0 (0)	1 (1)	1 (1)
19	Signs/Clinical testing	Tear production/volume	19 (95)	86 (62)	105 (67)
20	Other	Costs of treatment*	0 (0)	1 (1)	1 (1)
21	Signs/Clinical testing	Corneal staining	6 (30)	38 (28)	44 (28)
22	Safety-related	Adverse events (non-ocular)	4 (20)	18 (13)	22 (14)
23	Signs/Clinical testing	Conjunctival hyperemia	3 (15)	19 (14)	22 (14)
24	Signs/Clinical testing	Ocular surface staining	11 (55)	46 (33)	57 (36)
25	Signs/Clinical testing	Conjunctival staining	3 (15)	24 (17)	27 (17)
26	Laboratory measurements	Conjunctival impression cytology	2 (10)	16 (12)	18 (11)
Outcomes classified as "not important" (i.e., <75% of all patients assigned a rating of 5 or higher)					
27	Symptoms	Dryness of the mouth	2 (10)	15 (11)	17 (11)
28	Laboratory measurements	Salivary flow	4 (20)	17 (12)	21 (13)

* Outcomes that were unpopular in existing research (i.e., examined in <10% of studies), but were rated as important by patients.

eAppendix 7. Comparison of Ratings of Importance of Outcomes in Rounds 1 and 2 of the Delphi Survey

#	Category of outcome	Outcome	Rating assigned by ALL 622 PARTICIPANTS in ROUND 1			Rating assigned by ALL 420 PARTICIPANTS in ROUND 2		
			Median	(IQR)*	(Range)	Median	(IQR)*	(Range)
Outcomes classified as "important" (i.e., at least 75% of ALL participants assigned a rating of 6 or higher)								
1	Symptoms	Ocular burning/stinging	10	(9-10)	(0-10)	10	(10-10)	(2-10)
2	Symptoms	Ocular discomfort	10	(9-10)	(0-10)	10	(10-10)	(0-10)
3	Symptoms	Ocular pain**		N/A		10	(10-10)	(0-10)
4	Symptoms	Ocular dryness	10	(10-10)	(3-10)	10	(10-10)	(0-10)
5	Signs/Clinical testing	Visual acuity	10	(8-10)	(0-10)	10	(10-10)	(0-10)
6	Quality-of-life-related	Impact of dry eye disease on patient's daily life**		N/A		10	(10-10)	(0-10)
7	Quality-of-life-related	Vision-related quality-of-life**		N/A		10	(10-10)	(0-10)
8	Quality-of-life-related	Patient's acceptability/satisfaction with treatment**		N/A		10	(10-10)	(0-10)
9	Symptoms	Patient's overall assessment of ocular surface symptoms	10	(9-10)	(0-10)	10	(9-10)	(2-10)
10	Symptoms	Ocular foreign body sensation	10	(8-10)	(0-10)	10	(9-10)	(0-10)
11	Symptoms	Ocular gritty/sandy sensation**		N/A		10	(9-10)	(0-10)
12	Signs/Clinical testing	Tear film stability	10	(9-10)	(0-10)	10	(9-10)	(0-10)
13	Quality-of-life-related	Overall assessment of treatment effectiveness assessed by patients**		N/A		10	(9-10)	(0-10)
14	Safety-related	Adverse events (ocular)	10	(9-10)	(0-10)	10	(9-10)	(1-10)
15	Other	Artificial tear use	10	(8-10)	(0-10)	10	(9-10)	(0-10)
16	Symptoms	Ocular tiredness/fatigue**		N/A		10	(8-10)	(0-10)
17	Symptoms	Photosensitivity/photophobia**		N/A		10	(8-10)	(0-10)
18	Symptoms	Intolerance to air drafts**		N/A		10	(8-10)	(0-10)
19	Signs/Clinical testing	Tear production/volume	10	(8-10)	(0-10)	10	(8-10)	(0-10)
20	Other	Costs of treatment**		N/A		10	(8-10)	(0-10)
21	Signs/Clinical testing	Corneal staining	10	(8-10)	(0-10)	9	(8-10)	(0-10)
22	Safety-related	Adverse events (non-ocular)	10	(7-10)	(0-10)	9	(8-10)	(1-10)
23	Signs/Clinical testing	Conjunctival hyperemia	9	(6-10)	(0-10)	9	(7-10)	(0-10)
24	Signs/Clinical testing	Ocular surface staining	9	(7-10)	(0-10)	8	(7-10)	(0-10)
25	Signs/Clinical testing	Conjunctival staining	9	(7-10)	(0-10)	8	(7-10)	(0-10)
26	Laboratory measureme	Conjunctival impression cytology	9	(6-10)	(0-10)	8	(7-10)	(0-10)
Outcomes classified as "not important" (i.e., fewer than 75% of ALL participants assigned a rating of 5 or higher)								
27	Symptoms	Dryness of the mouth	7	(4-10)	(0-10)	5	(4-8)	(0-10)
28	Laboratory measureme	Salivary flow	6	(3-9)	(0-10)	5	(3-8)	(0-10)

*IQR = Interquartile Range

** Outcomes that were unpopular in existing research (i.e., examined in <10% of studies), but were rated as important by survey respondents.
Note that we participants did not provide ratings for unpopular outcomes in Round 1. Rather, participants selected them as "important" or "not important" from a list.