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Defining Ocular Surface Disease Activity and Damage Indices by an International Delphi Consultation

Priscilla A. Mathewson, MA(cantab), FRCOphth, Geraint P. Williams, PhD, FRCOphth, Stephanie L. Watson, PhD, FRANZCO, James Hodson, BSc(Hons), Anthony J. Bron, FRCOphth, FMedSci, Saaeha Rauz, PhD, FRCOphth, Sajjad Ahmad, Matthew Burton, John K. Dart, Francisco Figueiredo, Gerd Geerling, Nicholas Hawksworth, Deborah Jacobs, Stephen Kaye, S. Sai Kolli, D. Frank Larkin, Sanjay Mantry, Philip I. Murray, Christopher Liu, Alex Shortt, Paul J. Tomlins, David Verity, Colin Willoughby

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AUTHORS: Priscilla A. Mathewson, MA(cantab), FRCOphth,[1] Geraint P. Williams, PhD, FRCOphth,[1] Stephanie L. Watson, PhD, FRANZCO, James Hodson, BSc(Hons),[3] Anthony J. Bron, FRCOphth, FMedSci,[4] and Saaeha Rauz, PhD, FRCOphth[1¶] ;The OSDISS Study Group

Collaborators (17): Sajjad Ahmad, Matthew Burton, John K. Dart, Francisco Figueiredo, Gerd Geerling, Nicholas Hawksworth, Deborah Jacobs, Stephen Kaye, S. Sai Kolli, D. Frank Larkin, Sanjay Mantry, Philip I. Murray, Christopher Liu, Alex Shortt, Paul J. Tomlins, David Verity, Colin Willoughby.

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Drs. Priscilla A. Mathewson and Geraint P. Williams contributed equally.

[¶]Steering group chair.

From [1]Academic Unit of Ophthalmology, University of Birmingham, Birmingham, UK, [2]Save Sight Institute, University of Sydney, NSW, Australia, [3]Department of Statistics, Wolfson Computer Laboratory, Queen Elizabeth Hospital, Birmingham, UK, and [4]Nuffield Laboratory of Ophthalmology, John Radcliffe Hospital, Oxford, UK.

Memberships of participating groups are listed at end of article.

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Corresponding Author, Steering Group Chair and address for reprints: Saaeha Rauz PhD FRCOphth (Miss), Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, College of Medical and Dental Sciences, University of Birmingham, Birmingham and Midland Eye Centre, Dudley Road, Birmingham B18 7QU, United Kingdom. Tel 44-(0)121-507-6849. Fax 44-(0)121-507-6853. E-mail: s.rauz@bham.ac.uk

ABSTRACT Purpose: Unifying terminology for the description of ocular surface disease (OSD) is vital for determining treatment responses and ensuring robust clinical trial outcomes. To date, there are no agreed parameters describing 'activity' and 'damage' phases of disease. **Methods:** A working group of international experts in OSD, oculoplastics, and uveitis from a range of backgrounds (university, teaching, district general and private hospitals) participated in a modified Delphi consensus-building exercise (October 31, 2011 to March 20, 2015). Two steering group meetings took place in which factors based upon published literature were discussed and supplemented with anonymous web-based questionnaires to refine clinical indices according to 'activity' (reversible changes resulting directly from the inflammatory process) and/or 'damage' (persistent, >6 months duration) changes resulting from previously active disease that are cumulative and irreversible).

Results: The recommended set of clinical parameters for the assessment of OSD encompasses 68 clinical indices and 22 ancillary grading tools (in parenthesis) subdivided by anatomical domain as follows: 4(4) tear-film, eyelid 21(3), 17(3) conjunctiva, 15(10) cornea and 11(2) Anterior Chamber/Sclera. Of these; 17(2) were considered as measures of clinical activity, 27(3) as damage, 1(8) as measures of both activity and damage. Twenty-three clinical descriptors and 9 tools did not reach the threshold for inclusion into the main standard set. These were defined as 'second tier' parameters for use in special clinical settings. **Conclusion:** These core parameters provide the first description of 'activity' and 'damage' relevant to OSD and provide a platform for the future development of scoring scales for each parameter.

KEY WORDS cornea, conjunctiva, Delphi process, disease activity, disease damage, disease scoring, disease staging, ocular surface disease

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I. Introduction

The ocular surface is a specialized mucosa comprising an epithelium and stroma extending from the mucocutaneous junction at the eyelid margin and including the tarsal, fornical and bulbar conjunctiva, limbus, and cornea.[1] Obtaining nutrition largely from the tear film and vascular arcades, and for the cornea, from the aqueous humor, the system also includes associated adnexal structures, lacrimal glands, and eyelids. All components are linked by the continuity of the surface epithelia and through close interaction with innervation, endocrine, vascular, and immune systems. Disease processes affecting the ocular surface system, defined as *ocular surface disease* (**OSD**), have a diverse range of underlying pathologies, encompassing a spectrum of clinical entities, often with overlapping pathogeneses. Documentation of OSD includes the recording of physical signs of all components of the ocular surface system but also the posterior layers of the cornea, sclera and anterior chamber.

The breadth of OSD sequelae is exemplified by conditions forming the progressive conjunctival scarring subgroup, such as mucous membrane pemphigoid (**MMP**), Stevens-Johnson syndrome/toxic epidermal necrolysis (**SJS-TEN**) and graft-versus-host disease (**GVHD**).[2,3] These conditions are characterized by conjunctival inflammation often associated with destruction of the normal ocular surface architecture, fibrosis, dry eye disease and eyelid deformities leading to surface breakdown, vulnerability to infection, limbal epithelial stem cell destruction, corneal scarring, neovascularization and eventually ocular surface failure. Chronic SJS-TEN can additionally be accompanied by scleritis.[4]

While OcMMP, SJS-TEN and GVHD are relatively rare compared to many OSDs, they serve as model disease platforms for quantifying the wealth of clinical signs for stratification according to 'activity' and 'damage' that may be generalizable across the whole spectrum of OSD. A range of scoring systems have been proposed for OcMMP, including conjunctival inflammation,[5] scarring,[6-8] methods for quantifying scarring,[9] and for SJS-TEN the use of temporal-spacial staging (acute or chronic)[10, 11] accompanied by ordinal scales for tear film, eyelid, corneal and conjunctival involvement; these scoring systems cannot be applied across all OSDs.[3,11] 'Function' can also be used for documenting OSD indices, as illustrated by the dry eye and meibomian gland workshops.[11-14] These existing scoring systems are not in routine clinical use.

Disease 'activity' or 'damage' can also be determined by classifying a range of clinical parameters into 1) 'activity,' in which clinical manifestations are reversible and result directly from the inflammatory process, in which disease remission occurs spontaneously or following treatment such as immunosuppression; or 2) 'damage,' in which clinical manifestations are persistent, i.e., are present for greater than 6 months duration, ***and*** result in permanent changes in anatomy, physiology, pathology or function.[15] Damage results from previously active disease where changes are often cumulative and irreversible.[15]

This method of scoring specifically benefits patients who present with early disease when the diagnosis is uncertain, and detailed investigation and/or prolonged follow-up would be required before the phenotype of the disease would manifest a diagnosis. A similar model is obtained from rheumatologic conditions in which early diagnostic criteria and the distinctions between disease 'activity' and 'damage' have been established and extrapolated to disease entities such as systemic lupus erythematosis, rheumatoid arthritis, and Sjögren syndrome.[16-21] In such conditions, these terms are critical for defining relapse, remission and progression of disease, together with documenting treatment response, developing novel treatment response guidance, or ensuring robust outcomes for both small- and large-scale clinical trials.[12,20,22,23] OSD is not absolutely synonymous with rheumatological conditions, and patient perceptions of OSD can influence the ocular surface severity score. For instance, the OSD patient may describe neuropathic pain that outweighs observed clinical signs, but influences the patient-reported outcomes of a putative ocular surface severity score. Defining 'activity' and 'damage' parameters provides an excellent foundation to begin the process of developing an ocular surface disease scoring system (**OSDISS**).

To meet the same end point in OSD as has been achieved in rheumatology, unifying terminology to describe the stage of 'activity' and 'damage' is required in addition to agreement on the grading of each parameter to stage severity or progression of disease. One method for achieving this is a consensus statement derived through a Delphi process. Originally developed by the United States Air Force during the Cold War, the Delphi process is structured to obtain a consensus opinion from a group of experts.[24] The advantage of this approach is its ability to gather information from multiple experts without the risk of giving greater weight to input from senior or more vocal individuals.[25]

The objective of our study is to integrate specialist OSD knowledge through use of a modified Delphi technique to obtain consensus on a set of core clinical domains for the assessment of OSD and categorize according to activity/damage domains. Ultimately, our aim is to develop measurable scales for each clinical parameter, evaluate patient-reported outcomes, validate, and internationally adopt an agreed OSDISS that could be employed generically across all OSDs, particularly in the early stages when the diagnosis is not established.

II. Methods

The modified Delphi process was designed to conform to best practice described by Sinha and colleagues.[25]

A. Steering Group Formation

An expert steering group was established whose remit was to identify measurable disease parameters for consensus building. Experts were identified using inclusion criteria as described for the *Dysfunctional Tear Syndrome Delphi* process.[12] "Experts" met the following requirements:

1. Active clinicians (ophthalmologists).
2. Scientific contributions to clinical research on the ocular surface or expertise in ocular surface, as reflected by at least two of: peer-reviewed publications, other forms of written scientific communication, specialty meeting presentations, and membership in international ocular surface disease societies.
3. Comprised international representation.
4. Proficiency in English language to facilitate interaction.
5. Ability to respond to sets of questionnaires and available to steering group meetings at the University of Birmingham, United Kingdom.

Of the UK-based steering group members, panelists were selected to represent a cross-section of the geographical patient population centers identified through a surveillance study.[26] Additional advisors with expertise in oculoplastics and uveitis were included to increase breadth of knowledge required for describing the adnexae and inflammatory eye diseases as part of the spectrum ocular surface system disorders. All but one of the 22 invited panelists accepted the invitation.

B. Summary of the Modified Delphi Process

A modified version of the Delphi process was used to obtain group consensus. This included the essential features of a consensus method described by Hunter and Jones.[27]

- Anonymity – to avoid dominance of one individual within the group.
- Multiple iterations – giving participants the chance to change their views.

- Controlled feedback – showing the distribution of the group response.
- Statistical group response – expressing judgment using summary measures of the whole group response.

The consensus building exercise was divided into 5 key work packages (**WP**).

Work Package 1 (WP1): Preliminary Ballot

The first web-based ballot (eFigure 1) consisted of a nonexhaustive itemization of possible clinical parameters for inclusion in a scoring tool, derived from modification of existing scoring systems for OSD.[5-8,11-14,28-30] Steering group participants were encouraged to suggest additional variables for inclusion in the putative activity and damage OSD scoring system.

Work Package 2 (WP2): The First Steering Group Meeting

The Steering Group convened to discuss results of WP1 using the nominal group technique.[27,31] During this meeting, each clinical parameter was discussed. The group was invited to vote again in light of the discussion as to whether the clinical parameter should be included. Each member of the group was given an opportunity to chair part of the session, ensuring even representation from all group members. In order to encourage the inclusion of as many of the parameters as possible, a majority vote was accepted for inclusion of the clinical variable to a putative list of activity and damage indicators.

Work Package 3 (WP3): Web-based International Consultation

The results of the first steering group meeting were used to create a web-based questionnaire (eFigure 2) and disseminated to an international group of OSD clinical specialists invited via an undisclosed recipient electronic-mail communication to members of the *International Ocular Surface Society* and *UK Bowman Club* via their administrative secretaries. Additional invitations were extended to advisory group specialists in uveitis (n,10) and oculoplastics (n,10) extrapolated from the *International Uveitis Study Group (IUSG)* and *International Group of Oculoplastics Specialists*, using the criteria outlined for the members of the OSD steering group. This questionnaire formed an anonymous specialist consultation where a minimum

number of participants (n=30) commensurate with other published Delphi processes were defined to ensure validity of the consultation exercise.[12,32,33]

OSD specialist recipients were asked to rank the 76 agreed indices and 30 ancillary grading tools over the 5 clinical domains (tear-film, eyelids, conjunctiva and fornices, cornea and sclera/anterior chamber [**AC**]) in the context of eight common or important clinical disease entities:

1. Blepharitis
2. Mucous membrane pemphigoid or other progressive cicatrizing conjunctivitis
3. Bacterial keratitis
4. Viral keratitis (e.g., herpetic keratitis)
5. Dry eye disease
6. Sjögren's syndrome (primary or secondary)
7. Corneal melt including peripheral ulcerative keratitis
8. Chemical injury

Participants were asked to consider the 'best' ancillary grading tool by "assuming you have all of these available" (see supplementary figure 2) and a gauge of the 'real world' scenario was examined by asking: "Which of these (these tools) do you have available?" Oculoplastics and uveitis specialist consultations were restricted to domains relevant to their subspecialties comprising tear film/conjunctiva-fornices/cornea and cornea/anterior chamber-sclera, respectively.

Based upon the variation among published 'cut-off' limits ranging from 60% to 80% to determine consensus, [12,34-38] a 75% cut-off of the upper and lower quartiles in order to balance definite agreement ("agree" or "strongly agree"), disagreement ("disagree" or "strongly disagree") and areas of ambiguity was identified. A timeline of 10 weeks was set for completion. Information was anonymously populated into an Adobe Form Central data capture sheet (https://new.acrobat.com, 2013).

Work Package 4 (WP4): Second Steering Group Meeting

The results of the consultation questionnaire were presented at a second steering group meeting. The live anonymous web-based voting system using Adobe Form Central enabled unbiased arbitration during the following Expert workshops:

- *Workshop A (WSA): Unclassified Clinical Parameters*. Clinical parameters with ≥75% consensus were included into the scoring system; otherwise they were classed as 'second-tier.' Second-tier parameters were defined as parameters for specialist situations (but not essential for a general ophthalmology setting).
- *Workshop B (WSB): 'Activity' and 'Damage'*. The stratification of each parameter and grading tool into one of three activity-damage domain categories measuring 1) "activity", 2) "damage", and 3) both "activity and damage" was undertaken. A ≥75% consensus was required for classification where *activity* was defined as reversible/medically modifiable manifestations or *damage* as manifestations that are persistent (>6 months) and result from previously active disease. Parameters and tools that could not be successfully classified into an activity-damage domain, formed a fourth domain termed 'unclassified' (either 'activity' or 'damage') and were subject to further consultation in WP5.

Work Package 5 (WP5): Final Consultation Defining 'Activity' and 'Damage'.

Clinical parameters from WP5 Workshop B that remained unclassified were arbitrated through a final round of voting involving the OSD specialists where participants were asked to classify the ambiguous indices as 1) "activity," 2) "damage, " and 3) both "activity and damage." A ≥70% consensus enabled direct definition of ' activity' and 'damage' domains to ensure maximal classification of remaining parameters. The outcome dataset from *Work Package 5* produced a consensus statement on a set of five core clinical domains for the assessment of OSD stratified across three activity-damage domains.

C. Approvals

Institutional review board approval was not required because the study did not involve patient or registry data and this was confirmed by the Research Support

Group Research Ethics Team (ref ERN_15-1195) at the University of Birmingham (UK).

III. Results

A diagram of the work packages and summary of outcomes is outlined in Figure 1.

A. WP1 and WP2: Preliminary Ballot and The First Steering Group Meeting.

Seventy-six clinical indices were subdivided into five domains: Tear film; Eyelids, Lid Margins and Meibomian Glands; Conjunctiva and Fornices; Cornea; Anterior Chamber and Sclera were disseminated as part of *Work Package 1 (Preliminary Ballot)*. The Ballot 'included' the majority of proposed indices, with highest agreement in the fornix subset versus the tear film (lowest) (**Figure 2**).

Twelve clinical parameters were rejected from across all domains and two were reclassified as a new category, "ancillary grading tools," i.e. methods of examining and quantifying disease (see below). Fifteen new clinical parameters were added, giving rise to a revised total of 76 clinical indices (Figure 2). It was agreed that a list of 30 additional "ancillary grading tools" should be constructed and considered as part of the WP3 international consultation exercise (Table 1). A scoping exercise to define the availability of these tools in the Delphi responders' clinical practice was proposed to be integrated into WP3**.**

B. WP3: Web-based International Consultation

A total of 53 specialists responded (40 OSD, 5 oculoplastics, 8 uveitis) with most (47) practicing in a University Teaching Hospital. Specialists were from 8 countries (Australia 10, Belgium 1, Germany 3, Slovenia 1, New Zealand 1, Singapore 2, United Kingdom 32 and United States 2, one person did not specify their country of origin in the anonymous form)

Of the 76 clinical indices, 52 (68%) achieved ≥75% ranking for inclusion and none reached the 75% threshold for exclusion.

Twenty-two of 30 ancillary grading tools achieved the 75% threshold (Table 1, Figure 3). Table 1 also highlights the availability 13 (43%) ancillary grading tools that were available in clinical practice to ≥75% of participants.

C. WP4 and WP5: Second Steering Group Meeting and Final Consultation

Workshop A: Unclassified Clinical Parameters

Twenty-four of the 76 clinical parameters did not reach the ≥75% threshold. After Steering Group discussion, anonymous web-based arbitration included a further 15 unclassified indices and 1 novel clinical entity (scleral thinning) was introduced giving a total of 68 indices (Figure 3). The ten remaining indices formed '2nd tier' clinical parameters.

The steering group arbitrated that ancillary grading tools that did not reach the ≥75% threshold became '2nd tier' tools for use in refining scales in specialist situations (Figure 3)

Workshop B and WP5: Activity and Damage Stratification

During WP4 Workshop B, one parameter (palpebral aperture) was considered to be a physiological or anatomical descriptor that was not amenable to classification into activity and damage domains and was therefore not put forward to the final consultation forming WP5. This parameter formed an 'unclassified' category.

Following completion of the final round of questionnaires, 17 clinical parameters and two ancillary grading tools (in parenthesis) were classified as a measure of "activity": Tear film: 0(1), Lids: 4(0), Conjunctiva: 7(0), Cornea: 0(0), AC/Sclera: 6(1). Twenty-seven clinical parameters and 3 ancillary grading tools were classified as a measure of "damage": Tear film: 0(0), Lids: 10(2), Conjunctiva:10(1), Cornea: 4(0), AC/Sclera: 3(0). One of the clinical parameters and 6 of the ancillary grading tools were classified as a measure of both "activity and damage" with photography appearing in 3 clinical domains (lids, conjunctiva, cornea). The remaining clinical parameters and ancillary grading tools formed 2nd tier for activity and damage: Tear film: 4(3), Lids: 7(0), Conjunctiva: 0(1), Cornea: 11(5), AC/Sclera: 1(0). (Figure 4, eTable 1).

IV. Discussion

This is the first international consensus statement on putative descriptors of OSD and discriminators of 'activity' and 'damage' providing a platform for standardizing terminology when describing disease staging and progression. This is of considerable importance for identifying response to treatment and to enable robust

outcome comparisons between clinical trials or gauging response to novel tissue specific therapeutic interventions.[39]

Current OSD scoring systems are disparate, with multiple systems describing specific disease entities. While OSD-specific questionnaires relating to symptoms have been validated,[39] to date there is no generic consensus on accepted clinical indices and how these should be scored, independent of the underlying disease process. This is essential, as the overall end-stage for all OSD is ocular surface failure and, as such, it should be possible to assimilate a battery of clinical features and scales to apply broadly across numerous OSD processes, particularly at the early stages when the diseases may present with indistinguishable signs, e.g., red eye. To this end, we sought to establish an 'OSD Toolbox', where the clinician has the ability to select the most relevant 'tools' to accurately describe the clinical features of a patient who may not have a diagnosis or for whom the diagnosis is equivocal. This could provide the basis for stratifying the 'Tools' into descriptors of recognized disease entities. This process could allow retrospective analyses of clinical features at presentation, thereby identifying putative common features in stages of disease before the diagnosis is known. This methodology could enable clues to support earlier diagnosis and prediction of OSD clinical course thereby leading to earlier intervention and improved clinical outcomes.

The use of the Delphi approach in the healthcare setting is well established[12,40-42] and has been used effectively across multiple specialties (rheumatology,[16,32,43] ophthalmology,[12,31] palliative care,[40] orthopedics,[35] and anesthesiology[36, 37]). It excels when there is either a paucity of evidence, such as in the description of OSD, or when the available evidence is contradictory.[27, 42] Limitations include reliability and reproducibility, possibly due to group selection.[42,44,45] To overcome this, we identified participants based upon geographical distribution of the *British Ophthalmological Surveillance Unit* respondent data to ensure even expert representation of steering group attendees from across the United Kingdom.[26] As in other published literature, participant selection was non-random, so representativeness is not assured,[42] but potential bias was minimized through the use of anonymous web-based questionnaires throughout the process. Where group discussions were held, opportunity was given for each participant to lead part of the group discussion to reduce the effect of a dominant individual.

Often the Delphi process is used when evidence is limited or absent in a given subject field, leading to the possibility of collective group error.[41] Equally, the results may be in direct conflict with the available evidence. We included the majority of clinical parameters and ancillary grading tools, with the exclusion of very few indices. Since little has been excluded, collective group error has been attenuated, and the study has created an inclusive platform from which further refinements can be made. Work Package 2 saw a high level of agreement in Domain 5 (AC and Sclera), which has been the subject of a previous Delphi consensus endorsing reproducibility of the results of the Delphi process. [29]

High levels of agreement for were found for activity (conjunctival inflammation, foamy meibomian gland secretions, presence of anterior chamber cells, hypopyon) and damage (entropion, ectropion, horizontal forniceal involvement by fibrosis, iris atrophy). No clinical parameters or investigations were directly voted into the combined activity and damage domain. Some parameters failed reach sufficient consensus for classification as 'activity', 'damage' or 'activity and damage'. An example of this is tear film breakup time. This reached a 66.6% consensus for 'activity' in WP4, but only 50% consensus in WP5. A similar phenomenon occurred in the Cornea Domain, with none of the parameters being classified as measures of 'activity'. This is possibly because the votes were split across 'activity' and 'activity and damage'. Further iterations of the process are required for refinement. We acknowledge that setting a higher threshold resulted in exclusion of some parameters. The threshold was reduced to 70% for work package 5 to improve classification, but the Delphi process clearly highlighted significant disagreement among specialists, e.g., in corneal activity, and we believe this is likely to reflect the disparate nature of corneal disease. For this reason, no parameter was fully excluded, and those that did not meet a consensus were available in the reserve pool that was termed 'second tier'. We believe that corneal disease activity will be more easily defined in a disease specific context, beyond the remit of this exercise and will be focus for future validation work.

Following WP5, the distribution of votes among the remaining parameters highlighted sufficient uncertainty amongst participants such as the presence of filaments. This enabled these entities to default into a 2nd tier combined activity-damage domain rather than being excluded from the dataset.

The current list should be considered a platform for further development. Indeed, future work is required to refine the 'Tool Box' of clinical features describing OSD with scales for quantifying each parameter to enable its use in more specific disease processes.[12, 35-37] This will necessitate further group discussions, literature review, and definition of severity scales. Prospective collection of patient data, including patient-reported outcomes encompassing vision related quality of life and neuropathic pain (a clinical feature that has recently gathered considerable interest), are essential composites to computing an activity and damage score and generating an OSDISS. We recognize that the outcome of this Delphi process provides a 'first step' to achieving this goal and should not be seen as a final arbiter. It is hoped that by defining these in a disease-specific context, it will be clearer how to relate scales to activity or damage or both. This specifically benefits patients who present with early disease when the diagnosis is uncertain and only after detailed investigation and/or prolonged follow-up, the phenotype of the disease manifests a diagnosis. Furthermore, with wider application of certain ancillary tools, e.g., AS-OCT, this may alter the profile of how parameters and diseases are quantified.

This study considered 'activity' and 'damage' in the context of inflammation. While inflammation is the major contributor in many ocular surface diseases, we acknowledge that dysfunctional innervation or the mechanical breakdown of the corneal surface, e.g., in recurrent corneal erosion syndrome, may themselves relate to 'activity' and 'damage' independent of overtly manifest inflammation per se. There is, however, increasing awareness that all processes at a molecular level have an underlying inflammatory component, as tissue injury of any nature, whether exogenous or endogenous, will release cytokines, inflammatory mediators and promote recruitment of inflammatory cells. This has, for example, been recently recognized in the context of progressive conjunctival scarring in clinically quiescent eyes where neutrophils have been identified as critical in mediating disease progression.[46,47]

While the breadth of this toolbox may appear daunting, it is hoped that this Delphi process has taken the first step in pulling disparate indices into a single arena and for the first time gaining agreement. The most obvious utility for the OSIDSS scales outside the research setting is the provision of a matrix from which electronic patient records (**EPR**) can be developed. The purpose of this study was not to create individual scales for each disease, enabling those in current use to be adopted for EPR

prior to disease specific validation exercises. Ultimately, the point of this exercise was to create an environment for further development. For instance, in forniceal scarring, we would propose the adoption of the fornix depth measurer to measure scarring, as this has been through an intra- and inter- observer validation exercise.[9,48] In EPR development, this would be considered a continuous value that could be compared over time and for the purpose of recording damage. Conjunctival inflammation, however, may be considered through various ordinal scales, e.g., 1-4, 1-5 etc.[5,49] Until such validation exercises have been completed, developers may elect to choose one or the other in order to facilitate EPR completion. In turn these may provide benchmark data for national data collection and audit exercise.

V. Conclusion

The validation of longitudinal collection of clinical 'activity' and 'damage' with grading scales correlated to measures of patient perception, experience, and reported outcomes of disease will provide a valuable objective resource for interrogating accurately described clinical features at presentation when diagnosis is equivocal. This will provide clues to earlier diagnosis, prediction of disease course, and improved clinical outcomes. It will also allow standardization of research data and a unified approach to objective assessment of treatment response, specifically to novel interventions in a clinical setting.

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MEMBERSHIP OF PARTICIPATING GROUPS

Study group members, their qualifications and affiliations

Study group members contributed to steering group meetings and answered web-based questionnaires. They received reimbursement for travel expenses if they attended the steering group meetings. No other financial incentive was provided.

OSDISS Steering Group	
Sajjad Ahmad, MB BS, FRCOphth, PhD	St Paul's Eye Unit, Royal Liverpool University Hospital and Department of Eye and Vision Science, University of Liverpool, Mersey Side, L69 3BX. United Kingdom.
Anthony Bron, BSc, FRCOphth, FMedSci, FARVO	Nuffield Laboratory of Ophthalmology, John Radcliffe Hospital, Oxford, OX3 9DU. United Kingdom.
Matthew Burton, PhD, MA, DTM&H MRCP FRCOphth	1. London School of Hygiene and Tropical Medicine, Room 492, Keppel Street, London, WC1E 7HT, United Kingdom. 2. Honorary Consultant, Moorfields Eye Hospital, City Road, London, EC1V 2PD, United Kingdom.
John K. Dart, MA, DM, FRCS, FRCOphth	1. Moorfields Eye Hospital, City Road, London, EC1V 2PD, United Kingdom. 2. UCL Institute of Immunity and Transplantation, Royal Free Hospital, London, NW3 2PF, United Kingdom 3. Honorary Professor in Ophthalmology, Institute of Ophthalmology, UCL, London, EC1V 9EL.
Francisco Figueiredo, MD, PhD, FRCOphth	Ocular Surface Disease, Royal Victoria Infirmary, Queen Victoria Road, Newcastle upon Tyne, NE1 4LP. United Kingdom.
Gerd Geerling, MD	Dusseldorf University, Moorenstraße 5, 40225 Düsseldorf, Germany.
Nicholas Hawksworth, FRCS, FRCOphth	Singleton Hospital, Sketty Lane, Swansea, SA2 8QA. United Kingdom.
Deborah Jacobs, MD	Boston Foundation For Sight, 464 Hillside Avenue, Suite 205, Needham, MA 02494. United States.
Stephen Kaye, FRCS FRCOphth MD	Department of Ophthalmology, The Royal

	Liverpool University Hospital, Prescot Street, Liverpool, L7 8XP . United Kingdom.
S. Sai Kolli, MA(Cantab), FRCOphth, PhD	Queen Elizabeth Hospital Birmingham, Mindelsohn Way, Birmingham, B15 2WB. United Kingdom.
D. Frank Larkin, MD, MRCDPF, FRCS	1. Moorfields Eye Hospital, City Road, London, EC1V 2PD. United Kingdom. 2. UCL Institute of Immunity and Transplantation, Royal Free Hospital, London, NW3 2PF, United Kingdom
Sanjay Mantry, FRCSEd, FRCS (Glas), MRCOphth (Lond)	Tennent institute of Ophthalmology, Gartnavel general hospital, 1053 Great Western Road, Glasgow, GY2 0YN. United Kingdom.
Philip I. Murray, DO(RCS), PhD, FRCP, FRCS, FRCOphth	1. Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, United Kingdom. 2. Birmingham and Midland Eye Centre, Dudley Road. Birmingham. B18 7QU.
Christopher Liu, FRCOphth	Sussex Eye Hospital, Brighton BN2 5BF, Tongdean Eye Clinic, Hove, BN3 6QB. United Kingdom.
Saaeha Rauz PhD, FRCOphth (Chair)	1. Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, United Kingdom. 2. Birmingham and Midland Eye Centre, Dudley Road. Birmingham. B18 7QU.
Alexander Shortt, MSc PhD FRCOphth	1. UCL Institute of Immunity and Transplantation, Royal Free Hospital, London, NW3 2PF, United Kingdom 2. Moorfields Eye Hospital, 162 City Road,

	London, EC1V 2PD. United Kingdom.
Paul J. Tomlins, PhD, FRCOphth	1. Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, United Kingdom. 2. Birmingham and Midland Eye Centre, Dudley Road. Birmingham. B18 7QU.
David Verity, MD MA (Oxon) FRCOphth	Moorfields Eye Hospital, City Road, London, EC1V 2PD. United Kingdom.
Stephanie L Watson, PhD FRANZCO	Save Sight Institute, University of Sydney, NSW, Australia.
Geraint P Williams, PhD, FRCOphth	1. Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, United Kingdom. 2. Birmingham and Midland Eye Centre, Dudley Road. Birmingham. B18 7QU.
Colin Willoughby, FRCOphth, MD	Department of Ophthalmology, The Royal Liverpool University Hospital, Prescot Street, Liverpool, L7 8XP. United Kingdom.
Oculoplastics advisory group	
Brigita Drnovsek-olup, MD PhD.	Ljubljana University Medical Centre, Ljubljana, Slovenia.
Carole Jones, *FRCS FCOphth*	Maidstone Hospital, Hermitage Ln, Maidstone, Kent ME16 9QQ.
William R. Katowitz, MD	The Children's hospital of Philadelphia, 3401 Civic Centre Bvld, Philadelphia, PA 19104, United States.
Brian Leatherbarrow, FRCS, FRCOphth	Manchester Royal Eye Hospital, Oxford Road, Manchester, M13 9WL.
Raman Malhotra, FRCOphth	Corneo Plastic Unit, Queen Victoria Hospital NHS Trust, East Grinstead, West Sussex,

	RH19 3DZ.
David Verity, MD MA (Oxon) BM BCh FRCOphth	Moorfields Eye Hospital, City Road, London, EC1V 2PD. United Kingdom.
Uveitis advisory group	
Laure Caspers, MD.	Immune Eye Clinic, Ophthalmology, Brussels University Hospital, Centre Hospitalier, Universitaire St Pierre, 322 rue Haute, 1000 Brussels, Belgium.
Soon-Phaik Chee, FRCOphth, FRCS(G), FRCS(Ed), MMed(S'pore)	Head, Uveitis Service, Singapore National Eye Center, 11, Third Hospital Avenue, 168751. Singapore.
Alastair K. Denniston, PhD, FRCOphth, MB BChir	1. Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, United Kingdom. 2. Birmingham and Midland Eye Centre, Dudley Road. Birmingham. B18 7QU.
Douglas Jabs, MD, MBA	Professor and Chairman, Department of Ophthalmology, Mount Sinai School of Medicine, Mount Sinai Hospital One Gustave L. Levy Place, Box 1183, New York, NY 10029-6574. United States.
Peter McCluskey, FRANZCO	Director Save Sight Institute, University of Sydney & Sydney Eye Hospital, GPO Box 4337, Sydney NSW 2001. Australia.
Philip I. Murray, DO(RCS), PhD, FRCP, FRCS, FRCOphth.	1. Academic Unit of Ophthalmology, Institute of Inflammation and Ageing, University of Birmingham, Birmingham, United Kingdom. 2. Birmingham and Midland Eye Centre, Dudley Road. Birmingham. B18 7QU.
Miles Stanford, MD FRCP FRCOphth	Professor of clinical ophthalmology, St Thomas' Hospital Westminster Bridge Road,

	London, SE1 7EH. United Kingdom.
Manfred Zierhut, MD, PhD.	Associate Professor of Ophthalmology University Eye Hospital in Tübingen, Centre for Ophthalmology, Schleichstraße 12 230 72076, Tübingen.

Contributions

Mathewson P.A.	1(a) (b) (c); 2 (a); 3 (a) (c)
Williams G.P.	1(a) (b) (c); 2 (a); 3 (a) (d)
Watson S.L.	1 (b); 2 (b); 3 (c)
Hodson J.	1 (a); 2 (b); 3 (a) (c)
Bron A.J.	1 (b); 2 (b); 3 (c)
Rauz S.	1 (a) (b) (c) 2 (a) (b); 3 (a) (b) (c) (d)

1) (a) Providing conception and design
   (b) Data acquisition
   (c) Data analysis and interpretation
2) (a) Drafting the article
   (b) Revising it critically for important intellectual content
3) (a) Contributing to statistical analysis
   (b) Obtaining funding
   (c) Administrative, technical or material support
   (d) Supervision

The OSDISS Steering Group: (Lead Saaeha Rauz), Sajjad Ahmad, Anthony Bron, Matthew Burton, John K. Dart, Francisco Figueiredo, Gerd Geerling, Nicholas Hawksworth, Deborah Jacobs, Stephen Kaye, S. Sai Kolli, D. Frank Larkin, Sanjay Mantry, Philip I. Murray, Christopher Liu, Saaeha Rauz (Chair), Alex Shortt, Paul J. Tomlins, David Verity, Stephanie L Watson, Geraint P Williams, Colin Willoughby.

Oculoplastics Advisory Group: (Lead: David Verity), Brigita Drnovsek-olup, Carole Jones, William R. Katowitz, Brian Leatherbarrow, Raman Malhotra.

Uveitis Advisory Group: (Lead: Philip I. Murray), Laure Caspers, Soon Phaik Chee, Alastair K. Denniston, Douglas Jabs, Peter McCluskey, Philip I. Murray, Miles Stanford, Manfred Zierhut.

Figure legends

Figure 1: Diagrammatic representation summarizing the work packages forming the OSD Delphi process.

Figure 2: **Summary of the results from WP1 and WP2.** The results of the pre-meeting questionnaire (WP1) were discussed and categorized after anonymized voting at the first steering group meeting (WP2). Fifteen new parameters were added, 12 excluded and 2 were redeployed to a novel "ancillary grading tool" grouping (AGT). Some of the terms were altered at the first steering group meeting; 'tear meniscus' was changed to 'tear meniscus height', 'anterior blepharitis' was changed to 'anterior lid margin disease', 'measurement of upper/lower fornix' became 'measurement of upper/lower fornix central depth', 'central corneal ulceration' and 'central corneal depth' were changed to 'localized corneal ulceration' and 'localized corneal depth' respectively.

Figure 3: **Results of the second steering group meeting (WP3 and WP4 Workshop A).** Clinical parameters that met the ≥75% consensus threshold in the Web-based International Consultation (WP3) together with equivocal parameters that were positively considered by the Steering Group (WP4 WSA) are shown in column 1. Equivocal clinical parameters that did not reach the ≥75% consensus were placed in a "second tier". Similarly, Ancillary grading tools that achieved ≥75% consensus were included as tools essential for severity staging and the remainder were classified as 'second tier' to be used under specialist circumstances.
[♦added at the second meeting,* Term amended]

Figure 4: **Work Package 4 Workshop B and Work Package 5: Defining "activity" or "damage".** Attendees of the Second Steering Group Meeting (Work Package 4) were asked to participate in a web-based anonymous live voting exercise to determine clinical parameters and ancillary grading tools indicative of "activity" or "damage" or positively both "activity and damage". A ≥75% consensus was required to be classified as such for WP4 (percentage vote for classification is in parenthesis). The remaining clinical parameters and ancillary grading tools were arbitrated by a wider consultation of OSD specialists (WP5). A ≥70% consensus was required for WP5 to ensure classification of a greater number of parameters. Parameters highlighted in red were successfully classified following WP5 and those that did not meet 70% consensus, were defaulted to 'second tier' "activity" and "damage" to be used under specialist circumstances.

eFigure 1: **Preliminary ballot (Work Package 1)**. The first web-based questionnaire that was disseminated to participants prior to Work Package 2.

eFigure 2: **Web-based International Consultation (WP3).** Web-based International Questionnaire. Ocular Surface Disease Specialists were invited to vote on all 5 domains. Uveitis experts were asked to respond to Domains 4 (Cornea) and 5 (AC and Sclera) only. Oculoplastics experts were asked to respond to the Domains 1 (Tear film), 2 (Eyelids lid margins and Meibomian glands) and 4 (cornea).

Table 1: Summary of Ancillary Grading Tools

Considered	Included	Available in clinical practice

• Tear function index • Tear film osmolarity • Schirmer's test • Fluorescein staining • Lissamine green staining • Meibography (meibomian gland drop out) • Fornix depth measurement • Confocal microscopy - tarsus • Confocal microscopy - conjunctiva • Confocal microscopy - cornea • Endothelial cell morphology and counting - specular microscopy	**Domain 1: Tear film** • Tear film osmolarity • Schirmer's test • Fluorescein staining • Lissamine green staining **Domain 2: Lids, lid margins and meibomian glands** • Fornix depth measurement • Meibography • Photography **Domain 3: Conjunctiva and fornices** • Immunostaining • Fornix depth measurement • Photography	• B Scan ultrasound • Corneal topography e.g. Orbscan, pentacam • Endothelial cell specular microscopy • Fluorescein staining • Fluorescein angiography (but only 20% had a specific protocol for the anterior segment) • Impression and brush cytology for retrieval of cells • Histological and cell staining • Immunostaining • OCT – spectral domain • Pachymetry • Photography

• Tissue biomarkers (cells, proteins, lipids, gene expression) • Biofluid biomarkers (tears, aqueous humor, blood, serum) • Impression and brush cytology for retrieval of cells • Histological and cell staining • Immunostaining • Indocyanine green angiography • Fluorescein angiography	**Domain 4: Cornea** • Aethesiometry Orbscan/Pentacam • OCT - spectral domain • Pachymetry • Fluorescein staining • Lissamine green staining • Impression and brush cytology • Histological and cell staining • Photography • Endothelial cell specular microscopy	• Schirmer's test • Tonometry

• Aethesiometry (corneal sensation) • Corneal shape and thickness measurements; e.g. Orbscan and Pentacam • OCT - spectral domain • OCT - time domain • Wavefront aberrometry • Pachymetry • Corneal hysteresis • B-Scan Ultrasonography • High resolution anterior segment ultrasonography • Laser flare meter • Tonometry • Photography under standardized conditions	**Domain 5: AC and sclera** • Laser flare meter • Anterior segment ultrasound	

Footnote: A list of all tools considered is shown together with a summary of the grading tools that met the 75% threshold after WP3 (International consultation) categorized according to clinical domain. Those that did not meet this threshold became second tier investigations. These were; biofluid biomarkers, B-scan ultrasonography, Confocal microscopy (conjunctival), confocal microscopy (corneal), confocal microscopy (tarsal), corneal hysteresis, fluorescein angiography, indocyanine green angiography, OCT (time domain), tear function index, tissue biomarkers, tonometry, wavefront aberrometry. Availability of listed tools in clinical practice for >75% respondents is also shown. (Abbreviations: OCT, optical coherence tomography).

Figure 1

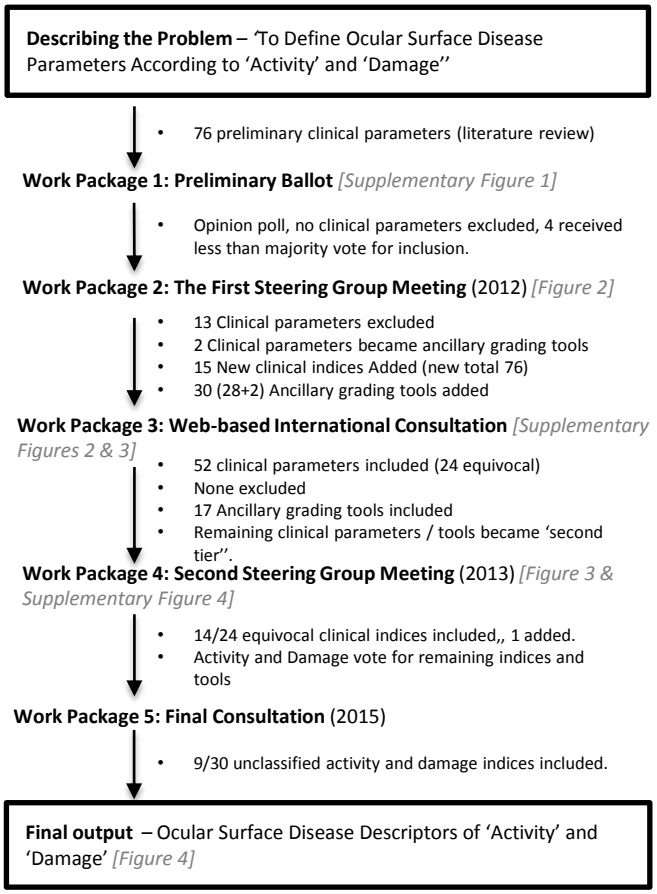

Describing the Problem – 'To Define Ocular Surface Disease Parameters According to 'Activity' and 'Damage''
• 76 preliminary clinical parameters (literature review)
Work Package 1: Preliminary Ballot *[Supplementary Figure 1]*
• Opinion poll, no clinical parameters excluded, 4 received less than majority vote for inclusion.
Work Package 2: The First Steering Group Meeting (2012) *[Figure 2]*
• 13 Clinical parameters excluded
• 2 Clinical parameters became ancillary grading tools
• 15 New clinical indices Added (new total 76)
• 30 (28+2) Ancillary grading tools added
Work Package 3: Web-based International Consultation *[Supplementary Figures 2 & 3]*
• 52 clinical parameters included (24 equivocal)
• None excluded
• 17 Ancillary grading tools included
• Remaining clinical parameters / tools became 'second tier''.
Work Package 4: Second Steering Group Meeting (2013) *[Figure 3 & Supplementary Figure 4]*
• 14/24 equivocal clinical indices included,, 1 added.
• Activity and Damage vote for remaining indices and tools
Work Package 5: Final Consultation (2015)
• 9/30 unclassified activity and damage indices included.
Final output – Ocular Surface Disease Descriptors of 'Activity' and 'Damage' *[Figure 4]*

Figure 2

	Included	Added	Excluded
Domain 1 Tear film	Tear film break up time Tear Meniscus Height Filaments	Tear clearance rate Tear film debris	InflammaDry **Schirmer's test (to ancillary grading tools)** **Tear film osmolarity (to ancillary grading tools)**
Domain 2 Lids and lid margins	**Lid position and margins** Lagophthalmos "close your eyes gently" Lid malposition Entropion Ectropion Lid margin irregularity Abnormal vascularity Anterior lid margin disease Medial Marx's line Central Marx's line Lateral Marx's line **Lashes** Lash loss Trichiasis Dystichiasis **Meibomian glands** Pouting/plugging Opaque/scarred Meibomian gland orifice retroplacement Visibility of acini Concretions Chalazion formation Foam Quality of secretions	Palpebral aperture Lid margin reflex distances (one and two) Completeness of the blink cycle Standardized meibomian gland expressibility Lid margin thickening	**Lid margins** Upper puncta Lower puncta **Mucocutaneous junction:** Anteroplacement Retroplacement Mucosal absorption Ridging **Meibomian glands:** Cystoid dilation of the main duct
Domain 3 Conjunctiva & fornices	**Conjunctiva** Conjunctival inflammation (with each outer quadrant scored separately) Ulceration of bulbar conjunctiva Limbitis (with each quadrant scored separately) Conjunctival mucus Conjunctival keratinization **Upper fornix** Measurement of upper fornix central depth Upper fornix number of symblephara Upper fornix horizontal involvement by symblephara Upper fornix horizontal fibrosis **Lower fornix** Measurement of lower fornix central depth Lower fornix number of symblephara Lower fornix horizontal involvement by symblephara Lower fornix horizontal involvement by fibrosis **Ocular mobility** Limitation in mobility	Punctate conjunctival staining Conjunctival papillae Conjunctival follicles	Peripheral ulcerative keratitis: degree of surface involvement Peripheral ulcerative keratitis: Depth.
Domain 4 Cornea	Sensation Punctate keratopathy Conjunctivalization Neovascularization (peripheral involvement) Neovascularization (encroaching on the visual axis) Corneal epithelial edema Corneal stromal edema Corneal opacification/scarring Corneal opacification/scarring encroaching on the visual axis Localized corneal thinning (no ulceration) Localized corneal ulceration Localized corneal ulcer depth Descemet's folds Reduced endothelial cell count (clinically apparent) Graft-host interface changes	Corneal Ischemia Endothelial guttatae	Endotheliitis Conjunctival keratinization (also on conjunctiva and kept there)
Domain 5 Anterior chamber & Sclera	***Anterior Chamber*** Keratitic precipitates Anterior chamber cells Flare Hypopyon Posterior synechiae ***Iris*** Iris nodules ***Sclera*** Anterior scleritis Posterior scleritis	Anterior synechiae (peripheral or central) Iris atrophy Intra-ocular pressure	Nil

Figure 3

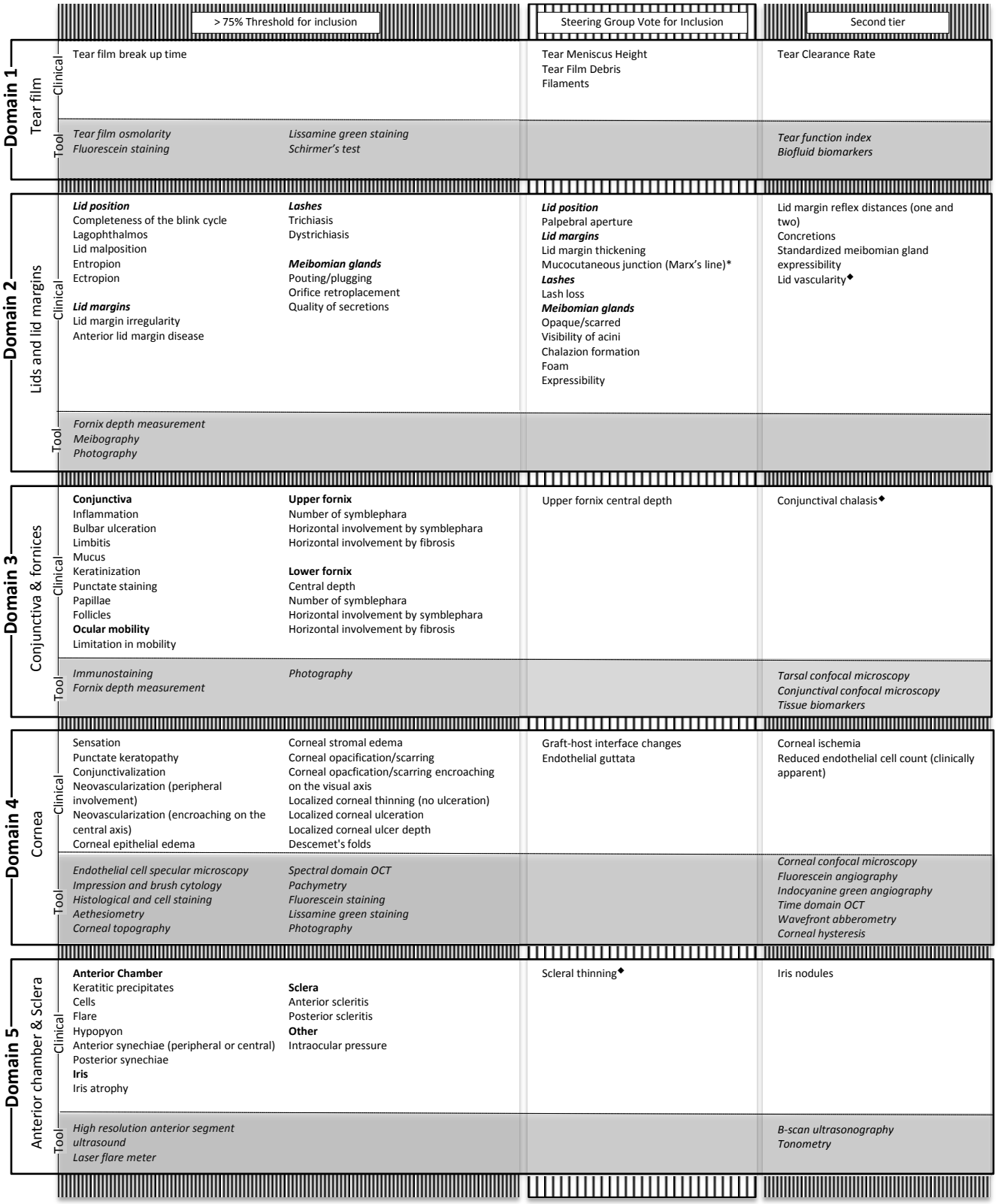
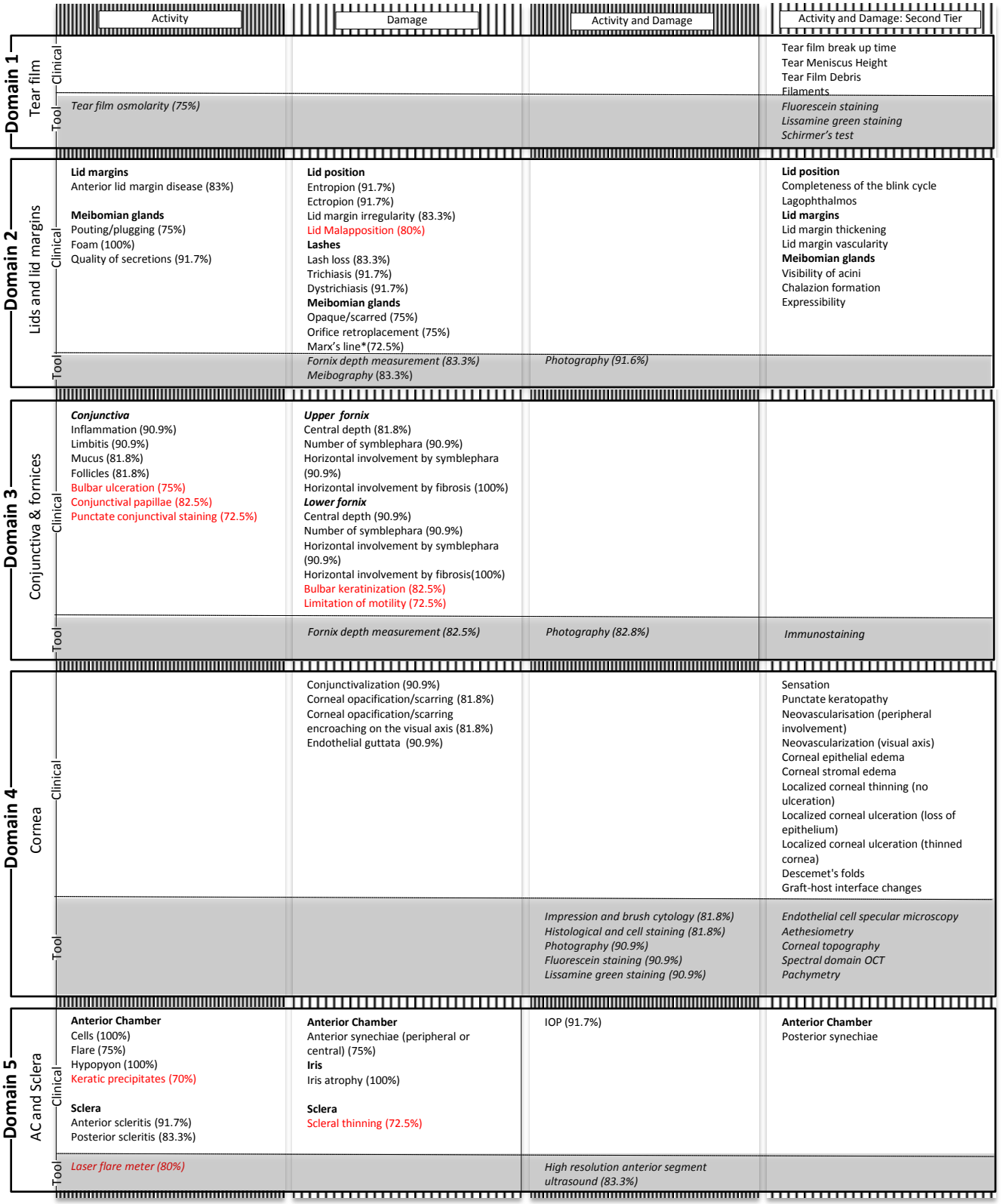

> 75% Threshold for inclusion
Steering Group Vote for Inclusion
Second tier
Domain 1
Tear film
Clinical
Tear film break up time
Tear Meniscus Height
Tear Film Debris
Filaments
Tear Clearance Rate
Tool
Tear film osmolarity
Fluorescein staining
Lissamine green staining
Schirmer's test
Tear function index
Biofluid biomarkers
Domain 2
Lids and lid margins
Clinical
Lid position
Completeness of the blink cycle
Lagophthalmos
Lid malposition
Entropion
Ectropion
Lid margins
Lid margin irregularity
Anterior lid margin disease
Lashes
Trichiasis
Dystrichiasis
Meibomian glands
Pouting/plugging
Orifice retroplacement
Quality of secretions
Lid position
Palpebral aperture
Lid margins
Lid margin thickening
Mucocutaneous junction (Marx's line)*
Lashes
Lash loss
Meibomian glands
Opaque/scarred
Visibility of acini
Chalazion formation
Foam
Expressibility
Lid margin reflex distances (one and two)
Concretions
Standardized meibomian gland expressibility
Lid vascularity◆
Tool
Fornix depth measurement
Meibography
Photography
Domain 3
Conjunctiva & fornices
Clinical
Conjunctiva
Inflammation
Bulbar ulceration
Limbitis
Mucus
Keratinization
Punctate staining
Papillae
Follicles
Ocular mobility
Limitation in mobility
Upper fornix
Number of symblephara
Horizontal involvement by symblephara
Horizontal involvement by fibrosis
Lower fornix
Central depth
Number of symblephara
Horizontal involvement by symblephara
Horizontal involvement by fibrosis
Upper fornix central depth
Conjunctival chalasis◆
Tool
Immunostaining
Fornix depth measurement
Photography
Tarsal confocal microscopy
Conjunctival confocal microscopy
Tissue biomarkers
Domain 4
Cornea
Clinical
Sensation
Punctate keratopathy
Conjunctivalization
Neovascularization (peripheral involvement)
Neovascularization (encroaching on the central axis)
Corneal epithelial edema
Corneal stromal edema
Corneal opacification/scarring
Corneal opacfication/scarring encroaching on the visual axis
Localized corneal thinning (no ulceration)
Localized corneal ulceration
Localized corneal ulcer depth
Descemet's folds
Graft-host interface changes
Endothelial guttata
Corneal ischemia
Reduced endothelial cell count (clinically apparent)
Tool
Endothelial cell specular microscopy
Impression and brush cytology
Histological and cell staining
Aethesiometry
Corneal topography
Spectral domain OCT
Pachymetry
Fluorescein staining
Lissamine green staining
Photography
Corneal confocal microscopy
Fluorescein angiography
Indocyanine green angiography
Time domain OCT
Wavefront abberometry
Corneal hysteresis
Domain 5
Anterior chamber & Sclera
Clinical
Anterior Chamber
Keratitic precipitates
Cells
Flare
Hypopyon
Anterior synechiae (peripheral or central)
Posterior synechiae
Iris
Iris atrophy
Sclera
Anterior scleritis
Posterior scleritis
Other
Intraocular pressure
Scleral thinning◆
Iris nodules
Tool
High resolution anterior segment ultrasound
Laser flare meter
B-scan ultrasonography
Tonometry

Figure 4


Activity
Damage
Activity and Damage
Activity and Damage: Second Tier
Domain 1
Tear film
Clinical
Tear film break up time
Tear Meniscus Height
Tear Film Debris
Filaments
Tool
Tear film osmolarity (75%)
Fluorescein staining
Lissamine green staining
Schirmer's test
Domain 2
Lids and lid margins
Clinical
Lid margins
Anterior lid margin disease (83%)
Meibomian glands
Pouting/plugging (75%)
Foam (100%)
Quality of secretions (91.7%)
Lid position
Entropion (91.7%)
Ectropion (91.7%)
Lid margin irregularity (83.3%)
Lid Malapposition (80%)
Lashes
Lash loss (83.3%)
Trichiasis (91.7%)
Dystrichiasis (91.7%)
Meibomian glands
Opaque/scarred (75%)
Orifice retroplacement (75%)
Marx's line*(72.5%)
Lid position
Completeness of the blink cycle
Lagophthalmos
Lid margins
Lid margin thickening
Lid margin vascularity
Meibomian glands
Visibility of acini
Chalazion formation
Expressibility
Tool
Fornix depth measurement (83.3%)
Meibography (83.3%)
Photography (91.6%)
Domain 3
Conjunctiva & fornices
Clinical
Conjunctiva
Inflammation (90.9%)
Limbitis (90.9%)
Mucus (81.8%)
Follicles (81.8%)
Bulbar ulceration (75%)
Conjunctival papillae (82.5%)
Punctate conjunctival staining (72.5%)
Upper fornix
Central depth (81.8%)
Number of symblephara (90.9%)
Horizontal involvement by symblephara (90.9%)
Horizontal involvement by fibrosis (100%)
Lower fornix
Central depth (90.9%)
Number of symblephara (90.9%)
Horizontal involvement by symblephara (90.9%)
Horizontal involvement by fibrosis(100%)
Bulbar keratinization (82.5%)
Limitation of motility (72.5%)
Tool
Fornix depth measurement (82.5%)
Photography (82.8%)
Immunostaining
Domain 4
Cornea
Clinical
Conjunctivalization (90.9%)
Corneal opacification/scarring (81.8%)
Corneal opacification/scarring encroaching on the visual axis (81.8%)
Endothelial guttata (90.9%)
Sensation
Punctate keratopathy
Neovascularisation (peripheral involvement)
Neovascularization (visual axis)
Corneal epithelial edema
Corneal stromal edema
Localized corneal thinning (no ulceration)
Localized corneal ulceration (loss of epithelium)
Localized corneal ulceration (thinned cornea)
Descemet's folds
Graft-host interface changes
Tool
Impression and brush cytology (81.8%)
Histological and cell staining (81.8%)
Photography (90.9%)
Fluorescein staining (90.9%)
Lissamine green staining (90.9%)
Endothelial cell specular microscopy
Aethesiometry
Corneal topography
Spectral domain OCT
Pachymetry
Domain 5
AC and Sclera
Clinical
Anterior Chamber
Cells (100%)
Flare (75%)
Hypopyon (100%)
Keratic precipitates (70%)
Sclera
Anterior scleritis (91.7%)
Posterior scleritis (83.3%)
Anterior Chamber
Anterior synechiae (peripheral or central) (75%)
Iris
Iris atrophy (100%)
Sclera
Scleral thinning (72.5%)
IOP (91.7%)
Anterior Chamber
Posterior synechiae
Tool
Laser flare meter (80%)
High resolution anterior segment ultrasound (83.3%)

	WP4 WSB Activity (%)	WP5 Activity (%)	WP4 WSB Damage(%)	WP5 Damage(%)	WP4 WSB Activity and Damage (%)	WP5 Activity and Damage (%)	Final Category
Domain 1: Tear Film							
Tear film break up time	66.6	50	8.3	2.5	25	47.5	2nd Activity/Damage
Tear meniscus height	41.7	37.5	25	32.5	33.3	30	2nd Activity/Damage
Tear film debris	58.3	57.5	8.3	10	33.3	32.5	2nd Activity/Damage
Filaments	58.3	57.5	8.3	10	33.3	32.5	2nd Activity/Damage
Tearfilm osmolarity	**75**		8.3		16.7		Activity
Schirmer's test	16.7	32	41.7	40	41.7	35	2nd Activity/Damage
Fluorescein staining	25	42.5	25	10	50	47.5	2nd Activity/Damage
Lissamine green staining	25	42.5	25	10	50	47.5	2nd Activity/Damage

	WP4 WSB Activity (%)	WP5 Activity (%)	WP4 WSB Damage(%)	WP5 Damage(%)	WP4 WSB Activity and Damage (%)	WP5 Activity and Damage (%)	Final Category
Domain 2: Eyelids, lid margins and meibomian glands							
Palpebral aperture	8.3		25		66.7		Unclassified
Completeness of the blink cycle	8.3	5	41.7	32.5	50	57.5	2nd Activity/Damage
Lagophthalmos	8.3	15	50	70	41.7	15	2nd Activity/Damage
Lid malposition	0	7.5	66.7	**80**	33.3	12.5	Damage
Entropion	8.3		**91.7**		0		Damage
Ectropion	8.3		**91.7**		0		Damage
Lid margin irregularity	8.3		**83.3**		8.3		Damage
Lash Loss	8.3		**83.3**		8.3		Damage
Trichiasis	8.3		**91.7**		0		Damage
Dystichiasis	8.3		**91.7**		0		Damage
Anterior lid margin disease	**83**		17		0		Activity
M. Gland pouting/plugging	**75**		8.5		16.7		Activity
M. Gland opaque/scarred	0		**75**		25		Damage
M. Gland orifice retroplacement	0		**75**		25		Damage
M. Gland visibility of acini	41.7	42.5	33.3	10	25	47.5	2nd Activity/Damage
Chalazion formation	41.7	42.5	25	47.5	33.3	10	2nd Activity/Damage
Foam	**100**		0		0		Activity

Quality of secretions	**91.7**		8.3		0		Activity
M.Gland expressibility	66.7	47.5	0	10	33.3	42.5	2nd Activity/Damage
Lid margin thickening	41.7	42.5	8.3	10	50	47.5	2nd Activity/Damage
Lid margin vascularity	41.7	42.5	8.3	10	50	47.5	2nd Activity/Damage
Position of Marx's line	8.3	5	58.3	**72.5**	33.3	12.5	Damage
Fornix depth measurement	0		**83.3**		16.7		Damage
Meibography	0		**83.3**		16.7		Damage
Photography	8.3		0		**91.6**		Activity/Damage

	WP4 WSB	WP5	WP4 WSB	WP5	WP4 WSB	WP5	Final Category
	Activity (%)	Activity (%)	Damage(%)	Damage(%)	Activity and Damage (%)	Activity and Damage (%)	
Domain 3: Conjunctiva and fornices							
Conjunctival inflammation	**90.9**		9.1		0		Activity
Bulbar ulceration	63.3	**75**	18.2	0	18.2	15	Activity
Limbitis	**90.9**		9.1		0		Activity
Mucus	**81.8**		18.2		0		Activity
Bulbar conjunctival keratinisation	9.1	10	72.7	**82.5**	18.2	7.5	Damage
Conjunctival punctate staining	63.3	**72.5**	18.2	5	18.2	22.5	Activity
Papillae	63.3	**82.5**	9.1	12.5	27.4	5	Activity
Follicles	**81.8**		9.1		9.1		Activity
Upper fornix central depth	9.1		**81.8**		9.1		Damage
Upper fornix number of symblephara	0		**90.9**		9.1		Damage
Upper fornix horizontal involvment by symblephara	0		**90.9**		9.1		Damage

Upper fornix horizontal involvement by fibrosis	0		**100**		0		Damage
Lower fornix central depth	0		**90.9**		9.1		Damage
Lower fornix number of symblephara	0		**90.9**		9.1		Damage
Lower fornix horizontal involvment by symblephara	0		**90.9**		9.1		Damage
Lower fornix horizontal involvement by fibrosis	0		**100**		0		Damage
Limitation of mobility	0	2.5	63.3	**72.5**	36.4	25	Damage
Immunostaining	54.5	27.5	9.1	52.5	36.4	20	2nd Activity/Damage
Fornix depth measurement	0	0	63.3	**82.5**	36.4	17.5	Damage
Photography	18.2		0		**82.8**		Activity/Damage

	WP4 WSB Activity (%)	WP5 Activity (%)	WP4 WSB Damage(%)	WP5 Damage(%)	WP4 WSB Activity and Damage (%)	WP5 Activity and Damage (%)	Final Category
Domain 4: Cornea							
Corneal sensation	18.2	10	45.5	65	36.4	20	2nd Activity/Damage
Punctate keratopathy	54.5	65	36.4	5	9.1	30	2nd Activity/Damage
Conjunctivalisation	9.1		**90.9**		0		Damage
Neovascularisation (peripheral)	18.2	7.5	18.2	37.5	63.6	55	2nd Activity/Damage
Neovascularisation (visual axis)	18.2	7.5	18.2	37.5	63.6	55	2nd Activity/Damage
Epithelial oedema	18.2	50	18.2	15	63.6	35	2nd Activity/Damage
Stromal Oedema	9.1	32.5	18.2	17.5	72.7	50	2nd Activity/Damage
Corneal opacification/scarring (peripheral)	0		**81.8**		18.2		Damage
Opacification/scarring (visual axis)	0		**81.8**		18.2		Damage
Localised thinning (no ulceration)	9.1	7.5	72.7	55	18.2	37.5	2nd Activity/Damage

Localised ulceration	18.2	60	18.2	10	63.6	30	2nd Activity/Damage
Localised ulcer depth (thinned cornea)	18.2	17.5	27.2	30	54.5	52.5	2nd Activity/Damage
Descemet's folds	27.2	55	9.1	7.5	63.6	37.5	2nd Activity/Damage
Graft-host interface changes	9.1	7.5	27.2	27.5	63.6	65	2nd Activity/Damage
Endothelial guttae	0		**90.9**		9.1		Damage
Specular microscopy	9.1	0	72.7	55	18.2	45	2nd Activity/Damage
Impression/brush cytology	18.2		0		**81.8**		Activity/Damage
Histological/cell staining	18.2		0		**81.8**		Activity/Damage
Anaesthesiometer	0	5	54.5	67.5	45.5	27.5	2nd Activity/Damage
Corneal shape/ thickness measurements	0	5	54.5	47.5	45.5	47.5	2nd Activity/Damage
Optical coherence tomography	9.1	5	18.2	30	72.7	65	2nd Activity/Damage
Pachymetry	9.1	7.5	18.2	27.5	72.7	65	2nd Activity/Damage
Fluorescein staining	9.1		0		**90.9**		Activity/Damage
Lissamine green staining	9.1		0		**90.9**		Activity/Damage
Photography	0		9.1		**90.9**		Activity/Damage

	WP4 WSB	WP5	WP4 WSB	WP5	WP4 WSB	WP5	Final Category
	Activity (%)	Activity (%)	Damage(%)	Damage(%)	Activity and Damage (%)	Activity and Damage (%)	
Domain 5: AC and Sclera							
Keratic Precipitates	58.3	**70**	0	5	41.7	25	Activity
Anterior chamber cells	**100**		0		0		Activity
Flare	**75**		0		25		Activity
Hypopyon	**100**		0		0		Activity
Anterior synechiae (peripheral/central)	0		**75**		25		Damage
Posterior synechiae	0	12.5	50	50	50	27.5	2nd Activity/Damage
Iris atrophy	0		**100**		0		Damage
Intraocular pressure	8.3		0		**91.7**		Activity/Damage
Anterior Scleritis	**91.7**		0		8.3		Activity
Posterior scleritis	**83.3**		0		16.7		Activity
Scleral thinning	0	7.5	70	**72.5**	30	20	Damage
Anterior segment ultrasonography	16.7		0		**83.3**		Activity/Damage
Laser flare meter	50	**80**	0	20	50	0	Activity