APPENDIX 10

DEWS	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	Mark Willcox	10th Jan 2006
TEST	**Tear meniscus radius, height and cross sectional area**	
TO DIAGNOSE	Aqueous tear deficiency (ATD).	REFERENCES
VERSION	[V 1] **Meniscometry**	Yokoi Komuro 2004
DESCRIPTION	A rotatable projection system with a target comprising black and white stripes is projected onto the lower central tear film meniscus. Images are recorded and transferred to computer in order to calculate radius of curvature	
CONDUCT of TEST	1. The subject is seated at a slit lamp 2. A rotatable projection system with a target comprising a series of black and white stripes (4 black and 5 white; each 4mm wide), is introduced coaxially using a half-silvered mirror 3. Images of the tear meniscus (of either or both eyes) are recorded with a digital video recorder 4. Images are transferred to a computer and image analysis software used to calculate the radius of curvature of the meniscus by applying the concave mirror formula	
Web Video	Not available	
Materials:	• Slit lamp • Rotatable projection system (see above) with half silvered mirror • Digital video recorder plus TV monitor • Computer plus software • Colour printer	Oguz et al 2000
Variations of technique	Several alternative methods have been published including: 1. Use of variable beam height on a slit lamp 2. Measurement and grading of meniscus integrity using slit lamp 3. Using a video slit lamp biomicroscope but no projected stripes 4. Measurement after instillation of fluorescein	Nichols et al 2004a Cermak et al 2003 Glasson et al 2003 Farrell et al 2003 Oguz et al 2000
Standardisation	Assumed to be influenced by: Time of day [√] Temperature [√] Humidity [√] Air speed [√] Illumination [√]	
Repeatability	Intra-observer agreement. [Not recorded for V1 – but poor in Nichols et al system]	
Sensitivity	Tear meniscus height: cut off of: < 0.18 mm (true positives) Farrell et al's technique = [72.8%]	Farrell et al 2003
Specificity	(100 – false positives) Farrell's technique = [66.6%]	
Sensitivity	Tear Meniscus Height: Small vol. fluorescein: cut off < 0.35mm (true positives) Mainstone et al = [93.3%]	Mainstone et al 1996
Specificity	(100 – false positives) Mainstone et al = [66.7%]	
Other Stats	For V1 – significantly lower meniscus height in dry eye subjects. Plugging puncta significantly increased meniscus height. Significant correlation between meniscus height and Schirmer test Cermak et al – significantly lower meniscus height in androgen insensitive female subjects who demonstrated dry eyes Farrell et al – significant decrease in dry eye subjects compared with controls; significant increase in dry eye subjects with puncta occluded Correlations noted between meniscus curvature and meniscus height in presence or absence of fluorescein Tear meniscus height and area reduced in subjects intolerant to contact lens wear compared with tolerant subjects Nichols et al (2004b) demonstrated lack of association between tear meniscus height and symptoms of dry eye.	Yokoi and Komuro 2004 Cermak et al 2003 Farrell et al 2003 Oguz et al 2000 Glasson et al 2003 Nichols et al 2004b
Test problems	Positioning of subject etc and use of specialized equipment	
Forward Look	To adapt the V1 method for general use.	

continued

APPENDIX 10 *continued*

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APPENDIX 11

DEWS	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	Eiki Goto, MD	15th Mar 2006
TEST	**Tear film lipid layer interferometry**	
TO DIAGNOSE	Aqueous tear deficient dry eye (ATD) or precorneal lipid tear deficiency.	REFERENCES
VERSION	[V6]	Goto et al 2003
DESCRIPTION	Superficial tear lipid layer is observed with tear interference camera. Interference images are graded on dry eye severity or analyzed to quantify lipid layer thickness.	Korb and Greiner 1994; King-Smith et al 1999; Yokoi et al 1996; Mathers et al 1997; Goto et al 2003
CONDUCT of TEST	1. The subject is seated comfortably at the tear interference camera and the head positioned on the chin rest. 2. With the eyes in normal blinking interference images are monitored. 3. After a few seconds of blinking, when the interference image becomes stable, the image is captured. 4. Lipid layer thickness is estimated using a color comparison table (Korb and Greiner). 5. Interference images are semi-quantitatively graded on the pattern and color. (Yokoi et al) 6. In a kinetic analysis, interference images are recorded on a video over several natural blink intervals for 30 seconds. In a representative blink interval, lipid spread time from eye opening to the cessation of lipid movement is measured. (Goto and Tseng) 7. When image analysis is needed, the captured, still, interference image is analyzed by its colour profile. Lipid layer thickness is quantified with the color chart system. (Goto et al)	Doane 1989; Korb and Greiner 1994; Yokoi et al 1996; Goto and Tseng 2003 Goto et al 2003 Korb et al 2005
Web Video	Not available	
Materials	• Tear interference camera (DR-1, Kowa, Nagoya, Japan), Dr. Korb's camera, Dr. Doane's camera or Tearscope (Keeler, Windsor) • Digital printer • Hopefully PC for image capturing	Yokoi et al 1996 Goto and Tseng 2003
Standardization	Time of day [√] Temperature [√] Humidity [√] Air speed [√] Illumination [√] Other: [blinking √]. Assumed to influence	
Variations of technique	V1, Tear lipid layer interference images were observed using devices such as Tearscope. V2, Lipid layer thickness was estimated using color comparison method. V3, Images were captured using modified specular microscope and graded on dry eye severity in Sjogren syndrome. V4, Interference camera was sophisticated (DR-1, Kowa, Japan) and images were graded on dry eye severity. V5, Kinetic analysis of interference images using DR-1 to measure lipid spread time. V6, Precorneal lipid layer thickness was quantified using colorimetric system in DR-1. V7, Lipid layer thickness topography was processed. * Tear interference patterns on contact lens are also evaluated by Guillon or Maruyama.	Guillon 1992 Korb and Greiner 1994 Danjo and Hamano 1995 Yokoi et al 1996 Tiffany et al 2001 Goto and Tseng 2003 Goto et al 2003 Goto et al 2004 Maruyama et al 2004
Diagnostic value	See references 4 and 5.	Yokoi et al 1996 Yokoi et al 1999
Repeatability	Intra-observer agreement. [+], V4 on grading and V5 on grading and Kinetic analysis Inter-observer agreement. [–]	Yokoi et al 1996; Yokoi et al 1999; Goto and Tseng 2003; Goto and Tseng 2003

continued

APPENDIX 11 *continued*

Test problems	a. Colour intensity of interference images are influenced by the refractive indices of tear lipid and aqueous layers and specular angle. b. Interference images are influenced by how to blink, thus to record the non-invasive status of the lipid layer, it is important for the subject to blink naturally. c. Lipid quality could not be indicated by interferometry. d. Amount of meibum secretion observed at lid margin does not always correlate with the precorneal lipid layer thickness (a phenomenon, not a test problem)	Goto et al 2003 King-Smith et al 1999 Tiffany 1986
Test solutions	a. Image analysis for lipid thickness quantification need to be developed more.	
FORWARD LOOK	a. Identify cut-off for MGD, and ATD diagnosis. b. Incorporate MGD diagnosis into diagnosis of evaporative dry eye or precorneal lipid deficiency. c. Image analysis on raw interference image and quantification of lipid layer thickness in a mapping form. Clinically useful index from mapping for comparison and stats.	
Glossary	ATD = Aqueous tear deficient dry eye	

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APPENDIX 12

DEW	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	Murat Dogru	24th Oct 2004
TEST	**Tear Stability Analyses System (TSAS)**	
TO DIAGNOSE	Test used to diagnose –Tear Instability Refs:	Kojima 2004 Goto 2004a,b
VERSION	[TMS-2N]	Kojima 2004
DESCRIPTION	Noninvasive and objective test for tear film stability analysis	
Study	To compare the sensitivity and specificity of TSAS with the BUT (based on slit-lamp examination and use of fluorescein), 48 volunteers without any eye disease, surgery or drug use within 1 year of study were recruited. See below.	Goto 2004a
CONDUCT of TEST	Subject seated in front of TMS-2N corneal topography unit. Subject asked not to blink for 10 seconds with test initiation Device automatically captures corneal topograms each second for 11 consecutive seconds, displayed as time plot curves of SRI, SAI, BUT area	
Results of Study	See study, above. 42.5% (34 eyes) of the 80 eyes of the volunteers studied had a normal BUT and 57.5% had an abnormal BUT. On the basis of the subjects' dry eye symptoms such as FBS, soreness, dryness etc, the sensitivity and specificity of the BUT were 75% and 60% respectively. Among 34 eyes with a normal BUT, 11 (32.35%) were found to have an abnormal TMS BUT. Of these eyes, 9 (81.8%) were from 6 subjects who had dry eye symptoms in their questionnaires. On the basis of symptomatology, the sensitivity and specificity of TMS BUT was 97.5 and 62.5% respectively. The difference of sensitivity between SLE BUT and TMS BUT was significant; however, the difference in specificity was not.	
Web Video	Not available	
Materials	TMS-2N corneal topography device TSAS software(Tomey Inc)	
Standardization	Time of day [√] Temperature [√] Humidity [√] Air speed [√] Illumination [√] . Assumed to influence.	
Sensitivity	(true positives) [97.5%]	Goto 2004a
Specificity	(100 – false positives) [62.5 %]	
Test problems	Although the test appears to be a promising, non-invasive method to test tear stability, it is not known whether the test is evaluating tear stability due to lipid layer or overall tear film changes. Only one study compares the test with the invasive fluorescein aided BUT measurement. Normal values of this test and age-specific cut off values on a large set of subjects not yet established. Comparative studies with other invasive and non-invasive tests of tear stability do not exist as yet. Needs a corneal topography device and the software which makes it expensive compared to fluorescein aided BUT testing.	
Test solutions	The above mentioned studies will prepare this test for general clinical prime time.	
Forward Look	The device is still being furnished with novel parameters such as BUT area. For dynamic analyses of tear functions in dry eye syndromes and ocular surface disorders, I believe that this new system is set to play an important role in the future.	
Glossary	TSAS: Tear Stability Analyses System	

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APPENDIX 13

DEWS	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	John M. Tiffany	12th Nov 2004
TEST	**MEIBOMETRY**	
TO DIAGNOSE	Meibomian Gland Dysfunction — (MGD)	REFERENCES
VERSION of TEST	[V1]	Komuro et al 2002
DESCRIPTION	Lipid on the lower central lid margin is blotted onto a plastic tape and the amount taken up read by optical densitometry. This provides an indirect measure of the steady state level of meibomian lipid.	
CONDUCT of TEST	1. The subject is seated, with the head resting comfortably at the slit-lamp. 2. With the eyes in upgaze, the right lower lid is drawn down lightly without pressure on the tarsal plate. 3. A standard loop of plastic tape, held in an applanation or ultrasonography probe holder, is applied to the central third of the everted lid margin for 3 seconds, at 0 mmHg exerted pressure. 4. The tape is air dried for 3 minutes to allow tear evaporation if necessary. 5. The increase in transparency induced by the lipid blot, is read in the laser meibometer. 6. The Casual Lipid level (expressed as arbitrary optical density units) is calculated as (C-B), where C is the casual reading, B is the reading from the untouched tape (background).	Komuro et al 2002
Video need	Not available.	
Materials	• Plastic tape: 8 mm wide (Courage and Khazaka, Köln) • Tape Holder:(eg. NIDEK ultrasonographic probe holder. • Laser Meibometer. Window size (2.5 x 5.0 mm2)	
Standardization	Time of day [x] The level is highest in the first hour after waking, but thereafter settles to a constant level through most of the day	
Variations of technique	In the original version, [V2] optical density was read using an adaptation of the Courage and Khazaka sebumeter. A point reading was taken at the centre of the blot. Other methods exist in which the blot is scanned and the increase in transparency is integrated over the length of the blot . The spring-clip holding the loop of tape can be mounted with wax, modeling clay or "Blu-Tack" to the end of a thin wooden rod (eg, a bamboo kitchen skewer) held upright by a lump of wax to the ultrasonography mounting-plate; this also exerts zero pressure on the eyelid. After blotting, the loop is opened and attached to a highly-reflective surface (mirror or polished metal) for scanning.	Chew et al 1993a,b Yokoi et al 1999
Test problems	a. In normal subjects the lipid blot is uniform and results can be extrapolated to the total lid length. In MGD, focal gland obstruction may vary along the lid length so that central readings may not truly reflect the overall picture. b. Calibrations and assumptions are required to convert raw densitometry readings into meibomian lipid equivalent values.	
Test solutions	a. Measurement should be made along the whole of the lower lid length in order to reflect variation in MGD. b. If the scanning method is used, either a maximally-wide or a very narrow area across the blot should be integrated, to give either an averaged reading including regions with non-functional glands, or a reading only from a selected area of full blotting.	
Forward Look	a. Develop a system to integrate lipid along full lid length. b. Identify cut-off for MGD diagnosis. c. Incorporate MGD diagnosis into diagnosis of evaporative dry eye.	
Glossary	MGD: Meibomian gland dysfunction	

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APPENDIX 14

DEWS	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	Gary N. Foulks	19th Oct 04
TEST	**MEIBOGRAPHY/MEIBOSCOPY**	REFERENCES
TO DIAGNOSE	Meibomian gland morphology and density and drop out. Diagnosis of Meibomian gland dysfunction (MGD)	Robin et al 1985 Jester et al 1982
VERSION	[V1]	*reference 1 above*
DESCRIPTION	Meiboscopy is the visualization of the meibomian gland by transillumination of the eyelid. Meibography implies photographic documentation	Mathers et al 1994
CONDUCT of TEST	Meiboscopy: The most basic version uses white light from a Finoff transilluminator. This is applied to the cutaneous side of the everted eyelid and allows observation from the conjunctival surface The presence and morphology of the glands can be observed and gland loss, or "drop out" quantified. Meibography is the photographic documentation of the image of the gland under such illumination. Variations on the theme include the use of infrared photography or videophotography.	
Web Video	Not available	
Materials	• Finoff head light, slit lamp biomicroscope • (variation: infrared light source and sensor; videography)	
Variations of technique	1) infrared photography 2) videography Variations in scoring systems.	Pflugfelder 1998 Shimazaki 1998 Yokoi 2007
Standardization	Illumination [√]	
Diagnostic value	This version : [x] Most reliable test in patients with ectodermal dysplasia syndrome Other version: [ ]	Kaercher et al 2004
Other Stats	Greatest value is determining presence or absence of gland. Morphological variations, while interesting, are more difficult to quantify.	
Test problems	The limitation is the subjective nature of the observation.	
Test solutions	An improvement could be standardized photographs as reference.	
Forward Look	Improved photographic documentation.	
Glossary	MGD: Meibomian gland dysfunction	

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APPENDIX 15

DEWS	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	Kazuo Tsubota	14th Dec 2004
TEST	**Brush Cytology Technique**	
TO DIAGNOSE	A variety of ocular surface diseases	REFERENCES
VERSION	[1]	
DESCRIPTION	Brush cytology is the technique which collects conjunctival epithelial samples from the patient, clinically. This method is different from impression cytology in that brush cytology can obtain basal cells as well as superficial cells.	Tsubota 1990 (a) Tsubota 1990 (b) Tsubota, 1991 Fukagawa 1993 Fujihara 1997 Miyoshi 2001 Takano 2004
CONDUCT of TEST	Brushing cytology of the conjunctiva is a moderately invasive but can provide a valuable snapshot of the surface of the eye to evaluate many conjunctival conditions.	
Video needed	Not available	
Materials	• Small Brush (Teikokuzouki Pty. Ltd., Japan), • Hank's buffered solution, • Millipore filter (Millipore Corp., Bedford, MA)	
Standardization	The strength of the pressure applied to the conjunctiva by brush should be moderate.	
Diagnostic value	This version is useful to evaluate: 1) squamous metaplasia, 2) detecting inflammatory cells, 3) expression of several surface markers on the ocular surface epithelium.	Tsubota 1990 (b)
Test problems	The procedure is slightly invasive to the patient as the cells are detached from the ocular surface	
Test solutions	Use a very soft brush (do not use a rough brush)	
Forward Look	Since more than 100,000 cells are obtained using brush cytology, this is a very good technique to see molecular expression by each cell. Thus this technique, combined with flow cytometry can give us more detailed information about events at the ocular surface at the cellular level.	

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APPENDIX 16

DEWS	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	Christophe Baudouin	7th Nov 2004
TEST	**Flow cytometry in impression cytology**	
TO DIAGNOSE	Conjunctival inflammation / apoptosis	REFERENCES
VERSION of TEST	[V 1] [V2] Also available: Brush cytology for cell collection before flow cytometry procedures (Fujihara et al., 1997).	Baudouin et al 1997 Fujihara et al 1997
DESCRIPTION	This technique is highly sensitive and specific for analyzing expression of any marker by conjunctival epithelial cells, or identification of inflammatory and goblet cells. HLA-DR normally not or weakly expressed. Strongly overexpressed in case of ocular surface inflammation	
NATURE of STUDY	Technique specially relevant in dry eye, allergy or assessment of antiglaucoma eyedrops	Brignole et al 2000, 2001
CONDUCT of TEST	1. Without or under topical anesthesia with one drop of 0.04% oxibuprocaine, one or more filters, 13 x 6.5 mm in size, are gently applied to the conjunctival surface. 2. After removal, the membranes are dipped into tubes containing 0.05% paraformaldehyde. The tubes have to be kept at 4°C before and after impression collection in order to avoid sample degradation during the phase of fixation. Under this condition the filters with the conjunctival specimens can be stored several days and sent to the laboratory in cold-conditioned containers before being processed for flow cytometry analyses. 3. Cell extraction is manually conducted by gentle agitation. After centrifugation in PBS, conjunctival cells are then immunostained and analyzed by flow cytometry. 4. Indirect or direct immunofluorescence procedures may be used. Simple or multi-color analysis can be performed commonly using 2 to 4 antibodies conjugated with different fluorochromes. A nonimmune isotype-matched mouse immunoglobulin has to be used as a negative isotypic control, fluorochrome-conjugated or not, according to direct or indirect immunofluorescence procedure. 5. At the end of incubation with specific antibodies, cells are centrifuged in PBS (1600 rpm, 5 minutes), resuspended in PBS and analysed on a flow cytometer. Intracytoplasmic markers can also be detected by using specific permeabilization techniques, such as 0.5% saponin, X100 triton X or ethanol. 6. Many markers available giving relevant information on ocular surface disorders; HLA DR expression by epithelial cells, gold standard for inflammatory assessment	Brignole et al 2004
Web Video	Not available	
Materials	1. Polyethersulfone filters (Supor®, Gelman Sciences Ann Arbor, MI, USA), 13 mm in diameter with pores of 0.20 µm 2. Paraformaldehyde freshly prepared and preserved at 4°C, monoclonal antibodies and material for immunostaining 3. Flow cytometer	
Variations of technique	[V2] Brush cytology for cell collection before flow cytometry procedures.	Fujihara et al 1997
Diagnostic value	This version : [√] HLA DR inferior to 45% of positive cells and 18,000 MESF (molecular equivalent of soluble fluorochrome) in normal eyes. Widely above these values in inflammatory ocular surface disorders Please cite statistics indicating the diagnostic value of the test.	Brignole et al 2004
Repeatability	Standardized technique reliable over time and from one laboratory to another	
Test problems	This procedure is highly technical and requires a laboratory equipped with a flow cytometer and a staff familiar with immunostaining processing and flow cytometry analysis on paucicellular specimens	
FORWARD LOOK	Many markers for a large variety of applications have yet to be tested with further improvement of pathophysiological knowledge of ocular surface diseases	
Glossary	HLA-DR: Major leukocyte antigen, human histocompatibility complex, class II cell surface receptor	

continued

APPENDIX 16 *continued*

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APPENDIX 17

DEWS	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	Maurizio Rolando	1st Nov 2004 11th Jan 2006
TEST	**Ferning Test (TFT)**	REFERENCES
TO DIAGNOSE	Quality of tears (electrolyte concentration), KCS, Hyperosmolarity	
VERSION of TEST	[V1] Tear ferning test (tear collection by rod) [V2] Tear collection by glass capillary)	Rolando 1984 Norn 1994
DESCRIPTION	A drop of tears is collected from the lower meniscus and dropped onto a microscope slide and allowed to dry by evaporation. Different forms of branching crystallization patterns can be observed and classified. The tear ferning test permits separation of normal from dry eyes on the basis of the ferning patterns.	Golding et al 1994 Rolando 1986-1988 Pearce, Tomlinson 2000
CONDUCT of TEST	1. The subject is seated, with the head resting comfortably, in a dim light. 2. With the eyes in upgaze, by means of a micropipette, nearly 1 microliter of tears is collected by capillarity from the lacrimal river of the lower meniscus. 3. The fluid is then dropped onto a microscope slide and exposed to evaporation at 20 ±3 C° for 10 minutes 4. The sample is then observed under a microscope at x 100-400 enlargement (better visibility is achieved with phase contrast microscopy) 5. The patterns of crystallization (ferning) are classified in 4 classes: Type 1: uniform large arborization, Type 2: ferning abundant but of smaller size; Type 3: partially present incomplete ferning; Type 4: no ferning. Types 1 & 2 are reported to be normal and Types 3 & 4 reported to be abnormal	Rolando 1984-1986
Web Video	Not available	
Materials	• capillary glass • clean microscope slides [ ] • light microscope (Phase contrast useful but not necessary)	
Standardization	Time of day: [any] Temperature: [20-28°C] Humidity: [high humidity slows down the time of appearance of the ferns] Air speed: [the effect of excessive air speed has not been studied but increasing the evaporation rate could affect the pattern of ferning]. Illumination: [the level of illumination seems irrelevant in the development of ferning patterns once the sample has been collected and dropped] Other: [Avoid excessive light and lid margin contact in order to decrease reflex tearing.]	
Variations of technique	In the original version, [V1] tear collection was acheived by capillary attraction by means of a 0.5 mm rod loop placed in contact with tears pooled in the lower fornix of the cul de sac The second version uses a capillary tube in contact with the fluid of the lower meniscus. This increases reproducibility, with a coefficient of variation of 6.4%.	Norn 1994
Diagnostic value	This version: [ ] Other version: [2] prognostic value 86.6%	Albach et al 1994
Repeatability	Intra-observer agreement. [Intraobserver agreement of 94.50% (kappa = 0.76; CI = 0.67-0.86). -] Inter-observer agreement. [Interobserver agreement 92.10% (kappa = 0.65; CI = 0.56-0.75]	Pensyl and Dillehay 1998
Sensitivity	(true positives) [82.2%] [Cut off: Type III or worse according to the previously reported classification 6-7)	Albach et al 1994
Specificity	(100 – false positives) [92.5%]	Albach et al 1994
Other Stats	94% sensitivity 75% specificity [Cut off: Type III or worse according to the previously reported classification 6-7] 92% sensitivity 83% specificity [Cut off: Type III or worse according to the previously reported classification 6-7]	Norn 1994 Rolando 1986

continued

APPENDIX 17 *continued*

Test problems	Care should be taken not to elicit reflex tearing during collections Light microscopy is often unavailable in the office. In spite of a good clinical ability of separating normal from dry eyes, the real meaning of the results is not known [Test affected by extreme conditions of temperature and humidity]	
Forward Look	It would be interesting to explore the correlation between the patterns of crystallization (test types I to IV) and the level of tear film osmolarity	
Glossary	TFT: Tear ferning test	

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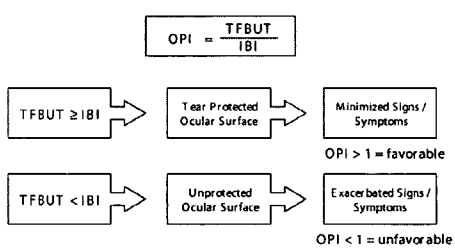
APPENDIX 18

DEWS	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	Mark B. Abelson and George W. Ousler III	5th Nov 2004
TEST	Ocular Protection Index (OPI)	Ousler et al 2002
TO DIAGNOSE	Ocular Surface Protection Risk of ocular surface damage	
VERSION	[V1]	
DESCRIPTION	The principle of the test is that when the tear film break up time (TFBUT) is shorter than the blink interval (IBI), the eyes are exposed to the risk of focal ocular surface damage. The Ocular Protection Index (OPI) is the ratio of the TFBUT and IBI (TFBUT/IBI). If the OPI score is < 1, then a patient's cornea is at risk of exposure and if the OPI score is ≥ 1, it's not.	Ousler et al 2002
General note	When studying the relationship between TFBUT and the inter-blink interval (IBI = time between complete blinks), it may be suggested that their interaction assists in regulating the integrity of an ocular surface. For example, the ocular surface is protected when the TFBUT either matches or exceeds than the IBI. In contrast, the surface is unprotected surface when the TFBUT is less than the IBI. This relationship can be clinically relevant since repeated, intermittent exposures of a tear film deficient cornea lead to symptoms and signs such as keratitis and redness. An index known as the Ocular Protection Index (OPI) can be used to quantify the interaction between the IBI and TFBUT. The OPI is calculated by dividing TFBUT by the IBI. If the OPI score is < 1, a patient's cornea is at risk for exposure, and if the OPI score is ≥ 1, it's not. This approach to measuring alterations in TFBUT has proven to be useful in assessing factors that cause dry eye and evaluating therapies.	
CONDUCT of TEST	1. Complete a visual count of the number of blinks per minute while your patient reads the ETDRS chart; 2. Calculate IBI = 60 divided by the number of blinks per minute; 3. Measure TFBUT; 4. Divide TFBUT by the IBI to determine OPI score – Ocular Protection Index (OPI)  	Ousler et al 2002
Web Video	Not available	
Materials	Blink Rate Recorder – • ETDRS chart or standard visual task; TFBUT Measurement – • Non-preserved, 2% sodium fluorescein; • Micro-pipette; • *Or* D.E.T. strip.	See TFBUT template for details of TFBUT test
Standardization	Time of day [√] Temperature [√] Humidity [√] Air speed [√] Illumination [√]	
Diagnostic value	OPI Score ≥ 1 = protected ocular surface OPI Score < 1 = unprotected ocular surface	Ousler et al 2002 Abelson et al 2002
Glossary	OPI = Ocular Protection Index: TFBUT =Tear film break-up time: IBI = Inter-blink Interval:	

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APPENDIX 19

DEW	**DRY EYE DIAGNOSTIC TEST TEMPLATE**	
RAPPORTEUR	Alan Tomlinson	10th Jan 2006
TEST	**Fluorophotometry (Fluorimetry) – Tear Flow**	
DIAGNOSES	Changes in tear flow in aqueous tear deficiency (ATD).	REFERENCES
VERSION of TEST	[Version 1] Scanning automated fluorophotometry (Fluorotron Master, Coherent Inc, Palo, Alto, CA)	
DESCRIPTION	To calculate tear flow from measurements of tear volume and turnover.	
CONDUCT of TEST	**Tear Turnover Rate** 1) Subject is seated at the chin rest of the Fluorotron (with the anterior segment adapter fitted). Horizontal and vertical adjustments are made to align the subject's eye in the instrument's optic beam. 2) Three scans are conducted to establish the intrinsic corneal autofluorescence. 3) A 1 µl drop of 2% sodium fluorescein is instilled into the lower fornix with a pipette. 4) Initial scans are taken 1 minute post instillation, then at 2 minute intervals for a further 20 minutes. 5) The intrinsic corneal autofluorescence value is substracted from all values obtained from tear film fluorescence, prior to data analysis. 6) Fluoroscein concentration at each time point is calculated from the Fluorotron scans obtained at all time points beyond 4 minute post instillation, to avoid initial reflex tearing caused by instillation. 7) The decay in fluorescence is calculated from the log of the curve obtained from the formula: $T_0(t_0) = 100 \frac{[C_t(t_0) - C_t(t_0+1]}{C_t(t_0)}$ (%/min) Where Ct(t) = fluorescein concentration in tear film at time t(min). Assuming a monophasic decay of fluorescence from 5 mins post instillation with a decay time constant β (min^{-1}): $C_t(t) = C_t(0).e^{\beta t}$ (ng/ml) the following is obtained: $T_t(t_0) = 100 (1 - e^{\beta t})$ (%/min) This calculation can be carried out using the software package ANT_SEGMENT tear. **Tear Volume** 1) Subject is seated at the chin rest of the Fluorotron (with the anterior segment adapter fitted). Horizontal and vertical adjustments are made to align the subject's eye in the instrument's optic beam. 2) Three scans are conducted to establish the intrinsic corneal autofluorescence. 3) One µl of 2% sodium fluorescein is instilled into the lower fornix with a pipette. 4) Initial scans are taken 1 minute post instillation, then at 1 minute intervals for a further 4 minutes. 5) The intrinsic corneal autofluorescence value is substracted from all values obtained from tear film fluorescence, prior to data analysis. 6) Fluorescein concentration at each time point is calculated from all the Fluorotron scans obtained. 7) The decay in fluorescence is calculated from the log of the curve obtained from the formula: $T_0(t_0) = 100 \frac{[C_t(t_0) - C_t(t_0+1]}{C_t(t_0)}$ (%/min) Where $C_t(t)$ = fluorescein concentration in tear film at time t(min). Assuming a monophasic decay of fluorescence from 5 mins post instillation with a decay time constant β (min^{-1}): $C_t(t) = C_t(0).e^{\beta t}$ (ng/ml) the following is obtained: $T_t(t_0) = 100 (1 - e^{\beta t})$ (%/min) This calculation can be carried out using the software package ANT_SEGMENT tear. Tear volume is then calculated from: $V_t = (C_d.C_m^{-1}.k^{-1}-1) V_d$ Where C_d = fluorescein concentration in the drop C_m = initial fluoroscein concentration calculated by back extrapolation with the Fluorotron in ng/ml k = correction factor (k = 250) for the limited spatial resolution of the Fluorotron and V_d = drop volume in ml Calculation of tear flow: $\text{Tear flow} = \frac{V_t}{T_0(t_0)}$ (µl/min)	Kuppens 1992 Van Best 1995 Van Best 1995 Kuppens 1992 Van Best 1995 Kuppens 1992 Mishima 1965

continued

APPENDIX 19 *continued*

Web Video	Not available	
Materials	Fluorotron Master 2% sodium fluorescein Mimims (Chauvin, UK) Air displacement pipette P2 Pipetman (Gilson, Villiers-le-Bel, France) Disposable sterile tips (Gilson, Villiers-le-Bel, France)	
Variations of technique	Varying concentrations and instillation volumes of fluorescein can be used, eg, 1% and 0.5 -2 µl.	
Standardization	Time of day [X] Temperature [ ] Humidity [ ] Air speed [still] Illumination [low ambient] Other: [Blink is initiated immediately prior to scan to ensure uniform tear thickness]	Pearce et al 2000
Diagnostic value	This version: [ ] Determination of tear flow an indication of aqueous tear deficiency. To obtain estimate of tear drainage from eye. Other version: [ ]	Mathers, Daley 1996 Mathers et al 1996 Gobbels et al 1992
Repeatability	*Intra-observer variation. [Not significant]* *Inter-observer variation. [Not significant]*	Mishima et al 1966 Van Best 1995
Test problems	High cost of basic equipment. Time required for measurement. Indirect (surrogate) measures of tear outflow and volume as it is assumed that fluorescein and aqueous tear are eliminated at the same rate from the eye. Absorption of fluorescein into the ocular tissue may be a factor in dry eye patients and may decrease apparent rate of decay.	
Test solutions	Use of high molecular weight conjugates.	McNamara et al 1998
Forward Look	Production of a cheaper automated scanning fluorophotometer. Development of reduced test incorporating 6 measurements for total of 10 minutes (tear turnover). Combination of tear flow (µl/min) with evaporation rate (µl/min) gives a value of "total tear flow" in the eye and an estimate of total tear production. This allows analysis of the proportion of tears eliminated by evaporation and/or drainage in various forms of dry eye.	Pearce et al 2000 Mathers, Daley 1996 Mathers 2004

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APPENDIX 20

DEW	DRY EYE: DIAGNOSTIC TEST TEMPLATE	
RAPPORTEUR	Stephen Kaye	18th April 2006
TEST	**Tear Function Index (*Liverpool modification*)** Email: TFI@clineng-liverpool-nhs.com	
TO DIAGNOSE	To evaluate the tear dynamics of production and drainage and detect subjects suffering from dry eye	Ono et al 1991 Xu et al 1995(a) Xu et al 1995(b) Kaye et al 2001
VERSION of TEST	The test is a modification of that described by Xu et al. (1995) and depends on using prepared filter paper strips containing fluorescein. The test has been designed to allow direct measurement of the TFI using prepared tear strips.	Kaye et al 2001
DESCRIPTION	TFI is the quotient of the Schirmer test value and the Tear clearance rate (TCR).	
CONDUCT of TEST	A fluorescein-coated tear strip is placed over the lower lid margin at the junction of the middle and lateral third of the lid. 1. The eye is closed and the strip is left in place for 3 minutes 2. On removal, the distance from the strip notch to the wetted dye front is recorded, using the scale provided. 3. The strip is air dried and 4. The intensity of staining is compared with that of the calibrated panel of dilutions, (ranging from 1:1 to 1:128), to determine the TCR. 5. The TFI is defined as the quotient of the Schirmer test and the TCR.	
Web Video	Not available	
Materials	• The standard kit provides a cardboard envelope, containing a docket with 4 see-through pouches. • Each pouch contains 4 sterile, single-use, fluorescein-coated tear-strips together with a calibrated colour scale for reference. • A ruled measurement scale is printed on the envelope, together with • a nomogram and • a set of instructions The kit, containing the prepared strips, together with instructions and calibrated measuring scale and colour scale are provided by the Dept. Clinical Engineering of the Royal Liverpool University Hospital, Prescot Street Liverpool L7 8XP. For further information: Email: TFI@clineng-liverpool-nhs.com	
Variations of technique	TFI as described by Xu et al (1995)	
Standardization	The procedure is standardised. Strips are calibrated for use in each pack.	
Diagnostic value	Identification of subjects suffering from aqueous tear deficiency, for instance in Sjögrens syndrome.	
Sensitivity	A TFI of less than 40 is 100% sensitive for patients with SS dry eye	Kaye et al 2001
Specificity	Patients with Sjögren's syndrome have a TFI upper 95% confidence interval of 15 (12 if anaesthetic has been used)	Kaye et al 2001
Other Stats	Less inter-ocular difference and less variability than the original method	Kaye et al 2001
Test problems	As with the Schirmer's test, it is uncomfortable. Also, staining of the ocular surface at the sites of strip contact with the conjunctiva occur after using fluorescein or Rose Bengal.	
FORWARD LOOK	Performing the TFI using prepared filter paper strips with the matched colour dilution is very sensitive for detecting patients with SS dry eye. The test can be used by non-ophthalmically trained personel. Subjects with a TFI of less than 40 can then be referred for an ophthalmic assessment.	
Glossary	TFI: Tear function index	

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臨床試験の計画および実施：
世界ドライアイ・ワークショップ（2007年）の臨床試験分科委員会による報告

要旨

本報告書は、臨床試験全般に関する普遍的なコンセプトならびにドライアイ疾患における治療的介入の研究用に特に計画された臨床試験のその他の問題をまとめたものである。また、本報告書では、そうした臨床試験の後方支援に関するデザインおよび実施に関する提言も行なっている。徴候と症状の関連性の欠如、ならびに対照介入における潤滑剤（プラセボ）効果の可能性など、臨床試験デザインを複雑化させるドライアイ疾患の特性も特定する。環境下での試験および管理された有害環境下での試験の戦略について考察する。

キーワード

臨床試験, DEWS, ドライアイ, ドライアイワークショップ

I. 序文

ドライアイ疾患の臨床試験は、臨床医、疫学者および生物統計学者、ならびに医薬品などの治療法の規制承認を求める者にとっての課題である。[1] 本報告書では、臨床試験全般に関する普遍的なコンセプトを概説し、ドライアイ疾患における治療的介入研究に特化した臨床試験に伴う他の問題を検討する。臨床試験データを裏付けるエビデンスのレベルは、修正後のAmerican Academy of Ophthalmology Preferred Practices guideline（米国眼科会議優先業務ガイドライン）に従い、文献目録で特定されている。報告書では、こうした臨床試験の後方支援に関するデザインおよび実施に関する提言も行なっている。

II. 臨床試験分科委員会の目標

臨床試験分科委員会の目標は、臨床試験全般に関係する文献、手順およびコンセプトを体系的に検討し、ドライアイ疾患に治療的介入を行う臨床試験独自の問題を考察し、さらに臨床試験の適切な実施に関するガイドラインを提示することである。

III. 臨床試験全般に関するガイドライン

臨床試験を開始する前に、均衡の状態が存在しなければならない。言い換えれば、検討中の特定の介入の有効性に関して、それを被験者の一部に使用しないことを正当化するだけの疑念がなくてはならず、同時に、臨床試験への参加を希望し、参加に適格な残りの被験者に曝露することを正当化するだけの治療の潜在的有効性に関して、十分な信頼がなくてはならない。これらの条件が満たされている場合、有効な結果が得られるように、臨床試験のデザインと実施においてその他多数の問題を検討する必要がある（表1）。重要なプロセスとして、簡潔かつ具体的な試験課題の構築、主要アウトカム指標の特定、必要なサンプルサイズの統計的予測、フォローアップ期間ならびにベースラインおよびフォローアップ評価の具体的スケジュールの特定、試験対象集団の選択、主要アウトカム指標の定義、介入／治療の無作為割付け、割り付けられた介入／治療へのコンプライアンス維持ならびにバランスの取れた高いフォローアップ率達成のための戦略の確立が含まれる。さらに、組織的かつ意思決定のための構造、ならびにデータ収集および患者の安全性モニタリングのための具体的な手順を確立することが重要である。

A. デザイン

臨床試験の最も望ましいデザインは、プロスペクティブ、無作為化、二重盲検、プラセボまたは溶媒対照、並行群間試験または交差試験である。その他、受容可能なデザインとして、新規治療法と既に承認されているあるいは一般的に利用されている治療法とを比較する同等性試験または優越性試験が含まれる。これらの臨床試験も、プロスペクティブ、無作為化、盲検試験でなければならない。[2-5] 並行群間試験は、人口学的および環境的傾向、あるいは活動の比較可能性を提供

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Proprietary interests of Subcommittee members are disclosed on pages 202 and 204.

Reprints are not available. Articles can be accessed at: www.tearfilm.org

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OUTLINE

するのが理想的である。サンプルサイズが十分な場合、無作為化により、治療群間における人口学的な特徴の均等な分布を確保しやすい。1つ以上の人口学的因子（例、性別年齢）に関して特定の懸念がある場合、小規模なブロックに無作為化を行うことで、治療群間におけるこれらの因子の均一な分布を達成できる。残念ながら、通常、この方法の実施は実用的でなく、適格な被験者を見つけるために、多数の患者のスクリーニングを行わなければならなくなる。

通常、交差試験は、対照として患者自身を使うという利点があるが、ドライアイの場合のように、1つの治療効果が別の治療効果より長く持続する可能性が存在する場合に、交絡因子の問題が生じる。また、1つの治療が別の治療を妨害する場合、試験対象の薬剤または治療法の逐次効果が交絡因子になる可能性がある。交差試験は、本来下記の3つを前提とする：

1) 治療によって疾患は治癒しない。
2) 治療期間の間で持ち越し効果はない。
3) 解析対象とするには、すべての患者がすべての治療期間を完了しなければならない。

並行群間試験と比較した交差試験の利点は、患者間の差異より患者内の差異のほうが小さいという前提に基づいて認識されている。これは必ずしも真実ではない。プラセボ治療のウォッシュアウト期間は、前回の治療の持ち越し効果を排除するために利用できるが、ウォッシュアウト期間の長さは、持ち越し効果を排除するのに十分でなくてはならず、十分な長さというのは、被験薬により、不明または変化すると考えられる。こうした懸念を考慮すると、交差試験における重要な補正デザイン戦略は、被験薬および対照薬の投与順序を無作為化することで、一部の被験者は最初に実薬を服用し、他の被験者は最初に対照薬を服用するようにすることである。

Table 1. Attributes of well-designed clinical trial

1. Formulation of a concise and specific study question
2. Specification of a primary outcome measure
3. Statistical estimation of the necessary sample-size
4. Specification of the length of follow-up and specific schedule for baseline and follow-up evaluations
5. Selection of the study population
6. Definition of the primary outcome measure
7. Random allocation of the intervention(s)/treatment(s)
8. Strategies for maintenance of compliance with the allocated intervention(s)/treatment(s), and for the achievement of high and balanced rates of follow-up
9. Establishment of an organizational and decision-making structure
10. Specification of procedures for intake of data and for patient safety monitoring

B. 選択基準および除外基準

臨床試験の完全性を確保するには、適切な選択基準および除外基準が不可欠である。選択基準では、試験する集団を明確に定義するために必要ないくつかの変数を特定する（表2)。これらの基準には、通常、1) 被験者のインフォームド・コンセントを提示する能力、2) 治験実施計画書を順守する能力、および3) 統計的に有意なおよび臨床的に重要な治療効果を示すために十分な疾患の重症度の存在が含まれる。疾患状態の同質性を確保するために、通常は具体的な診断基準が定義され、これにより、より正確な試験が可能になる。

除外基準は、例えば、1) 治療反応と交絡する可能性のある並存疾患のある被験者、2) 治験実施計画書を順守しない、あるいはフォローアップができない可能性のある被験者、ならびに3) 提示されている治療への過敏性または不耐性が分かっている被験者を除外するために利用される（表3)。

選択基準および除外基準を選ぶ場合、治験責任医師は、試験内部での有効性と、対象疾患を有するより大規模な集団に対する有効性の一般化との間の本質的な二律背反性を認識すべきである。選択基準および除外基準の制限を最小限にすれば被験者の募集が容易になり、試験結果を一般化するための基盤が大きくなるが、治療効果は、疾患状態の異質性によって曖昧になると考えられる。

C. アウトカム指標

治療の比較に使用するアウトカム指標は、臨床イベントまたは代理アウトカム指標のいずれかと考えられる。主要アウトカム指標については、その発生率が試験期間やサンプルサイズを含め、試験デザインの様々な側面に影響すると考えられることから、データ収集の開始前に選択すべきである。一部の臨床試験は、アウトカム変数の事後解析を採用しているが、規制当局は、ピボタル試験におけるそうした解析の受理

Table 2. Inclusion criteria for clinical trial

1. Subjects must be capable of providing informed consent.
2. Subjects must be able to comply with the protocol.
3. Disease severity must be sufficient to demonstrate a statistically significant and clinically meaningful effect of therapy.
4. Specific diagnostic criteria must be defined to ensure homogeneity of disease status, which can lead to a more precise study.
5. Subjects must be capable of responding to the proposed mechanism of action of the intervention to be studied

Table 3. Exclusion criteria for clinical trial

1. Subjects have concurrent disease that could confound the response to therapy.
2. Subjects are unlikely to comply with the protocol or likely to be lost to follow-up.
3. Subjects have known hypersensitivity or intolerance to the proposed therapy.
4. Subjects use concomitant therapy that affects either tear function or ocular surface integrity.
5. Subjects have had surgical or other manipulation of the eye that could confound the outcome parameters or interfere with the mechanism of action of the proposed intervention to be studied.

に消極的なことが多い。ただし、ほとんどの試験において、いくつかの副次的アウトカム指標に関する情報の収集と解析を行うことが適切である。これらにより、対象の治療法の全体的評価に役立つ詳しい情報を提供することができる。

代理アウトカム指標は、疾患の測定可能な特徴で、臨床的意義はあるものの、正確な同定が難しいアウトカム指標を確実に反映しているものである。例えば、comfort dropの必要点眼頻度の測定は、1日に生じる不快感の頻度／長さを定量化した代理的主観的指標と言える。同様に、涙液層浸透圧の客観的代理指標は、涙液サンプルの電導性と考えられる。代理アウトカム指標は、アウトカムをモニタリングする確実かつ適切な指標として検証されなければならないが、徴候と症状の相関が弱く、疾患における変化の客観的エビデンスが必要なドライアイなどの病状においては、特別な価値を持つと考えられる。

D. サンプルサイズ、無作為化およびデータ解析

臨床試験のサンプルサイズは、試験の主要仮説について統計的検出力の高い解析が可能となる十分な規模とすべきである。また、治療反応を明確化する方法として望ましい、あるいは必要と見なされる場合、サブグループ内での統計的比較を可能にするものでもある。臨床的に有意義な治療効果、ならびに統計的有意な効果を検出するために十分なサイズの試験であることが必須である。統計的解析は、試験の規模、デザイン、アウトカム指標および期間に関して、適切でなくてはならない。治療間の特定の違いを検出できる能力は、サンプルサイズおよび治療の違いと直接相関し、アルファレベルおよび可変性と間接的に相関する。主な要素は、試験計画者による臨床的有意差の選択であり、検出可能レベル以上の違いを検出するために必要な患者の数が存在すれば、それを決定することができる。

被験群あるいは対照群への無作為化は、一般に、治療選択バイアスを防ぐために、臨床試験において利用できる最善の戦略である。無作為化の確立には多数の方法がある。現在、研究者の大半は、コンピュータによる無作為化リストを使用しているが、これは試験施設および試験前の特徴（例、疾患の重症度）によってさらに層別化することができる。治療の割付けを行うために使用する無作為化計画の書面での説明を記録する必要がある。この説明には、割付けスケジュールの再現を可能にする十分な詳細が含まれ、割付けプロセスにおいて明確な監査証跡を確立すべきである。

治療の割付けは、患者が試験に正式に登録され、無作為化されるまで、患者、医師および割付けを発表する人物に対して明らかにしない。できれば、試験終了まで、患者および医師に明かさないことが望ましい。これは、診療施設外の人物またはグループが割付けを行ったほうが容易に実行できる。治験責任医師は、管理または評価が必要な無作為化バイアスが、特に小規模な試験において起こりやすいことも認識すべきである。試験群のベースライン特性も多様である可能性があり、規模が大きければ、そうした違いが治療の比較に影響することがある。臨床試験データの解析戦略は、事前に概説し、適切な解析方法を用いて具体的なアウトカム変数形式に対応するものでなければならない。

臨床試験の解析における主な特徴として、「intention-to-treat」の原則の順守がある。これは、試験データの一次解析は、被験者が実際に受けた治療、あるいは治験実施計画書の順守に関わらず、被験者に割付けられた最初の治療に基づいて被験者を分類して実施しなければならないことを意味する（表4）。GCP（医薬品の臨床試験の実施の基準）では、適格な患者および受診の評価は、治療割付けを明らかにする前に、臨床管理者（組織チーム）が行なうよう指示されている。さらに、治験実施計画書および統計解析計画には、どの集団が主要かを記述すべきである。

欠損しているデータへの対応には、統計的手法、例えば*last observation carried forward*（直前に計測した値による補完）（**LOCF**）またはエンドポイント代替を用いることができる。すべての集団から得た有効性および安全性に関する結果が概して一致していることが理想である。ただし、例えば、不十分な有効性や安全性の問題から被験者が試験を中止した場合に、差が生じることがある。治療の交差、コンプライアンスの不良、ならびにフォローアップ不能などが、臨床試験の有効性に対する主な脅威であり、治験実施計画書の順守およびフォローアップをできるだけ完全に確保するために、できる限りの努力をすべきである。フォローアップ不能がある場合、フォローアップ不能患者のイベント発生率に関して、さまざまな仮定の下で一連の解析が行われる。同様に、二次解析では、行った治療、ならびにコンプライアンスの違いを説明できるが、これらは、主要な「intention-to-treat」解析に代わるものではない。

臨床試験に関する基本的解析法は、さまざまな生物統計学の教書などのリソースで説明されている。対象アウトカムを経験した患者の比率の比較に基づいたアウトカム解析は、試験データ解析の一般的な方法である。これらは、通常、フォローアップの強度が2つの治療群において同等で、フォローアップ不能が少なく、治療群のベースライン特性が同等である限り、有効である。

比率の差に関する統計的評価は、フィッシャーの直接確率

Table 4. Data analysis: populations to analyze

1. Intent to Treat (ITT): All subjects randomized.
2. Modified Intent to Treat (Mod ITT): All subjects randomized who received at least one dose of medication
3. Per Protocol (PP): All subjects randomized who completed the treatment according to protocol

検定、または適切であればカイ二乗検定を用いて実施できる。ただし、アウトカムを経験した患者の比率の単純解析では、フォローアップ期間の検討が行われない。このことは、長期間かけて患者の募集が行われ、所定のスケジュールに従ってフォローアップを行うことで、患者のフォローアップ期間に差が生じるといった多くの臨床試験の設定において重要になることがある。こうした試験のデータ解析は、さまざまなフォローアップ期間に対応する統計手法を提供する生命表解析法によって通常行なわれる。ベースライン特性における差の調整は、階層化または多変量解析のいずれかによって行われる。治験責任医師は、統計的有意性を構成するものは何かという問題は複雑であることを認識し、大半の試験が多数のアウトカム指標に基づいてデータを提供していることから、注意してP値の解釈を行なうべきである。これらの統計的比較は、相互依存的であるとは考えられない。複数の比較の適切な調整を検討することが不可欠である。

E. 臨床試験の管理

臨床試験の計画と管理は、その成功において特に重要である。大規模多施設共同試験では、組織的構造が望ましい。典型的な組織チャートを図1に示す。

データの誤りや欠損の高リスクを回避するために、臨床試験の実施において、各段階に対する事前の準備および書面による標準化手順が必要である。本章の終わりに引用した付録は、www.tearfilm.orgで閲覧できる。手順マニュアルを用意すべきである。適切なマニュアルの要素を付録1に示す。[6-11]

品質保証については、GCP基準を適用する。治験依頼者および治験責任医師用のガイドラインは、付録2に詳述されており、1) 治験依頼者の役割、2) 治験責任医師の役割、3) 臨床および機能的調査研究機関の役割、4) 倫理委員会または個人保護委員会、5) 医薬品規制調和国際会議、ならびに6) 規制ガイドラインなど、規制要件の順守が盛り込まれている。[12-30] 被験薬に関する治験薬概要書の作成が適切である（付録3）。[31] 試験対象の医療製品の使用について概説する（付録4）。[32-36] 有害事象およびその管理について特定する（付録5）。[37-43] 倫理承認プロセスは、臨床試験審査委員会または試験責任医師に適した指定の治験審査委員会を通じて行なわれる。臨床試験データは、試験およびデータ解析の完了後に公表する。[43]

IV. ドライアイ疾患における臨床試験のガイドライン

ドライアイ疾患の試験に対する一般的な検討事項には、臨床試験全般に当てはまる主要なコンセプトが適用される。ドライアイ疾患の臨床試験には、プロスペクティブ環境下デザインおよびプロスペクティブ負荷デザインを含めることができる。検証する医薬品または介入法について仮定された作用機序に応じた治験実施計画が望ましい。

環境下試験では、プロスペクティブ、無作為化、二重盲検、プラセボ／溶媒対照という特徴を持った上記の一般的なデザインガイドラインを採用すべきである。有効性および安全性を証明するには、十分な試験期間が必要である。

選択および除外基準では、潜在的に反応性のある集団を特定し、平均への回帰または観察バイアスを回避、または最小限にできるものを選択すべきである。このアプローチでは、下記を除外するべきである：1) 医薬品または医療用具の試験対象となる症状以外のドライアイを誘発し得る眼表面の疾患の有無、2) ドライアイを誘発する主要症状以外のドライアイ関連の全身疾患の有無、3) 涙液層、涙液分泌、眼表面に影響する可能性のある全身薬の使用、4) 評価対象の医薬品または医療用具の効果を変化させる局所点眼薬の同時使用または使用歴、5) 屈折矯正手術、眼瞼への入れ墨、眼瞼の手術、角膜手術など、眼科手術歴、6) 試験パラメータに適したマイボーム腺疾患の有無、7) コンタクトレンズ装用の有無。患者が、試験する医薬品または介入法の作用機序を特に阻害しない潤滑剤による治療を安定的に受けている場合、そのバックグラウンド治療を継続する限りその患者の試験への登録を認めても良い。ただし、バックグラウンド治療の状況は監視する必要がある。

サンプルのサイズは、有効な統計解析、ならびに必要に応じたサブグループの統計的比較が可能な規模にするべきであり、試験の結論を裏付ける統計的検出力を持つべきである。試験の結論が２つの治療群間で同等の場合、臨床的有意差を検出できる試験の検出力を検討することが重要である。通常、最低80%の検出力（β）が必要とされる。試験結果が肯定的または否定的な治療反応に歪曲されないように、疾患の重症度レベルを認識し、均等に配分するべきである。被験者が試験計画を順守し、試験を完了できる能力を確認する。

管理された有害環境（CAE）デザインは、臨床試験中の環境、被験者の活動、あるいはその両方の組み合わせの管理に利用され、ドライアイの臨床症状および徴候を悪化させるストレス性の環境を提供する。[44] このようなストレス試験は、短期的薬理学的影響の同定において特に有効である。湿度、温度および気流は、モニタリングおよび操作し得る環境変数である。活動としては眼を使うタスクが含まれ、瞬眼率および涙液層安定性をモニタリングすることができる。試験デザインには、プロスペクティブ、無作為化、（可能な範囲での）盲検化、比較対照試験の特徴を含める。環境負荷の条件に対して予想される患者の適応力を認識するには、データ解析における補正調整が必要である。[45,46] 負荷環境への初期反応に基づいて患者集団を選択する場合、そのような選択により、ドライアイ集団全体に対する試験結果の一般化の可能性が低下すると考えられる。

V. ドライアイに関する過去の臨床試験の観察結果

A. ドライアイに関する臨床試験の特性

症状および徴候の間の密接な関係が観察された試験もあれば、そうでない治験もあった。大半の薬剤に関する試験では、徴候と症状の不一致が認められた。[47-76] ドライアイ疾患の局所治療を評価したほとんどの臨床試験において、外見上顕著なプラセボまたは溶媒反応が存在した。[1] プラセボ効果は、症状を評価した多数の試験で観察されているが、ドライアイの臨床試験において観察された客観的パラメータについても、顕著なプラセボ反応が認められた。この顕著なプラセボ反応の理由は不明であるが、平均への回帰によって一部説明できる。過去の臨床試験の大半では、登録基準をアウトカム指標における重症度の最低レベルに設定していた。この方法により、測定可能な効果を証明できる重症度のレベルが確保されたが、平均への回帰も起こりやすくなった。