CLINICAL TRIAL PROTOCOL

Protocol Title - Long:	The effects of dietary supplementation with a combination of flaxseed oil, borage oil and fish oil omega-3 fatty acids on ocular comfort including symptoms of dry eye.
Protocol Title - Short:	Dietary supplementation and dry eye
Protocol ID Number:	SOVS-2016-045
Amendment Number:	N/A
Version Date:	24th January 2017

CONFIDENTIALITY

APPROVALS

Jacqueline Tan, Author/Principal Investigator	**Date**
Fiona Stapleton, Head of School	**Date**

SUMMARY OF FINAL PROTOCOL & AMENDMENTS			
Initial/ Amend #	**Version Date**	**Author**	**Main Changes**
Final	**24th January 2017**	Jacqueline Tan	N/A
A1			
A2			
A3			

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1. PROTOCOL SYNOPSIS

Table 1

Protocol Title	The effects of dietary supplementation with a combination of flaxseed oil, borage oil and fish oil omega-3 fatty acids on ocular comfort including symptoms of dry eye.	
Protocol ID Number	SOVS2016-045	
Trial Classification	Evaluation	
Investigator(s)/Site(s)	Eye Research Group @ SOVS The University of New South Wales Sydney, Australia	
Overall Duration of Trial	1 year	
Number of Trial Participants Planned	138	
Planned Start Date	February 2017	
Primary Objective	To investigate the efficacy of a nutraceutical formulation (combination of flaxseed oil, borage oil and fish oil omega-3 fatty acids) on ocular symptoms including dry eye, compared to a placebo control.	
Secondary Objective	To evaluate the safety of a nutraceutical formulation (combination of flaxseed oil, borage oil and fish oil omega-3 fatty acids) over a 3 month period.	
Primary Safety Variable(s)	Visual acuity Biomicroscopy: ocular redness, corneal and conjunctival staining	
Primary Efficacy/Performance Variable	Subjective symptom scores measured using OSDI, OCI and DEQ-5	
Experimental design	☐ Retrospective ☒ Prospective ☐ Single group ☐ Multiple group ☒ Parallel group ☐ Cross over ☐ Contralateral	☐ Single masked (Trial Participant) ☐ Single masked (Investigator) ☒ Double masked ☐ Sponsor masked ☐ Open label ☐ Other
Inclusion criteria	▪ Able to read and comprehend English and give informed consent as demonstrated by signing a record of informed consent; ▪ Be at least 18 years old; ▪ Have symptoms of ocular discomfort as measured with the Ocular Surface Disease Index (OSDI) score of >12 at the Baseline visit; ▪ Willing to comply with the dosage and study visit schedule as directed by the investigator; ▪ No contact lens wear in the last 30 days and willing to refrain from contact lens wear for the duration of the study; ▪ No planned changes to diet and willing not to substantially alter their usual diet for the duration of the study, including their typical intake of fish; ▪ Willingness to notify the study investigator if instructed to alter their diet by health/medical practitioner; ▪ Willing to continue using any artificial tear supplements at the	

	same frequency throughout the study, as used prior to the study ▪ Have health and ocular health findings which would not prevent the participant from safely ingesting dietary supplementation with combination omega oils.
Exclusion criteria	▪ Any systemic disease that would preclude participants from safely ingesting dietary supplementation with combination omega oils; ▪ Self-reported allergy/sensitivity to any of the study product ingredients; ▪ Use of any polyunsaturated fatty acid-containing dietary supplements (such as fish oil, evening primrose oil, linseed oil) up to 12 weeks prior to the start of the study; ▪ Use of any of the following medications (including steroids) up to 12 weeks prior to start of the study or during the course of the study: o Ocular medication, category S3 and above; o Any systemic or topical medications that will affect ocular physiology e.g. anti-acne medications such as Roaccutane and corticosteroid or immunosuppressant medications such as Hydrocortisone, Prednisolone and antihistamine medications such as Claritine; ▪ Any systemic disease that may affect ocular health e.g. Graves disease, and auto-immune diseases such as ankolysing spondylitis, multiple sclerosis and systemic lupus erythematosis; ▪ Epilepsy or history of migraines exacerbated by flashing, strobe-like lights; ▪ Eye surgery within 6 months immediately prior to enrolment for this study; ▪ Rigid or soft contact lens wearer, including orthokeratology in the last 30 days; ▪ Previous corneal refractive surgery; ▪ Pregnancy or breastfeeding; ▪ The Investigator may, at his/her discretion, exclude anyone else who they believe may not be able to fulfil the study requirements, or if it is believed to be in the participant's best interests.
Formulae	*Test capsules (per capsule) – "Supplement"* Concentrated Omega-3 Triglycerides-fish 332 mg Equiv. Eicosapentaenoic Acid (EPA) 134 mg Equiv. Docosahexaenoic Acid (DHA) 66.8 mg Flax Seed Oil (Linseed Oil) 334 mg Equiv. Oleic acid 58.5 mg Equiv. Linoleic acid 58.5 mg Equiv. Linolenic acid 192 mg Borago officinalis seed oil fixed (Borage) 434 mg Equiv. gamma-Linolenic acid 95.5 mg *Placebo control capsules (per capsule)* Polyethylene glycol 400 400 mg Oleic acid BP/EP 659 mg Propylene glycol 115 mg
Administration	3 capsules per day, orally for 40 days. 2 capsules per day, orally thereafter for approximately 50 days.
Human Research Ethics Committee Status /	This trial requires Human Research Ethics Committee approval prior to study initiation, any advertising, and participant consent/enrolment.

Regulatory Status	This trial requires approval from the Therapeutic Goods Administration.

2. INVESTIGATOR(S)

Table 2

Name:	Jacqueline Tan
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3. MEDICAL EXPERT

Table 3

Name:	The Ophthalmology Registrar
Title:	Ophthalmologist
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Telephone:	+61 2 9382 7111

4. BACKGROUND INFORMATION

4.1. Product

The normal tear film is a relatively stable, thin film composed of a superficial lipid layer and an aqueous layer intermixed with a mucous gel layer, which is partially adherent to the corneal and conjunctival surface epithelium. Dysfunction of one or more components of the tear film can lead to loss of tear film stability and symptoms of dry eye.

The chronicity of dry eye disease suggests that dysregulation of immune mechanisms leads to a cycle of continuous inflammation. Accordingly, because of better understanding of the inflammatory-mediated pathogenesis of dry eye disease, anti-inflammatory therapy is considered a causative therapeutic approach, since its objective is to interrupt the inflammatory cascade, rather than other treatment modalities aimed at providing symptomatic relief.

Essential polyunsaturated fatty acids omega-3 and omega-6 are the precursors of eicosanoids, which are locally acting hormones that mediate the inflammatory processes. There is good evidence that the consumption of oily fish has a protective effect against dry eye, and other studies have provided evidence of the beneficial effect of supplementation with omega-3 essential fatty acids in the treatment of dry eye disease.

However, there have been limited well designed randomised clinical trials published. Therefore, the purpose of this study is to conduct a randomised, placebo-controlled, double-masked study to investigate the effects of dietary supplementation with a combination of flaxseed oil, borage oil and fish oil omega-3 fatty acids on ocular comfort including signs and symptoms of dry eye.

4.2. Summary

4.2.1. Risks and Benefits

Risks of the Clinical Trial

It is possible that participants may have an adverse reaction to ingesting the study product. Potential problems associated with ingesting nutraceutical supplements are likely to be gastric/digestive in nature.

Any untoward signs or symptoms will be treated by immediate discontinuation of use of the study product and participation in the study until all signs and symptoms have returned to normal. The participant will be referred for appropriate medical treatment if required.

Any potential participants with a self-reported allergy/sensitivity to any of the ingredients in the study product will be excluded from the study.

Benefits of the Clinical Trial

Participants may experience reduced symptoms of ocular discomfort and dry eye during the study. However, there is no guarantee or promise that the participants will receive any health benefits from this clinical trial. The study product and participants' optometric care will be provided free of charge for the duration of the clinical trial.

4.2.2. Treatment Rationale

Few studies have investigated the potential for nutraceutical dietary supplementation to impact ocular comfort, and to date, no controlled, randomised clinical trials have been conducted to evaluate the "supplement" nutraceutical formulation.

Therefore, the objective of this study is to investigate the effects of the "supplement" nutraceutical formulation (combination of flaxseed oil, borage oil and fish oil omega-3 fatty acids) on ocular symptoms including dry eye, compared to a placebo control.

4.2.3. Guidelines and Regulations

The clinical trial will be conducted in accordance with the protocol, the Declaration of Helsinki (see Appendix 1), ICH GCP and local regulations as applicable including TGA and NH&MRC guidelines.

4.2.4. Trial Population

138 participants will be enrolled.

5. STUDY OBJECTIVES AND CLINICAL HYPOTHESIS

5.1. Study Objective

The objective of this study is to evaluate ocular symptoms and signs when consuming the supplement nutraceutical formulation (combination of flaxseed oil, borage oil and fish oil omega-3 fatty acids) daily over a 3 month period, compared to a placebo control.

5.2. Clinical Hypothesis

A greater reduction in ocular discomfort and/or signs of dry eye will be observed after daily consumption of the supplement nutraceutical formulation (combination of flaxseed oil, borage oil and fish oil omega-3 fatty acids) over a 3 month period compared to a placebo control.

6. STUDY DESIGN

This study will be a prospective, randomised, placebo-controlled, double masked study conducted over a 3-month period.

One hundred and thirty-eight (138) participants who meet the inclusion / exclusion criteria and give informed consent will be randomised to either the test capsules containing a combination of flaxseed oil, borage oil and fish oil omega-3 fatty acids ("supplement") or placebo capsules, identical in appearance, containing non-active ingredients polyethylene glycol (500mg), oleic acid (659mg) and propylene glycol (115mg) to be taken by mouth three times daily for 40 days and then two times daily for the remainder of the study, as per the manufacturer's guidelines. Every effort will be made to stratify enrolment by disease severity to ensure participants with mild, moderate and severe dry eye are represented in the study population. Stratification will be in a 2:2:1 fashion i.e. OSDI score >12 (55 participants), OSDI score >20 (55 participants) and OSDI score >45 (28 participants). Participants will be stratified according to dry eye severity prior to randomisation.

There will be a total of 3 scheduled study visits over a period of approximately 3 months - Day 1, 1 month and 3 months. Ocular comfort and symptoms of dry eye will be assessed via questionnaires. The tear film and ocular surface will be assessed using specialised instruments (slit lamp biomicroscopy, Lipiview, Vapometer and Oculus Keratograph) and stains. Safety will be assessed through measurement of visual acuity, ocular redness (eyelid and bulbar conjunctival redness), evaluation of the ocular surface using the slit lamp biomicroscope and the administration of a questionnaire to assess general health and wellbeing.

In addition, at the first visit only, body mass index and body fat composition will be measured to investigate the potential relationship between nutrition, body composition, and dry eye (Ho et al, Eye Contact Lens; Epub ahead of print 27 May 2016).

All proposed procedures conform to the NHMRC Statement on Human Experimentation.

Participants are considered enrolled when they have signed the informed consent form and are regarded as part of the clinical trial population.

6.1. Methodology / Study Visits

6.1.1. Data Requirements per Visit with Visit window (± days)

The data requirements for each visit are shown in Table 4.

Table 4

Procedures/ Data (Y/N)	Visit 1 BL	Visit 2 (1M from BL)	Visit 3/Study Exit (3M from BL)	Unscheduled / Adverse Events
Visit Window	N/A	± 7 days	± 14 days	N/A
Informed Consent	Y	N	N	N
Meet Inclusion/Exclusion Criteria	Y	N	N	N
Ocular and Medical History, Medications, Demographics	Y	N	N	N
Updated History, Symptoms and Problems	N	Y	Y	Y
Vision Tests (Visual Acuity)	Y	Y	Y	Y
Symptom Survey	Y	Y	Y	*
Nutrition Questionnaire	Y	N	Y	N
Comfort Questionnaires	Y	Y	Y	*
Health and Wellbeing Questionnaire	N	Y	Y	*
Body Mass Index and Body Fat Composition	Y	N	N	N
Tear Film Evaluation	Y	Y	Y	*
Slit-Lamp Biomicroscopy: Anterior ocular health including evaluation of cornea & conjunctiva	Y	Y	Y	Y
Dispense Study Product	Y	Y	N	N
Return Unused Study Product	N	Y	Y	*
Adverse Event Data	(Y)**	(Y)**	(Y)**	Y

Y = Yes, required information, N = No, not required
* *At optometrists discretion* *M = Month*
** *If adverse event detected at time of visit*

6.1.2. Randomisation and Masking

Prior to initiation of study treatment, each subject who provides informed consent will be assigned to a subject number that will serve as the subject identification number on all study documents. Subject numbers will be assigned in ascending order and should not be omitted or reused.

Eligible subjects will be stratified according to dry eye severity (mild, moderate or severe) and then randomly assigned to 1 of the 2 study treatments. A randomization scheme will be prepared in advance.

Test and placebo capsules will be manufactured in accordance with local regulations including the TGA guidelines. All capsules will be identical in appearance as the outer capsule will be the same as the commercial test product. The manufacturer will code, bottle and label the test and placebo capsules to ensure that participants and investigators will be masked throughout the study duration. Both test and placebo capsules will have the same outer packaging and will be labelled as capsule “A” or “B”. The code will be broken after completion of the study and data analysis, or if required for participant safety.

The recommended dosage will be 3 capsules per day by mouth to be taken with a meal for 40 days, and then 2 capsules per day thereafter for approximately 50 days, as per the manufacturer’s guidelines.

6.1.3. Clinical Trial Population

A total of 138 participants will be recruited for the study, which includes allowance for a 10% drop-out rate).

This sample size was calculated on the basis of detecting a difference in Ocular Surface Disease Index (OSDI) score of 10, with a standard deviation of 20, assuming an estimate of type 1 error a =0.05 and power of 80% for a two tailed test. These values were obtained from Schiffman et. al. who demonstrated a mean difference in OSDI score of 10 between normal subjects and those with mild to moderate dry eye, with a standard deviation of up to 20.

Every effort will be made to stratify enrolment by disease severity to ensure participants with mild, moderate and severe dry eye are represented in the study population. Stratification will be in a 2:2:1 fashion i.e. OSDI score >12 (55 participants), OSDI score >20 (55 participants) and OSDI score >45 (28 participants).

Trial participants will be recruited from the local population at the investigational site. An e-mail invitation will be circulated to all SOVS staff, the Brien Holden Vision Institute, the Centre for Eye Health, SOVS post-graduate students, UNSW administrative staff and previous study participants who have indicated their willingness to be contacted to participate in future research studies. Advertisements may also be posted in University newsletters, notice boards, websites, local newspapers, social media (e.g. Facebook), on the SOVS clinic TV screen and other local advertising and community websites.

6.1.4. Trial Duration

This is a 3 month dispensing study. Participants will attend a total of 3 scheduled visits at Baseline, 1 month and 3 months.

Table 5: Visits

Visit Type:	Abbreviation
Baseline	BL
1 month	1M
3 months	3M

For the purpose of these studies, 1 month will be considered the same as 30 days.

6.1.5. Enrolment

A study participant is considered enrolled when they have signed the Participant Information Statement and Consent Form.

6.1.6. Primary Endpoint

Subjective ocular comfort and symptoms assessed using validated questionnaires.

6.1.7. Secondary Endpoint(s)

Non-invasive tear film break-up time, tear evaporation rate, tear meniscus height, tear volume and lipid layer thickness.

7. SELECTION AND WITHDRAWAL OF PARTICIPANTS

7.1. Participant Selection

One hundred and thirty-eight (138) participants, both male and female, age 18 years and upwards who experience symptoms of ocular dryness will be enrolled into the study.

Every effort will be made to stratify enrolment by disease severity to ensure participants with mild, moderate and severe dry eye are represented in the study population. Stratification will be in a 2:2:1 fashion i.e. OSDI score >12 (55 participants), OSDI score >20 (55 participants) and OSDI score >45 (28 participants).

Informed consent will be obtained prior to any clinical trial procedures.

All participants will conform to the clinical trial entry criteria listed below:

7.1.1. Inclusion Criteria

- Able to read and comprehend English and give informed consent as demonstrated by signing a record of informed consent;
- Be at least 18 years old;
- Have symptoms of ocular discomfort as measured with the Ocular Surface Disease Index (OSDI) score of >12 at the Baseline visit;
- Willing to comply with the dosage and study visit schedule as directed by the investigator;
- No contact lens wear in the last 30 days and willing to refrain from contact lens wear for the duration of the study;
- No planned changes to diet and willing not to substantially alter their usual diet for the duration of the study, including their typical intake of fish;
- Willingness to notify the study investigator if instructed to alter their diet by health/medical practitioner;
- Willing to continue using any artificial tear supplements at the same frequency throughout the study, as used prior to the study;
- Have health and ocular health findings which would not prevent the participant from safely ingesting dietary supplementation with combination omega oils.

7.1.2. Exclusion Criteria

- Any systemic disease that would preclude participants from safely ingesting dietary supplementation with combination omega oils;
- Self-reported allergy/sensitivity to any of the study product ingredients;
- Use of any polyunsaturated fatty acid-containing dietary supplements (such as fish oil, evening primrose oil, linseed oil) up to 12 weeks prior to start of the study;

- Use of any of the following medications (including steroids) up to 12 weeks prior to the start of the study or during the course of the study:
  - Ocular medication, category S3 and above;
  - Any systemic or topical medications that will affect ocular physiology e.g. anti-acne medications such as Roaccutane and corticosteroid or immunosuppressant medications such as Hydrocortisone, Prednisolone and antihistamine medications such as Claritine;
- Any systemic disease that may affect ocular health e.g. Graves disease, and auto-immune diseases such as ankolysing spondylitis, multiple sclerosis and systemic lupus erythematosis;
- Epilepsy or history of migraines exacerbated by flashing, strobe-like lights;
- Eye surgery within 6 months immediately prior to enrolment for this study;
- Rigid or soft contact lens wearer, including orthokeratology in the last 30 days;
- Previous corneal refractive surgery;
- Pregnancy or breastfeeding.
- The Investigator may, at his/her discretion, exclude anyone else who they believe may not be able to fulfil the study requirements, or if it is believed to be in the participant's best interests.

7.2. Participant Withdrawal

Participants may be permanently discontinued from the clinical trial for any of the following reasons:

- If, in the Investigator's opinion, it is in the best interest of the participant;
- Persistent clinical trial-related symptoms/complaints that are not correctable;
- Has a serious adverse event/serious adverse device event that is eye/lens/solution related and/or which, in the Investigator's or Sponsor's opinion, requires withdrawal of the participant;
- Participant voluntarily withdraws consent from the clinical trial (i.e. Revocation of Consent);
- Participant is lost to follow-up, or relocates and cannot attend the clinic;
- If a participant is not compliant with the clinical trial requirements and instructions e.g. visit schedule;
- Repeated protocol violations/deviations.

7.3. Withdrawal and Follow-up Procedure

Participants who are permanently withdrawn from the study should be seen as soon as possible after stopping use of the study product for a final visit to assess participant safety and to return any unused study product. This may be done at a routine clinic visit or an unscheduled visit if it occurs between routinely scheduled visits.

7.3.1. The Final Study Exit Visit

Where possible, the data requirements for the final study exit visit are the same assessments as for the 3 month visit shown in Table 5. However, the minimum data requirements include:

- Visual acuity
- Slit-lamp biomicroscopy (ocular redness, corneal and conjunctival staining)

For withdrawal of consent, a 'Revocation of Consent' document should also be signed, if possible.

7.3.2. Lost to Follow-up

A participant will be considered lost to follow-up, after three documented and failed attempts have been made to contact the participant – two phone calls and one written. Any contact should attempt to gain the following information:

- reason participant has not returned to clinic
- safety (previous/new adverse events status), and
- concomitant therapies.

7.3.3. Event Follow-up

If a participant has experienced an adverse event that is continuing at the end of the study participation, the event is marked as ongoing. The Investigator should ensure appropriate follow-up care is arranged/provided to the participant as appropriate.

If an adverse device event, or a serious adverse event/serious adverse device event has occurred and is continuing, the participant should be followed until the event has resolved, or stabilised if there is no chance of improvement. Source notes and the reporting form should be updated as appropriate, and the information forwarded to the Sponsor/HREC/TGA as necessary.

7.3.4. Whether and How Participants are to be Replaced:

Participants who experience an adverse response during the course of the study, that requires early discontinuation from the study, will not be replaced. Participants who are not suitable at Baseline will be replaced, until the enrolment target is reached.

7.4. Early Termination of Trial

The trial may be stopped early for any one or more of the following reasons:

- If the monitoring of the clinical trial reveals unacceptable levels of device-related adverse events, even though some of the participants may not be affected;
- If the Investigator does not adhere to the protocol;
- If the Sponsor decides to stop the study for any reason, with appropriate notification.

In the event of early termination of the trial, the HREC will be notified.

8. NUMBERING

Participant numbering will occur sequentially commencing with '001'.

9. EQUIPMENT TO BE USED / STANDARD & NON-STANDARD PRACTICE PROCEDURES

9.1. Standard Equipment and Procedures:

- ***Visual Acuity:*** Measurement of the standard of vision achieved with spectacles or contact lenses using standard letter charts. Measurements are taken under monocular and/or binocular conditions.
- ***Slit-Lamp Biomicroscopy:*** A specialised microscope with its own light source is used to examine the anterior eye.
- ***Corneal and Conjunctival Staining:*** The corneal surface is assessed by instilling a harmless fluorescent dye called 'fluorescein' using a sterile fluorescein strip moistened with saline. The eye is assessed with the slit-lamp biomicroscope using a cobalt blue filtered light and a Wratten 12 filter. The conjunctival surface is assessed by instilling a harmless dye called "lissamine green' using a sterile lissamine green strip moistened with saline. The eye is assessed using the slit-lamp biomicroscope and white light.
- ***Questionnaires:*** Questions assessing eye symptoms, diet, product usage and general health and wellbeing will be administered on paper forms.
- ***LipiView® Ocular Surface Interferometer (TearScience®):*** Will be used to measure the absolute thickness of the tear film lipid layer. The participant's eye is positioned in front of an illumination source that is directed toward the tear film on the corneal surface. The camera records a 20-second video of the tear film interference and subsequently displays a value in interferometric colour units (ICU), where 1 ICU approximates 1nm of lipid layer thickness.
- ***Phenol red thread test:*** Will be used to measure tear volume.
- ***Participant History File:*** Created at commencement of study and maintained throughout the trial. Contains relevant references to participant's medical history (both prior to participation in the trial and ongoing throughout the trial); and contains details of any problems encountered during the trial (either through observation by the investigator or as volunteered by the participant).

9.2. Non-Standard Equipment and Procedures:

Non-standard procedures that may be performed include:

- ***Tear Evaporation Rate:*** The Vapometer is a closed chamber device which is used for measuring transepidermal water loss. Participants will be seated upright on a chair and provided with a distance fixation target. To minimize the effect of skin evaporation, petroleum jelly (Vaseline_, http://www.unilever.com.au/brands-in-action/detail/Vaseline/299339/) will be applied over the upper eyelid and the surrounding areas. The VapoMeter will then be placed over the eye and a non-invasive measurement of tear evaporation will be taken within 10 seconds. Participants will be instructed not to blink during open eye measurement and to maintain a normal straight gaze at the fixation target. Evaporation rates with the eyes closed will also be taken, in order to account for the skin evaporation from eyelids and surrounding skin tissue.

- ***Oculus Keratograph 5M (Oculus®):*** Will be used to measure non-invasive tear break-up time and tear meniscus height. The participant's eye is positioned in front of a placido disc illumination which allows detection of the tear film and tear prism non-invasively. The associated software measures non-invasive tear break-up time and tear meniscus height.

- ***Photography/Video:*** A photograph of the eye will be taken, and photographic/video recording of any interesting/unusual findings may also be made for documentation and/or follow-up purposes.

- ***Body Mass Index (weight/height^2):*** Will be measured using a digital scale (Charder Scale MS 3400; Charder Electronic Co. Ltd., Taichung City, Taiwan).

- ***Body Fat Composition:*** Will be measured using a Tanita monitor. This is a non-invasive procedure that uses bioelectrical impedance analysis and sends a very low, safe electrical signal from four metal electrodes through the participant's feet to measure body fat composition (Tanita BC-601, Tanita, Australia).

9.3. Maintenance and Calibration of Equipment

Equipment will be monitored regularly for maintenance and calibration as per relevant company and product manuals.

10. TREATMENT OF PARTICIPANTS

10.1. Administration of Study Product

Participants will be instructed to take one capsule by mouth with meals, three times daily for 40 days, and then two times daily for the remainder of the study, as per the manufacturer's recommended guidelines.

10.2. Study Product Storage and Accountability

10.2.1. Storage Requirements

Study product is to be stored at room temperature in a secure storeroom/cupboard. The storage facility should be kept locked to prevent unauthorised access and to ensure accountability of the study product at all times.

10.2.2. Accountability

A Product Tracking spreadsheet is used for keeping track of who, where and when study product have been issued or dispensed to.

- ***Receipt of Study Product:*** Once invoice has been checked, the study product will be entered into the Study Product Tracking spreadsheet.
- ***Issue of Study Product to Clinical Trial Participants:*** The Optometrist is responsible for documenting the dispensing of the study product on the participant case record form.
- ***Disposal of Unused Supplies:*** Instruction will be obtained from the sponsor as to how to handle returned, unused study product.

10.3. Concomitant Therapy

Whilst participating in this clinical trial participants are not permitted to enrol in other clinical trials.

Participants must not use or have a need for any systemic or topical medications which may alter normal ocular findings/are known to affect a participant's ocular health/physiology either in an adverse manner or risk providing a false positive.

10.4. Participant Instructions

General instructions to all participants

- Contact the clinic immediately if problems are experienced or if they have any questions or concerns
- Ingest the study product daily as per manufacturer's recommendation
- Return the unused study product at each follow-up visit
- Store the study product at room temperature and keep out of reach of children
- Continue to use any artificial tear supplements at the same frequency throughout the study, as used prior to the study
- Do not make any substantial changes to your intake of fish/diet for the duration of the study, unless instructed to do so for health/medical reasons. If so, please advise the study investigator as soon as possible.

11. ASSESSMENT OF EFFICACY

11.1. Parameters

- Ocular comfort
- Product usage
- Visual acuity
- History
- Tear lipid layer thickness
- Tear evaporation rate
- Non-invasive tear break-up time
- Tear meniscus height
- Tear volume (phenol red thread test)
- Eyelids: redness and swelling
- Bulbar conjunctival redness
- Corneal and conjunctival staining
- Body mass index
- Body fat composition

11.2. Methods

Ocular comfort and product usage will be assessed by completion of a paper questionnaire (Appendix II).

History (including medical and general health) will be recorded on the Participant History File at all visits.

Habitual visual acuity will be measured at each visit using standard letter charts.

Tear lipid layer thickness will be measured using the LipiView Ocular Surface

Interferometer. The participant's eye is positioned in front of an illumination source that is directed toward the tear film on the corneal surface. The camera records a 20-second video of the tear film interference and subsequently displays a value in interferometric colour units (ICU), where 1 ICU approximates 1nm of lipid layer thickness.

A photograph of the anterior eye will be taken at the Baseline visit for participants who are eligible to be randomised into the study. From the photograph, ocular surface area will be measured in order to calculate the absolute tear evaporation rate.

Tear evaporation rate will be measured using the Vapometer. To minimize the effect of skin evaporation, petroleum jelly (Vaseline_, http://www.unilever.com.au/brands-in-action/detail/Vaseline/299339/) will be applied over the upper eyelid and the surrounding areas. Three measurements will be taken for each eye under open eye and closed eye conditions. Each measurement will be recorded and the absolute evaporation rate will be calculated for each eye.

Non-invasive tear break-up time will be measured using the Oculus Keratograph 5M. The participant's eye is positioned in front of a placido disc illumination which allows detection of the tear film. Participants will be asked to blink three times and then to hold their eyes open for as long as possible, or until instructed to blink again by the study investigator. Three consecutive measurements of non-invasive tear break-up time will be recorded for each eye.

Tear meniscus height will be measured using the Oculus Keratograph 5M. The participant's eye is positioned in front of a placido disc illumination which allows detection of the tear film. Participants will be asked to blink once and an image of the tear prism will be captured immediately after the blink. Tear meniscus height will be obtained using the measuring guide software.

Tear volume will be measured using the phenol red thread test. The folded 3mm end of the thread is placed at a point approximately 1/3 of the distance from the lateral canthus of the lower eyelid with the eye in primary position. Participants are instructed to look straight ahead and blink normally during the test. When 15 seconds have elapsed, the thread is gently removed and the entire length of the red portion of the thread is measured in millimetres from the very tip, regardless of the fold.

Slit lamp biomicroscopy will be performed at each visit. This will be used to assess the following variables and rated using the CCLRU (Appendix III) and CIBA Grading Scales (Appendix IV).

- Eyelids: redness and swelling
- Bulbar conjunctival redness

- Corneal and conjunctival staining

Body mass index and body fat composition will be measured at the first visit only. To calculate body mass index (weight/height^2), participants will be asked to stand on a digital scale (Charder Scale MS 3400; Charder Electronic Co. Ltd., Taichung City, Taiwan) whereby weight and height will be measured. Body fat composition will be measured using a Tanita monitor (Tanita BC-601, Tanita, Australia). Participants will be asked to stand on the Tanita monitor, which sends a very low, safe electrical signal from four metal electrodes through the participant's feet, and uses bioelectrical impedance analysis to calculate body fat composition.

12. ASSESSMENT OF SAFETY

12.1. Parameters

- Discomfort
- History
- Visual acuity
- Ocular redness: bulbar conjunctiva
- Corneal and conjunctival staining
- Health and wellbeing questionnaire

12.2. Methods

Discomfort and Health and Wellbeing will be assessed using questionnaires and the Participant History File at all scheduled visits.

History (including medical and general health) will be recorded on the Participant History File at all visits.

Ocular examination using slit-lamp biomicroscopy will be carried out at Baseline and at every visit. Ocular bulbar conjunctival roughness and corneal and conjunctival staining will be assessed and recorded using the CCLRU (Appendix III) and CIBA Grading scales (Appendix IV).

An optometrist will be available for the duration of the study. Participants will be advised to contact the optometrist immediately of any problem or event not normal with their eyes e.g. unusual redness, pain, irritation, etc. At the clinic, the optometrist will briefly assess the eye on a slit-lamp under low illumination to ascertain the nature of the condition, if any. If an adverse event occurs, the appropriate procedures will be conducted, including referral for medical treatment if necessary. Any adverse events will be followed until complete resolution to the reasonable satisfaction of the participant and the investigator.

12.3. Definitions

12.3.1. Adverse Events

Adverse Event: Any undesirable clinical occurrence in a participant, whether it is considered to be device-related or not, that includes a clinical sign, symptom or condition and/or observation of an unintended technical performance or performance outcome of the device.

Adverse Events may be classified as Serious, Significant, Non-significant or Unanticipated as defined further on.

12.3.2. Serious Adverse Events

Any adverse medical occurrence that:

- led to death.
- led to a serious deterioration in health of a Participant user or other. This would include:
  - a life threatening illness or injury.
  - a permanent impairment of body function or permanent damage to a body structure.
  - a condition requiring hospitalisation or increased length of existing hospitalisation.
  - a condition requiring unnecessary medical or surgical intervention.
  - foetal distress, foetal death or a congenital abnormality/birth defect.
- might have led to death or a serious deterioration in health had suitable action or intervention not taken place. This includes:
  - a malfunction of a device such that it has to be modified or temporarily/permanently taken out of service.
  - a factor (a deterioration in characteristics or performance) found on examination of the device.

12.4. Reporting

In the event of persistent irritation, redness, reduced visual acuity or any other unusual signs or symptoms, the participants will be advised to remove their lenses immediately and contact the clinic.
Non-serious and anticipated device-related adverse events and adverse events should be recorded as part of Good Clinical Practice. Sponsors are expected to maintain up-to-date tabulations and/or line listings of all adverse device events.

All Serious Adverse Events should be reported within 24 hours to the HREC as per their reporting requirements. This should be followed by a more detailed written report commenting on potential confounding factors, results of investigations, treatment required and outcome. The Co-sponsor and the Principal Investigator should review the events in conjunction with the known information about the device, and make a determination as to whether the event is device-related or not.

All adverse events should be reported to the Co-sponsor no later than 10 days after the event.

12.4.1. Foreseeable Adverse Events

Risks associated with the use of the study product are likely to be gastric/digestive in nature and may include:

- Stomach pain (<2%)
- Diarrhoea (<1%)

Potential risks associated with the study procedures include:

- Eye irritation/discomfort (less than 1 in 20 chance)
- Watery eyes (less than 1 in 100 chance)

12.4.2. Other Observations

There may be other situations that may necessitate rapid communication to regulatory authorities. Scientific and medical judgment should be applied for each situation. In general, information that might materially influence the benefit-risk assessment of a product or that would be sufficient to consider changes in product administration or in the overall conduct of a clinical investigation represent such situations.

12.5. Follow-up

Participants who experience an adverse response during the course of the trial will be followed up until the condition resolves or the participant is referred to another practitioner. ***Permanent discontinuation:*** will occur when, in the optometrist's opinion (or ophthalmologist's, if participant has been referred), continued use of the study product will be detrimental to ocular or general health.

12.6. Referrals

Participants will be referred to a medical expert when judged by the optometrist to be necessary. After hours, participants will be referred to Sydney Eye Hospital.

Table 6

Title:	The Ophthalmology Registrar
Address:	**Sydney Eye Hospital** South Block Number 8 Macquarie Street Sydney NSW 2000
Telephone:	+61 2 9382 7111

13. STATISTICS

13.1. Description

Data stored in relational databases will be imported into SPSS software for statistical purposes. Statistical analysis will initially be reported in Excel. The study may employ at least one interim analysis. Data will be investigated for quality using range checks and frequency distribution. Underlying distributions of variables will be tested. In general, variables measured on an interval scale with a sufficiently large sample size will be considered to follow a normal distribution. Details of statistical analysis are described in Section 13.1.3.

13.1.1. Number of Participants

138 participants will be recruited (69 in each group, which includes allowance for a 10% drop-out rate).

This sample size was calculated on the basis of detecting a difference in OSDI score of 10, with a standard deviation of 20, assuming an estimate of type 1 error α =0.05 and power of 80% for a two tailed test. These values were obtained from Schiffman et. al. who demonstrated a mean difference in OSDI score of 10 between normal subjects and those with mild to moderate dry eye, with a standard deviation of up to 20.

13.1.2. Significance

A p-value less than or equal to 5% will be considered to be statistically significant.

13.1.3. Analysis

Participants who have commenced the study treatment will be included in the analysis dataset. Reasons and frequency distribution of participants discontinued at Baseline will be reported. The analysis of efficacy variables such as subjective ratings will employ only scheduled and evaluable visits.

The analysis of safety variables such as adverse responses will include all visits, including all unscheduled visits.

Data will be summarised as means ± standard deviations for variables measured on an interval scale and median ± inter-quartile range for ordinal variables. Statistical tests will be employed to determine significant differences between between visits and $p \leq 0.05$ will be considered statistically significant. Multiple comparisons will be adjusted using Bonferroni's correction. Commonly used tests of significance at each visit may include paired t-tests and group t-test for parametric data and Wilcoxon sign rank test and rank sum test for non-parametric data or repeated measures Analysis of Variance (ANOVA) for parametric data to determine differences between within-subject factors. Ranked variables will be analysed non-parametrically using Friedman's analysis of variance or Wilcoxon Signed Rank test to determine differences. Paired categorical variables will be compared using McNemar's test and grouped categorical variables will be analysed using Chi-Square tests.

13.2. Criteria for Termination of the Trial

The trial will be terminated upon completion of the final visit by the last active participant or unless any of the conditions of Section 7.4 are met. An active participant is one who is enrolled in the study and has not been discontinued.

13.3. Accountability of Data

Individual data points that are missing will be excluded from analysis involving only those specific variables. A participant's complete visit data will not be excluded if some of the observations are missing. Data from unscheduled visits will be used only for adverse response analysis. Inclusion of outliers in the analysis will be based on the magnitude of change in test statistic with and without the outliers. Outliers will preferably be retained unless there is significant change in test results.

14. DATA HANDLING AND RECORD KEEPING

14.1. Source Data

The Investigator/Institution is to maintain the trial documents as specified in ICH GCP guidelines and as required by the applicable local regulations. The Investigator/Institution is to also take measures to prevent accidental or premature destruction of clinical trial-related documentation.

Paper Case Report Forms are utilized for this clinical trial, and will be entered into Excel spreadsheets for importing into statistical software. For tests conducted that produce printed results, these should be included in the participant's file. Source data includes, but is not limited to printouts, diagrams, videos, photos, and any other paper, electronic or digital data that is the first recording of that information, and these must be maintained by the Investigator in the source files for the participant, or if unable to file (e.g. digital images), then reference should be made to their location. The clinic records will maintain a record of trial participation but will not be considered as the source.

14.2. Direct Access to Source Data/Documents

The Investigator will conduct this clinical trial under HREC review. As necessary the Investigator will provide the HREC, the Sponsor and the Sponsor's representatives, and appropriate regulatory authorities direct access to source data/documents for review.

14.3. Data Management

The data will be accessible to study personnel only, secured and backed up regularly.

14.4. Data Archiving

Electronic data will be stored in a secure off-site storage facility. Paper records are archived approximately 3 months after study closeout or as agreed with the Sponsor and/or the Principal Investigator. The records are initially kept on site in a secure location, and may later be transferred to a secure off-site storage facility.

14.5. Retention of Essential Documents

The Investigator/Institution is to retain essential documents until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region. However, these documents should be retained for longer if required by local regulatory agencies or by an agreement with the Co-sponsor.

The Sponsor must retain essential documents for the periods as specified above per ICH GCP and per TGA for 15 years following the completion of a clinical trial. However, per TGA requirements, essential documents may need to be retained longer after consideration of the following: product liability and the potential need for sponsors of products to produce records at any time during, and possibly beyond, the life of a product in the event of a claim against the Sponsor as a result of an adverse outcome associated with the use of the product.

15. QUALITY CONTROL AND QUALITY ASSURANCE

15.1. Ethical Considerations

This trial requires HREC approval prior to start.

The Investigator is to ensure that the protocol, Participant Information Statement and Consent Form, available safety information, information about payment and compensation to participants, advertising or any clinical trial specific information provided to participants (including potential participants), the Investigator's CV and/or evidence of appropriate qualifications and any other documentation they may request are submitted, reviewed and approved. Any subsequent amendments will be reviewed and approved by an HREC prior to implementation.

The HREC must be appropriately constituted, and will perform its functions in accordance with the applicable local regulatory requirements (TGA and NHMRC) and GCP.

This trial will be conducted in accordance with local guidelines and requirements (including those of the NHMRC and TGA, as applicable).

15.1.1. Confidentiality

Confidentiality will be maintained throughout the clinical trial by all parties involved in accordance with guidelines under section 95 of the Privacy Act 1998, and guidelines approved under section 95a of the Privacy Act 1998 (December 2001). Data will be secured against unauthorised access.

Privacy and confidentiality of information about each clinical trial participant will be preserved in the reports and any publication of the clinical investigation data.

15.1.2. Informed Consent

The nature and purpose of the trial will be fully explained to each participant. Written informed consent must be obtained from each participant prior to any trial procedures being performed.

The informed consent documentation to be used for the trial will include all the elements of informed consent per GCP, and TGA requirements as applicable, and will be reviewed and approved by the HREC prior to use.

15.1.3. Protocol Amendments

It is agreed between the Co-sponsor and the Investigator that deviations will be reviewed to determine the need to amend the protocol or to terminate the investigation. Justification for any changes must be provided.

Protocol amendments will be submitted to the Co-sponsor and HREC for review and approval prior to implementation, unless the change required is to eliminate an immediate hazard to trial participants, or involves only administrative and/or logistical aspects of the trial (eg. Change in contact numbers).

15.1.4. Investigator Responsibilities

The Investigator is responsible for ensuring participant safety and data quality by: protocol compliance, adherence to GCP and local regulatory requirements, and the Declaration of Helsinki. The Investigator should be appropriately qualified and legally entitled to practice, and be trained in the proper method of obtaining informed consent.

The Investigator must have the appropriate resources to conduct the clinical trial, be familiar with the protocol and agree to adhere to it, support monitoring and auditing activities, communicate with the Sponsor regarding any clinical trial issues or need for protocol modifications, make the necessary arrangements to ensure proper conduct and completion of the clinical trial, and ensure the protection and welfare of the participant, including arranging any emergency treatment as needed.

The Investigator must ensure written HREC approval is received prior to the start of the clinical trial, that the HREC and Sponsor is kept informed of the clinical trial progress, including serious/adverse events and deviations as required by them, and that any changes to the protocol are notified to the HREC and receive written approval prior to implementation.

The Investigator must try to ensure adequate participant recruitment; that all necessary and appropriate information is given to potential participants to ensure informed consent; to ensure informed consent is taken and documented; and that clinical records indicate the participant is enrolled in a clinical trial. The Investigator must ensure that clinical trial participants are provided with emergency contact details along with a procedure to follow in the case of an emergency, and that clinical trial participants are kept informed as pertinent new information becomes available that may affect their decision to participate.

The Investigator has primary responsibility for the accuracy, legibility and security of all clinical investigation data, documents and participant records at the investigator site during and after the clinical trial. Case Report Forms are to be signed by the Investigator, and any alterations to data are to be by authorised personnel, initialled and dated by same.

The Investigator must ensure that data be kept for the minimum time as specified by this protocol, investigational product must be accounted for (the quantity of the devices received must be reconciled with the quantities of the device used, discarded or returned), and must also be responsible for the supervision and assignment of duties to all responsible for the conduct and evaluation of the clinical trial for the investigator centre involved.

16. FINANCING AND INSURANCE

Memorandum of Agreement can be provided on request.

17. PUBLICATION POLICY

Please refer to Memorandum of Agreement

INVESTIGATOR AGREEMENT

"I agree to conduct the trial outlined above according to the terms and conditions of the protocol, Good Clinical Practice Guidelines and with the applicable regulatory requirements. All information pertaining to the trial shall be treated in a confidential manner."

Principal Investigator's Signature: _____ Date:_____

Principal Investigator's Printed Name: _____

APPENDIX I

DECLARATION OF HELSINKI

APPENDIX I: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

The Declaration of Helsinki (Document 17.C) is an official policy document of the World Medical Association (WMA), the global representative body for physicians.

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964 and amended by the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

APPENDIX I: Declaration of Helsinki *(cont.)*

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

APPENDIX I: Declaration of Helsinki *(cont.)*

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

APPENDIX II

QUESTIONNAIRES

APPENDIX II: QUESTIONNAIRES

OCULAR COMFORT INDEX (OCI)

Ocular Comfort Index

ID:

This questionnaire was designed to grade the comfort of your eyes.
For each question please circle your answer.

Example: In the last week, how often were your eyes *red* ?

Never						Always
0	1	2	(3)	4	5	6

There are no right or wrong answers. Do not spend too long on any one question.

1 In the last week, how often did your eyes feel *dry* ?

Never						Always
0	1	2	3	4	5	6

When your eyes felt dry, typically, how intense was the *dryness* ?

Never had it						Severe
0	1	2	3	4	5	6

2 In the last week, how often did your eyes feel *gritty* ?

Never						Always
0	1	2	3	4	5	6

When your eyes felt gritty, typically, how intense was the *grittiness* ?

Never had it						Severe
0	1	2	3	4	5	6

3 In the last week, how often did your eyes feel *stingy* ?

Never						Always
0	1	2	3	4	5	6

When your eyes stung, typically, how intense was the *stinging* ?

Never had it						Severe
0	1	2	3	4	5	6

4 In the last week, how often did your eyes feel *tired* ?

Never						Always
0	1	2	3	4	5	6

When your eyes felt tired, typically, how intense was the *tiredness* ?

Never had it						Severe
0	1	2	3	4	5	6

5 In the last week, how often did your eyes feel *painful* ?

Never						Always
0	1	2	3	4	5	6

When your eyes felt painful, typically, how intense was the *pain* ?

Never had it						Severe
0	1	2	3	4	5	6

6 In the last week, how often did your eyes *itch* ?

Never						Always
0	1	2	3	4	5	6

When your eyes itched, typically, how intense was the *itching* ?

Never had it						Severe
0	1	2	3	4	5	6

OCULAR SURFACE DISEASE INDEX (OSDI)

Ocular Surface Disease Index© (OSDI©)[2]

Ask your patient the following 12 questions, and circle the number in the box that best represents each answer. Then, fill in boxes A, B, C, D, and E according to the instructions beside each.

HAVE YOU EXPERIENCED ANY OF THE FOLLOWING *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time
1. Eyes that are sensitive to light?	4	3	2	1	0
2. Eyes that feel gritty?	4	3	2	1	0
3. Painful or sore eyes?	4	3	2	1	0
4. Blurred vision?	4	3	2	1	0
5. Poor vision?	4	3	2	1	0

Subtotal score for answers 1 to 5 (A)

HAVE PROBLEMS WITH YOUR EYES LIMITED YOU IN PERFORMING ANY OF THE FOLLOWING *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
6. Reading?	4	3	2	1	0	N/A
7. Driving at night?	4	3	2	1	0	N/A
8. Working with a computer or bank machine (ATM)?	4	3	2	1	0	N/A
9. Watching TV?	4	3	2	1	0	N/A

Subtotal score for answers 6 to 9 (B)

HAVE YOUR EYES FELT UNCOMFORTABLE IN ANY OF THE FOLLOWING SITUATIONS *DURING THE LAST WEEK*:

	All of the time	Most of the time	Half of the time	Some of the time	None of the time	
10. Windy conditions?	4	3	2	1	0	N/A
11. Places or areas with low humidity (very dry)?	4	3	2	1	0	N/A
12. Areas that are air conditioned?	4	3	2	1	0	N/A

Subtotal score for answers 10 to 12 (C)

ADD SUBTOTALS A, B, AND C TO OBTAIN D (D = SUM OF SCORES FOR ALL QUESTIONS ANSWERED) (D)

TOTAL NUMBER OF QUESTIONS ANSWERED (DO NOT INCLUDE QUESTIONS ANSWERED N/A) (E)

Please turn over the questionnaire to calculate the patient's final OSDI© score.

DRY EYE QUESTIONNAIRE 5 (DEQ-5)

1. Questions about **EYE DISCOMFORT**:
   a. During a typical day in the past month, **how often** did your eyes feel discomfort?
      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly
   b. When your eyes felt discomfort, **how intense was this feeling of discomfort** at the end of the day, within two hours of going to bed?

Never have it	Not at all Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

2. Questions about **EYE DRYNESS**:
   a. During a typical day in the past month, **how often** did your eyes feel dry?
      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly
   b. When your eyes felt dry, **how intense was this feeling of dryness** at the end of the day, within two hours of going to bed?

Never have it	Not at all Intense				Very Intense
0	**1**	**2**	**3**	**4**	**5**

3. Question about **WATERY EYES**:
   During a typical day in the past month, **how often** did your eyes look or feel excessively watery?
      0 Never
      1 Rarely
      2 Sometimes
      3 Frequently
      4 Constantly

Score: 1a + 1b + 2a + 2b + 3 = Total
___+___+___+___+___= ____

Figure 3 The DEQ-5 (5-item Dry Eye Questionnaire), which is designed for patient self-assessment of dry eye severity on a typical day during the past month.
Notes: A composite score >6 suggests dry eye.

SYMPTOM SURVEY

Think about how your eyes have felt **during a typical day in the last week**. Then, using the scales provided below, please mark a vertical line at the place that best describes your experience with these symptoms during this time period:

1. Watery Eyes

No watering Maximum watering

0_____100

2. Grittiness/Foreign Body Sensation

No grittiness/foreign body sensation Maximum

0_____100

3. Dryness

No dryness Maximum dryness

0_____100

4. Blurry/Fluctuation Vision

No blurry/fluctuating vision Maximum

0_____100

5. Overall Ocular Pain/Discomfort

No ocular pain/discomfort Maximum

0_____100

6. On average, how many times per day did you use eye drops during the past week?

_____

HEALTH AND WELLBEING SURVEY

1. Since your last visit, have you:

a) Been hospitalized? **Yes / No**

b) Used any new medication or changed medication regimens? **Yes / No**

c) Experienced any Gastrointestinal irritation e.g. diarrhea, heartburn, bloating or nausea? **Yes / No**

d) Experienced unusual bleeding? **Yes / No**

e) If you answered yes to any of the above, please explain:

_____

_____

_____

_____

2. On average, how many times per day did you ingest the study product during the past week?

_____

NUTRITION QUESTIONNAIRE

DIETARY SUPPLEMENTS AND OCULAR COMFORT

ON AVERAGE, HOW MANY SERVES PER WEEK WOULD YOU EAT OF THE FOLLOWING (PLEASE REFER TO THE DIET GUIDE FOR FOOD TYPES WITHIN EACH GROUP AND SERVING SIZES.)

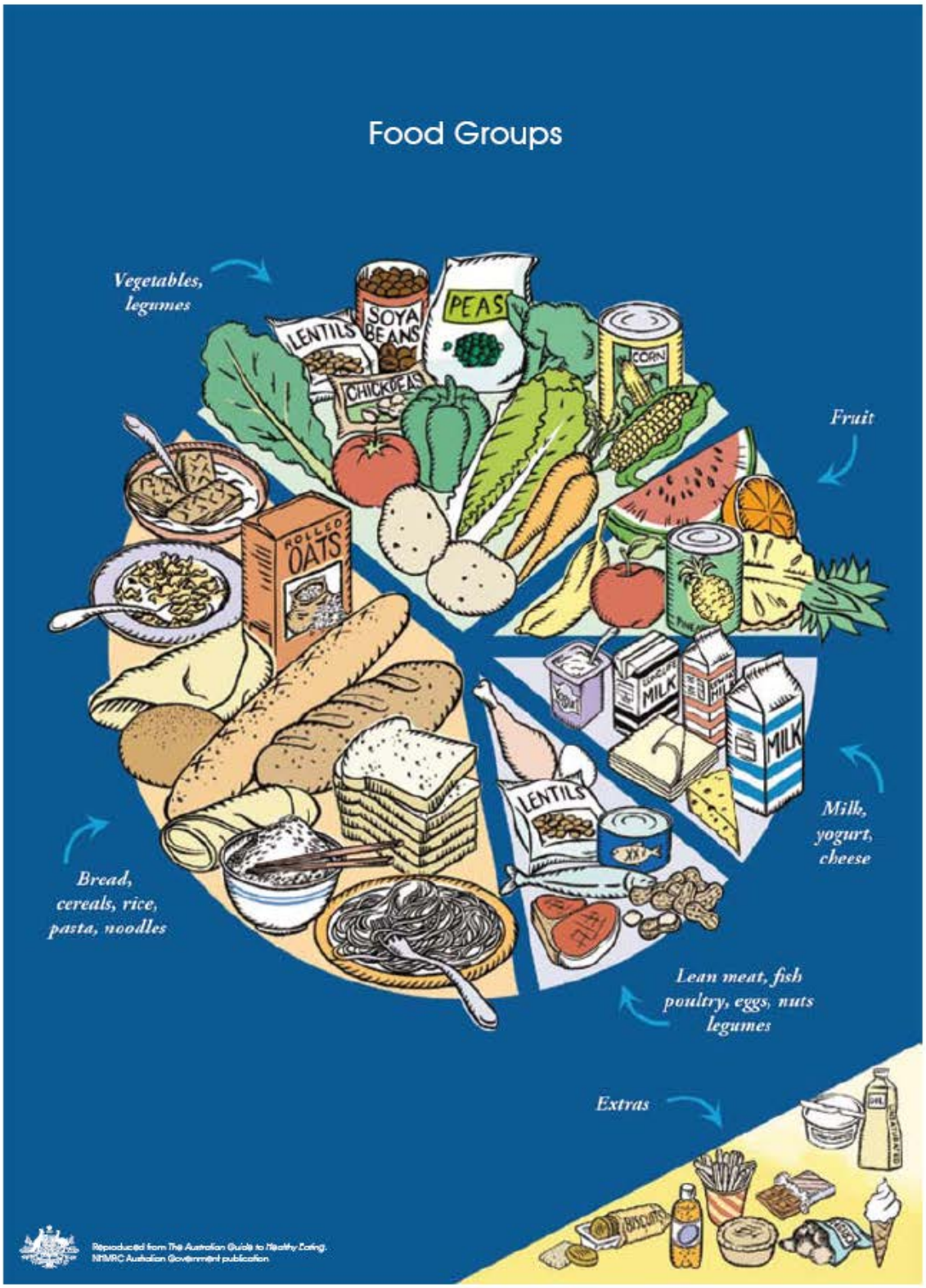
FOOD TYPE	**SERVES PER WEEK**
CEREALS	
VEGETABLES, LEGUMES	
FRUIT	
MILK, YOGHURT, CHEESE	
LEAN MEAT, FISH, POULTRY, NUTS	
EXTRA FOODS (E.G. CAKES, PIES, SWEETS, SOFT DRINKS, ALCOHOL, ETC)	

HOW MANY TIMES PER WEEK DO YOU EAT OILY FISH (SALMON, TUNA, ETC)?: _____

ARE YOU VEGETARIAN OR VEGAN?

NEITHER	
VEGETARIAN (EAT FISH)	
VEGETARIAN (DO NOT EAT FISH)	
VEGAN	

Diet Guide


Food Groups
Vegetables, legumes
Fruit
Bread, cereals, rice, pasta, noodles
Milk, yogurt, cheese
Lean meat, fish poultry, eggs, nuts legumes
Extras
LENTILS
SOYA BEANS
PEAS
CHICKPEAS
CORN
ROLLED OATS
MILK
LENTILS
BISCUITS
Reproduced from The Australian Guide to Healthy Eating.
NHMRC Australian Government publication

What is a serve? Here are some examples

Cereals, breads etc		
2 slices of bread	1 medium bread roll	1 cup cooked rice, pasta, noodles
1 cup porridge	1 cup breakfast cereal flakes	or ½ cup muesli

Vegetables and legumes		
Starchy vegetables		
1 medium potato or yam	½ medium sweet potato	1 medium parsnip
Dark green leafy vegetables		
½ cup cabbage, spinach, silverbeet, brocolli, cauliflower or brussels sprouts		
Legumes and other vegetables		
1 cup lettuce or salad vegetables	½ cup broad beans, lentils, peas, green beans, zucchini, mushrooms, tomatoes, capsicum, cucumber, sweetcorn, turnips, swede, sprouts, celery, eggplant etc	

Fruit		
1 piece medium sized fruit eg apple, orange, mango, mandarin, banana, pear, peach etc		
2 pieces of smaller fruit eg apricots, kiwi fruit, plums, figs		About 8 strawberries
1 cup diced pieces or canned fruit	½ cup fruit juice	¼ medium melon (rockmelon, honeydew)
Dried fruit eg 4 dried apricots	1½ tablespoons sultanas	About 20 grapes or cherries

Milks, yoghurt, cheese & alternatives		
250 ml glass or one cup of milk (can be fresh, longlife or reconstituted milk)		
½ cup evaporated milk	40g (2 slices) of cheese	250ml (1 cup custard)
200g (1 small carton) of yoghurt, plain or fruit, *or*		
a cup of calcium-fortified soy milk	1 cup almonds	½ cup pink salmon with bones

Meat, fish, poultry & alternatives		
65-100gm cooked meat or chicken (eg ½ cup mince, 2 small chops or 2 slices roast meat)		
80-120g cooked fish fillet, *or*		
2 small eggs	½ cup cooked (dried) beans, lentils, chick peas, split peas or canned beans	1/3 cup peanuts or almonds

Extras		
1 medium piece of plain cake or 1 bun	3-4 sweet biscuits	Half a chocolate bar
60g jam, honey (1 tablespoon)	30g potato crisps	Slice pizza = 2 extras
1 can soft drink or 2 glasses cordial	2 scoops icecream	1 meat pie or pasty = 3 extras
2 standard glasses of alcohol (for adults only)		

APPENDIX III

CCLRU GRADING SCALES

APPENDIX III: CCLRU Grading Scales

The CCLRU Grading Scale uses a 0-4 scale in 0.5 steps, as shown in the following table:

Table 7

Grade	Description
0	Absent
1	Very Slight
2	Slight
3	Moderate
4	Severe

The scale is to be used in conjunction with the colour photographs as a standard to compare the observed finding and grade accordingly.

APPENDIX IV

CIBA GRADING SCALES

APPENDIX IV: CIBA Grading Scales

SLIT-LAMP QUANTIFICATION CHART

BIOMICROSCOPY SIGNS

Eyelid and Bulbar Conjunctival Redness

0 = **None:** White and clear
1 = **Trace:** Regional hyperemia
2 = **Mild:** Diffuse hyperemia
3 = **Moderate:** Marked regional or diffuse hyperemia
4 = **Severe:** Diffuse episcleral or scleral hyperemia

Corneal Staining

0 = **None:** No staining
1 = **Trace:** Regional superficial stippling and/or foreign body tracks
2 = **Mild:** Regional or diffuse punctate staining and/or F.B. tracks
3 = **Moderate:** Dense coalescent staining and/or abrasions
4 = **Severe:** Epithelial loss, or full thickness abrasion

Conjunctival Staining

0 = **None:** No staining
1 = **Trace:** Minimal regional staining
2 = **Mild:** Regional or diffuse punctate staining
3 = **Moderate:** Significant dense coalescent staining
4 = **Severe:** Severe dense geographical staining