PROTOCOL TITLE

Narrow band UVB phototherapy for patients with Clinically Isolated Syndrome

Protocol: PhoCIS

Original Protocol: Version 5.0 Dated: 22 March 2016

This trial is funded by a project grant from the National Health and Medical Research Council of Australia (ID 1067209)

CO-ORDINATING PRINCIPAL INVESTIGATOR

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STUDY ACKNOWLEDGMENT/CONFIDENTIALITY

By signing this Protocol, the Principal Investigators (on behalf of all Investigators) acknowledge and agree that the Protocol contains all necessary details for conducting the study. The Investigator team will conduct this study as detailed herein, in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements, and will make every reasonable effort to complete the study within the time designated.

The Protocol and all relevant information on narrow band UVB phototherapy will be made available to all physicians, nurses and other personnel who participate in the conducting of this study. The Investigator team will discuss this material with them to assure that they are fully informed regarding narrow band UVB phototherapy and the conduct of the study.

The conduct and results of this study will be kept confidential. The results of this study may be published. Upon completion of the Study it is the intention of the parties to prepare a joint publication describing the trial and the results.

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ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse Event
ANRI	Australian Neuromuscular Research Institute
CIS	Clinically Isolated Syndrome
CRF	Case Report Form
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EBV	Epstein Barr Virus
EDSS	Expanded Disability Status Scale
FDE	First Demyelinating Event
FSS	Fatigue Severity Scale
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
ICH	International Conference on Harmonisation
KFS	Kurtzke Function System
MS	Multiple Sclerosis
MSFC	Multiple Sclerosis Functional Composite
NHMRC	National Health and Medical Research Council
RCT	Randomised Controlled Trials
SAE	Serious Adverse Event
SF-36v2	Short Form-36 Version 2
TGA	Therapeutic Goods Administration
UVB	Ultraviolet B radiation

1. Investigators and Qualifications

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2. Site Location:

Recruitment and narrow band UVB-phototherapy will be performed at the St John of God Medical Centre, Subiaco in Perth, Western Australia. Study visits by the participants will occur at the St John of God Medical Centre, Subiaco, and the clinics of the Australian Neuromuscular Research Institute, Sir Charles Gairdner Hospital, Nedlands, Western Australia. The healthy controls will be recruited by advertisement at the Telethon Kids Institute, Subiaco, Western Australia.

3. Purpose of the Study:

In this study (the PhoCIS trial, Phototherapy for CIS patients) we aim to examine the effects of narrow band UVB therapy on immune and inflammatory markers of disease, MRI and a unique transcription signature for MS, in patients with Clinically Isolated Syndrome (CIS).

4. Protocol Synopsis

Study Title:	Narrow band UVB phototherapy for patients with Clinically Isolated Syndrome
Indication:	Patients at high risk of Multiple Sclerosis [patients with Clinically Isolated Syndrome (CIS) defined by a First Demyelinating Event (FDE)]
Intervention:	Participants will be randomised to either no phototherapy or narrow band UVB phototherapy, 3 times per week for 8 weeks. All participants will wear a UVB dosimeter.
No. Subjects:	60 CIS patients from Perth, Western Australia, and surrounding districts. There will be 2 groups of healthy individuals of similar age and sex recruited in Perth. The first group includes 10 healthy

	individuals donating blood monthly for 12 months for biomarker analysis. At recruitment, these individuals will have no known autoimmune disease and have not had a cold, flu or other illness in the last 7 days. They will not be taking strong immunomodulatory drugs. Measurement of biomarkers of these healthy controls from the same location as the CIS patients will allow precise comparison of the relative extent of change in biomarker expression by UVB phototherapy. Another group of up to 40 healthy individuals of similar age and sex in Perth will be invited to donate blood on a single occasion for analysis of their blood cells. These individuals will have no known autoimmune disease and have not had a cold, flu or other illness in the last 7 days. They will not be taking strong immunomodulatory drugs. Measurement and characterisation of blood cells from these healthy controls from the same location as the CIS patients will allow comparison of cell changes related to the clinical condition of the CIS patients when first diagnosed.
Study Duration:	Recruitment will occur all year round in Perth. Participants will participate for one year.
Objectives of the Study:	To test the hypothesis that narrow band UVB phototherapy compared with no phototherapy, is associated with a decreased risk of developing Multiple Sclerosis over 12 months following a first demyelinating event.
Aims	• To determine the efficacy of narrow band UVB phototherapy in reducing the risk of recurrent disease activity (clinical demyelinating event or MRI activity) in the 12 months following onset of a first demyelinating event. • To assess whether narrow band UVB phototherapy affects the clinical and/or radiological responses in high-risk CIS participants associated with development of Multiple Sclerosis. • To determine whether narrow band UVB phototherapy alters the phenotype, function and transcriptional profile of immune cells in blood drawn 1 week, and 1, 2, 3, 6 and 12 months after initiation of phototherapy in comparison with those in blood taken immediately before phototherapy. • To examine whether narrow band UVB phototherapy reduces immunological biomarkers in blood that have been associated with active Multiple Sclerosis. • To determine if narrow band UVB phototherapy has an

	acceptable side effect and safety profile and is an acceptable treatment option for CIS patients.
Study Endpoints: (Primary and Secondary):	Primary: • Phototherapy-associated changes in transcriptome profiling in whole blood • Phototherapy-associated changes in the phenotype of cells in freshly isolated peripheral blood • Phototherapy-associated changes in T regulatory cells in the peripheral blood as measured by Foxp3 expression and by Foxp3 demethylation analysis • Phototherapy-associated changes to immunological function of cells in the peripheral blood • Development of a new demyelinating event defined as either • A confirmed clinical relapse or • A new cerebral T2 lesion and/or newly Gadolinium-enhancing cerebral lesion at either the 6 month or 12 month MRI scan compared to the study baseline scan. Secondary: • Baseline to 12 month EDSS change • Baseline to 12 month change in SF36v2 Quality of life score • Baseline to 12 month change in Fatigue score • Baseline to 12 month cerebral MRI grey matter volume change • Baseline to 12 month cerebral MRI white matter volume change • Safety: Adverse Events (including SAE) reported for narrow band UVB phototherapy
Study Design:	Participants will be randomised to treatment, or not, with narrow band UVB phototherapy. During the first 8 weeks (whether receiving phototherapy or not), all participants will wear a UVB dosimeter to measure their background environmental UVB exposure.
Eligibility Criteria:	Inclusion Criteria • Aged between 18 and 65 years old inclusive. • Recently diagnosed (within 120 days) with a first isolated, well-defined, uni- or multi-focal first demyelinating event (FDE).

	• Able to receive their first phototherapy within 120 days of FDE symptom onset. • An MRI brain scan that is supportive of demyelinating disease (Paty A or Paty B criteria, i.e. the presence of at least four T2 lesions greater than 3 mm, or at least three T2 lesions greater than 3 mm, one of which must be periventricular, respectively). • An EDSS between 0 - 6.5 (inclusive) • Must be able to give informed consent and sign the informed consent form • Must be able to comply with all study procedures, and attend 24 phototherapy sessions and centres for venepuncture on multiple occasions during and after phototherapy • If female of child-bearing age, must be willing to use effective contraception • Must be willing to avoid use of sunbeds • Must be able to stand in the phototherapy cubicle for up to 5 minutes at a time
Exclusion Criteria	• Known co-morbid illnesses that might be exacerbated by phototherapy, including lupus erythematosus and xeroderma pigmentosum • A history of melanoma, multiple non melanoma skin cancers • Previous prolonged courses of UVB or photochemotherapy (PUVA), or use of sunbeds • Cardiovascular or respiratory disease that would prevent standing in the treatment cubicle • Bullous disease • Use of photosensitizing medications • Very fair skin that burns with very minimal sun exposure (as judged by the dermatologist involved) • Planning on becoming pregnant or breast feeding a child • Current immunosuppressive drug therapy (beta-interferon, glatiramer acetate, natalizumab, mitoxantrone, or other chemotherapy agent specifically for demyelinating disease) prior to CIS diagnosis. (*Note that requirement for immunomodulatory therapy in the course of MS disease management will not exclude patients during follow-up; treatment variables will be collected and analysed in both the intervention and control arms in the planned analysis). • Current pregnancy, breastfeeding or planning to become pregnant in the next 12 months. • A second clinical demyelinating event prior to randomisation

	• Concurrent diagnosis of other neurological, psychiatric or other disease, which, in the opinion of the investigator, could impair capacity to provide informed consent or interfere with study compliance. • Current enrolment in another interventional trial • Any contraindication to MRI scanning or intravenous Gadolinium including: o Cardiac Pacemaker o Cardiac Defibrillator o Metal fragments in the eye o Any other non-MRI compatible medical device/implant or medical condition o Previous allergic reaction to Gadolinium o Severe claustrophobia
Study Procedures:	As per Study Schedule in Appendix 1: • Treatment schedule of phototherapy for 8 weeks and biomarker monitoring for 12 months from date of starting phototherapy • Screening Questionnaire covering inclusion/exclusion criteria • Blood collection for safety and laboratory parameters • Saliva collection for Epstein Barr Virus (EBV) analysis • Neurological reviews (including EDSS) • Imaging: Best standard of care MRI • Vital signs and physical examination, anthropometric measures, blood pressure • Kurtzke Function System (KFS), Multiple Sclerosis Functional Composite Evaluation (MSFC) • Quality of Life Questionnaires (SF36v2) • Fatigue Severity Scale (FSS) • Lifestyle Questionnaires (Baseline, Serial and Exit) • Spectrophometric reading of skin UV reflectance, silicone cast of the back of the hand
Safety Parameters/analysis:	Adverse Events
Laboratory Parameters/Analysis:	As per Study Schedule in Appendix 1 Blood collection for • Transcriptome analysis of cells in whole blood • Analysis of cell populations in fresh non-coagulated blood • Serum for 25(OH)D levels

	• Isolation of peripheral blood mononuclear cells from non-coagulated freshly-taken blood for analysis of cell function and storage for further biomarker analysis • DNA extracted from peripheral blood cells • RNA extracted from peripheral blood cells Saliva collection for EBV analysis. At screening, blood and urine for pregnancy testing.
Total Blood Volume:	50 ml at screening/baseline visit prior to phototherapy and each study visit after the commencement of phototherapy (n=7) to a maximum of 360 ml over the entire study. For the additional group of 10 age and sex matched healthy individuals in Perth donating blood monthly for biomarker analysis, 11 ml blood will be collected monthly for biomarker analysis. The healthy control participants will be required to fill out the lifestyle questionnaires (see Appendix) at the beginning of the study, then again at the 6 and 12 month visits. For the additional group of up to 40 age and sex matched healthy individuals in Perth donating a single blood sample for cell isolation and characterisation, up to 45 ml blood will be taken.
Imaging Parameters/Analysis:	Best standard of care MRI as per Study Schedule in Appendix 1.
Sample Size Determination:	Our power calculations assume recruitment of 30 subjects to receive UVB phototherapy and 30 patients to not receive phototherapy (but allow study of seasonal effects). If new MRI lesions are expected in 90% of CIS patients over 1.5-2 years (CHAMPS, ETOMS, BENEFIT, PRECISE studies), then a treatment effect (ie reduction of 10%) should be discernible with a sample size of 30 patients. Power calculations for analysis of a biomarker (transcriptome) change based on standard deviation and means for each gene in winter indicated that between 11 and 27 patients need to be compared for a $P<0.05$.
Statistical Analyses:	Participants who have undergone 2 weeks (6 sessions) of narrow band UVB phototherapy will qualify for intention-to-treat analysis.

	Differences in continuous responses between groups will be tested for significance using one-way ANOVA/t-tests or Kruskal-Wallis/Mann-Whitney tests as appropriate to the characteristics of the data. Covariate adjustment will be accommodated via general linear models. Comparisons of binary or categorical variables will be based on Fisher exact or Chi-squared tests, or logistical regression models to incorporate covariate adjustment. Repeated measurements over time will be analysed by longitudinal mixed models.

5. Introduction

Executive Summary

Several trials internationally are testing vitamin D supplementation as a modulatory therapy for Multiple Sclerosis. In Australia, the PrevANZ study (including Professors Lucas and Carroll on the steering committee) is testing whether vitamin D supplementation can slow or prevent progression to clinically definite MS in patients presenting with Clinically Isolated Syndrome (CIS). ***In this application (the PhoCIS trial, Phototherapy for CIS patients) we aim to examine the effects of narrow band UVB therapy on immune and inflammatory markers of disease, MRI and a unique transcription signature for MS, in patients with CIS.*** They are not on complicating therapy as yet and are ideal candidates for our trial. The intervention will be very similar to that given to patients with another autoimmune disease, namely psoriasis, where narrow band UVB phototherapy has proven safe and efficacious [1,2]. We anticipate that the intervention should give the patients not only the benefits of UV-induced vitamin D production but also the benefits of the other biological pathways stimulated in skin by UVB exposure [3-9].

This study has been funded as an NHMRC Project Grant, ID 1067209, for 2014-2016. This is a randomised controlled trial to assess the efficacy of narrow band UVB phototherapy to prevent or reduce the progression of patients with CIS (participants with a first demyelinating event, FDE) from development of MS. After agreeing to participate, participants will be randomly assigned to receive, or not receive, narrow band UVB phototherapy for 8 weeks and their biomarkers studied for a total of 12 months.

We will enroll 60 participants with CIS in Perth and surrounding districts. There will be an extra group of 10 age and sex matched healthy individuals recruited in Perth to donate blood monthly for biomarker analysis in their blood. Measurement of biomarkers of these healthy controls from the same city as the CIS patients will allow precise comparison of the relative extent of change in biomarker expression by UVB phototherapy.

Hypothesis to be tested:

Narrow band UVB phototherapy will benefit patients with CIS; it will alter in a sustainable manner the immunological biomarkers in blood that are associated with subsequent transition to clinically-definite MS. Narrow band UVB phototherapy will increase the ratio of regulatory to effector T lymphocytes, reduce the functional capacity of circulating dendritic cells (DCs), and ensure that the transcriptional profile in their peripheral blood mononuclear cells is similar to one associated with healthy controls and not one characterised for MS patients.

6. Background

Multiple Sclerosis (MS) is a progressive incurable immune mediated disease of the central nervous system that affects ~21,000 Australians. Both genetic and environmental factors contribute to disease risk, largely through effects on immune pathways [10,11]. Increasing MS incidence, prevalence and mortality with increasing latitude, and association of MS risk in observational studies with past sun exposure [12-15], has led to a focus on vitamin D as a major risk factor. However, studies in humans and mice by us and others [reviewed in (3-5)] suggest that immunoregulation by UV radiation is by both vitamin D-dependent and vitamin D-independent pathways. Our epidemiological work [16,17] indicates that vitamin D and sun exposure are additive independent risk factors for MS development. A Swedish study supports these findings [18]. Further, direct effects of sun exposure on MRI measures of neurodegeneration in MS, independently of vitamin D, have been reported [19].

6.1 Genes and immunological basis of MS. Recent genome wide association studies (GWAS) have implicated genes involved in homeostatic regulation of T cell-dependent immune activation and effector functions versus regulatory (immunosuppressive) immune responses [1,20]. These data have reinforced the view that T cell activation is a fundamental feature of MS pathogenesis. There is now evidence that this immunological 'signature' can be detected and monitored in peripheral blood samples [10,11,21-23]. Importantly for this application, disease-relevant blood biomarkers have been identified and independently validated in large cohort studies, including novel transcriptome signatures that have been incorporated into this research project.

6.2 Systemic immunomodulation by UV irradiation of skin. The immunomodulatory effects of UV radiation were first observed in the 1970s [24], with the demonstration that after transplantation of a UV-induced skin tumour onto a UV-irradiated mouse the tumour grew; while the tumour was immunologically destroyed by a naïve mouse. This systemic immune-suppressing effect of UV exposure has been extensively demonstrated in humans [25, 8]. Human and murine studies suggest a prominent role in UV-induced immune suppression for DCs and induced Treg [5,26-29], and reduced memory T cell responses [30]. Several chromophores in skin for UVB photons have been implicated [31-34]. All may initiate pathways involved in signalling from skin

to immune cells in draining lymph nodes, and tissues beyond. Importantly for this study proposal, sub-erythemal amounts of UVR in humans can suppress both local and systemic immunity, measured functionally in terms of reduced cell-mediated immune responses. Recent studies by the investigators using chimeric mice engrafted with bone marrow from UV-irradiated mice, suggest that UV irradiation of skin alters the differentiation program of myeloid progenitors in bone marrow so terminally differentiated DCs and macrophages are less immunogenic and more regulatory [28,35]. Importantly, the effect of suberythemal UVR to skin on bone marrow myeloid cell progenitors is by a vitamin D-independent, prostaglandin E_2 (PGE_2)-dependent process. As recently published [35-38], our data suggest that epigenetic modification of an early myeloid progenitor in the bone marrow is involved. We propose that in patients with CIS, exposure to narrow band UVB will similarly alter the immunogenic properties of circulating DCs towards a regulatory profile.

6.3 Identification of MS biomarkers: transcriptional and immunophenotyping profiles. MS and its preclinical condition CIS are caused, at least in part, by pathogenic leukocytes that transit from lymphoid tissue to the brain via the peripheral circulation, with measurable changes in gene expression profiles in peripheral blood mononuclear cells associated with disease activity [39]. This paradigm is supported by studies on genetic susceptibility: most genes identified so far as associated with MS are primarily expressed in immune cells, especially involving the DC/ T cell axis [10]. In the context of this proposal, recent advances by Investigator Booth and colleagues have identified specific transcriptional signatures associated with MS, which are also modified in a seasonally-dependent manner [40].

6.4 The intervention, Narrow band UVB phototherapy. Narrow band UVB phototherapy is a routine treatment for patients with psoriasis. As for psoriasis patients, a Wayne Electronics, Series M.S.1, phototherapy cabinet with output (between wavelengths 311-312 nm) of 0.6 mW/cm^2 will be used. Phototherapy will be given three times/week for eight weeks (24 exposures in total). Phototherapy will be delivered according to the Dundee protocol which is based on the patient's skin type. The starting dose of 20 mJ/cm^2 is based on knowledge of the skin type and will be well below the likely erythema threshold. Patients start with 40% increments on their initial dose, which will be reduced to 20% increments after 6 exposures. At each visit the dose given and any adverse effects will be recorded.

All participants will wear a calibrated UVB dosimeter (Scienterra Limited, Otago New Zealand). This will measure their UVB (as in sunlight) exposure. The UVB dosimeter is the size of a watch and is worn around the wrist. The dosimeter will collect daily UVB exposure data. The dosimeters will not be worn in the photobooth.

6.5 Known and potential risks and benefits of UVB phototherapy, if any, to human participants. Psoriasis has been successfully treated using narrow band UVB (TL-01) lamps with a 311 nm peak emission [1,2]. No increase in oncogenic risk for narrow band UVB phototherapy has

been reported [2]. The face and eyes are protected during sessions of otherwise total body irradiation. Multiple mechanisms are involved in the control of psoriasis by narrow band UVB, including reduced inflammatory DCs infiltrating the skin [41], increased regulatory T cell number and function [8] and modulation of the IL-17/IL-23 axis [41].

A search of the literature has not revealed any studies of phototherapy for MS patients. There was one study of extracorporeal photochemotherapy used in 5 patients with refractory Relapsing Remitting MS with some success [42]. Phototherapy for MS patients is also supported by demonstration that UVR can suppress the severity of experimental autoimmune encephalomyelitis (a murine model of MS) when there were minimal changes in serum 25(OH)D levels [43].

This trial of narrow band UVB phototherapy will be documented in compliance with the protocol, GCP and the applicable regulatory requirements.

6.6 Description of the population to be studied. Patients at high risk of MS [patients with CIS defined by a First Demyelinating Event (FDE)].

7. Hypothesis, Aims and Objectives

Hypothesis: Narrow band UVB phototherapy will benefit patients with CIS; it will alter in a sustainable manner the immunological biomarkers in blood that are associated with subsequent transition to clinically-definite MS. UVB phototherapy will increase the ratio of regulatory to effector T lymphocytes, reduce the functional capacity of circulating dendritic cells (DCs), and ensure that the transcriptional profile in their peripheral blood mononuclear cells is similar to one associated with healthy controls and not one characterised for MS patients.

Aims and Objectives of the PhoCIS trial: In 30 patients with CIS given a course of narrow band UVB phototherapy (3 exposures/week for 8 weeks) and 30 CIS patients without phototherapy wearing UVB dosimeters, we will examine whether:

1. UVB phototherapy reduces the risk of a recurrent disease activity (clinical demyelinating event or MRI activity) in the 12 months following onset of a first demyelinating event.
2. UVB phototherapy affects the clinical and/or radiological responses associated with development of MS in high-risk CIS participants.
3. UVB phototherapy alters the phenotype, function and transcriptional profile of immune cells in blood drawn 1 week, and 1, 2, 3, 6 and 12 months after initiation of phototherapy in comparison with those in blood taken immediately before phototherapy.
4. UVB phototherapy reduces immunological biomarkers in blood that have been associated with active MS.
5. UVB phototherapy is a safe and acceptable treatment option for CIS patients.

8. Methodology

8.1 Participants in the PhoCIS Trial

We will recruit 60 patients who have had a first demyelinating event (i.e. diagnosed with CIS). Of these, 30 will receive phototherapy in addition to standard-of-care, while the remaining 30 will receive standard-of-care treatment. All participants will wear a UVB dosimeter.

As part of standard-of-care, all patients will receive sufficient vitamin D supplementation to achieve serum 25(OH) D levels of ≥100 nmol/L.

Patients with CIS will be approached by Professors Kermode or Carroll to join the trial.

There will be two additional groups donating blood. In the first group, 10 age and sex matched healthy individuals in Perth will donate 11 ml blood monthly for 12 months for selected biomarker analysis (transcriptome analysis of cells in whole blood and serum 25(OH)D levels). Measurement of these particular biomarkers of these healthy controls from the same city as the CIS patients will allow precise comparison of the relative extent of change in expression of those biomarkers by UVB phototherapy, and during the different seasons of the year. Additionally, this group of healthy controls will be required to fill out the lifestyle questionnaires (see Appendix) at the beginning of the study, then again at the 6 and 12 month visits. The healthy individuals donating blood monthly for 12 months will be recruited by advertisement from the staff at the Telethon Kids Institute in Subiaco, Western Australia. They will not be paid.

In the second group, up to 40 age and sex matched healthy individuals in Perth will donate up to 45 ml blood on a single occasion. The profile of their cells will be compared with those from blood taken from the study participants with CIS at baseline. They will not be paid.

8.2 Expected duration of participation in the trial – Time Frame

CIS patients will be invited to join the trial for 12 months. After agreeing to join the trial, participants will be randomized into two groups. Participants in one group will receive narrow band UVB phototherapy which will be administered 3 times per week for 8 weeks. They will also wear a UVB dosimeter. Participants in the other group will not receive phototherapy but will wear a UVB dosimeter for 8 weeks. Blood will be taken from all participants for biomarker analysis at baseline (before phototherapy commences), and 1 week, and 1, 2 (ie when phototherapy ceases), 3, 6 and 12 months after initiation of phototherapy (see Appendix 1).

One group of the healthy controls will also join the trial for 12 months (those donating blood monthly). In the other group donating blood once for blood cell characterization, they will be

invited for a single blood donation.

8.3 Accountability Procedures for UVB phototherapy

Prior to commencing narrow band UVB phototherapy, a risk factor profile including previous phototherapy or PUVA treatment, sun exposure history, occupation, personal and family history of skin cancer, and medication will be ascertained. Upon examination, sun damage and presence of skin disease including skin cancers will be documented. Phototherapy will be given three times/week for eight weeks (24 exposures in total). Phototherapy will be delivered according to the Dundee protocol which is based on the patient's skin type. The starting dose of 20 mJ/cm^2 is chosen based on knowledge of the skin type and will be well below the likely erythema threshold. All patients will start with 40% increments on their initial dose, which will be reduced to 20% increments after 6 exposures. At each visit the dose given and any adverse effects will be recorded.

If a participant develops a confirmed second demyelinating event (confirmed relapse), the participant should be managed by Professors Kermode and Carroll, or other neurologists associated with the study. Subjects will be withdrawn from UVB phototherapy if they experience a significant or serious adverse event, which, in the opinion of Dr Cole or Professors Kermode or Carroll or other neurologists associated with the study, is related to UVB phototherapy.

The schedule is to give narrow band UVB phototherapy 3 times a week for 8 weeks Participants will be asked to exit the trial if there is more than one week between phototherapy sessions and they cannot complete 24 phototherapy sessions within 12 weeks. We will ask participants to return to the clinic for an early withdrawal/Exit visit.

8.4 Randomisation

Selection of active treatment versus control subjects will be randomised 1:1 by an independent investigator at the patient Baseline visit, with matching on demographic variables (age and sex) to optimize balance between groups. It will be obvious to the patients into which group they have been randomised.

8.5 Trial design description

Participants will be randomised to treatment, or not, with narrow band UVB phototherapy. Narrow band UVB phototherapy will be given at St John of God Medical Centre, Subiaco, Perth.

8.6 Endpoints of the study

Primary Endpoints:

- Phototherapy-associated changes in transcriptome profiling in whole blood
- Phototherapy-associated changes in the phenotype of cells in freshly isolated peripheral blood
- Phototherapy-associated changes in T regulatory cells in the peripheral blood as measured by Foxp3 expression and Foxp3 demethylation analysis
- Phototherapy-associated changes to immunological function of cells in the peripheral blood
- Development of a new demyelinating event defined as either
- A confirmed clinical relapse or

- A new cerebral T2 lesion and/or newly Gadolinium-enhancing cerebral lesion at either the 6 month or 12 month MRI scan compared to the study baseline scan.

Secondary Endpoints:

- Baseline to 12 month EDSS change
- Baseline to 12 month change in SF36 Quality of life score
- Baseline to 12 month change in Fatigue score
- Baseline to 12 month cerebral MRI grey matter volume change
- Baseline to 12 month cerebral MRI white matter volume change
- Safety: Adverse Events (including SAE) reported for UVB phototherapy

8.7 Statistical justification of participant numbers

Our power calculations assumed recruitment of 30 subjects to receive UVB phototherapy and 30 patients to not receive phototherapy (but allow study of seasonal effects). If new MRI lesions are expected in 90% of CIS patients over 1.5-2 years (CHAMPS, ETOMS, BENEFIT, PRECISE studies), then a treatment effect (ie reduction of 10%) should be discernible with a sample size of 30 patients. Power calculations for analysis of a biomarker (transcriptome) change based on standard deviation and means for each gene in winter indicated that between 11 and 27 patients need to be compared for a $P<0.05$.

8.8 Measures taken to minimise/avoid bias

Participants will be randomised at the screening visit by an independent investigator. It is not possible to blind the treatment group/non-treatment group, but investigators will be blind to the treatment status of participants in clinical and laboratory assessments.

8.9 Pilot study

There has been no pilot study.

8.10 Concepts and terminology

These have been clearly defined at the beginning of this protocol, page 6.

8.11 Principles of informed consent

All potential participants in this study must provide informed consent before any study related procedures are undertaken (including screening procedures to determine eligibility). The Patient Information Sheet will describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation. It will also include the contact details of the study team that can be contacted should the participant have any questions. The recruiting neurologists will conduct the informed consent discussion and will check that the participant comprehends the information provided and answer any questions about the study at this time also. If in agreement to proceed with the study, participants will sign the Participant Informed Consent Form. Participants will be provided with a copy of the Participant Informed Consent Form and the fact that the subject has been consented to the study will be documented in the subject's record.

If potential participants wish to discuss their joining the study with their family or friends, they may request that one of the project co-ordinators contact them within a week to further discuss their participation. If they give verbal consent, a 'Baseline' visit with a member of the study team will be arranged and written consent obtained. At this visit, it will be confirmed that they are eligible to participate in the study and any questions that they have would be answered.

9. Selection of participants

All patients presenting with CIS during 2014, 2015 and 2016 will be invited to join this trial.

The healthy individuals in Perth recruited to donate blood monthly for biomarker analysis will be of similar age and sex to the CIS patients participating in the trial. At the time of their recruitment by advertisement at the Telethon Kids Institute, these individuals will have no known autoimmune disease and have not had a cold, flu or other illness in the last 7 days. They will not be taking strong immunomodulatory drugs (the taking of agents such as vitamin D, NSAIDs or aspirin will be permitted). Measurement of selected biomarkers of these healthy controls from the same city as the CIS patients will allow precise comparison of the relative extent of change in biomarker expression by UVB phototherapy, and during the different seasons of the year.

For the additional group of up to 40 age and sex matched healthy individuals in Perth donating a single blood sample for cell isolation and characterisation, up to 45 ml blood will be taken. At the time of their recruitment by advertisement at the Telethon Kids Institute, these individuals will have no known autoimmune disease and have not had a cold, flu or other illness in the last 7 days. They will not be taking strong immunomodulatory drugs (the taking of agents such as vitamin D, NSAIDs or paracetamol will be permitted). The profile of the cells in the blood of the healthy individuals will be compared with that of the CIS participants at baseline.

9.1 Participant reimbursement

Participants (including healthy individuals) will not be reimbursed for their involvement in the trial. It is anticipated to reimburse reasonable travel costs and/or provide parking vouchers.

9.2 Participant insurance

If a participant becomes ill or is injured, they must immediately advise a member of the study team of their condition. In the first instance their study doctor will evaluate their condition and then discuss treatment with both the participant and their regular treating doctor. As this trial is not sponsored by a Company, any questions about compensation to the participants must initially be directed to the Co-ordinating Principal Investigator. It is the recommendation of the independent ethics committee responsible for the review of this trial that the participants seek independent legal advice. The University of Western Australia has provided indemnity cover for participants in this trial.

10. Study Assessments and Procedures

For the Schedule of Events, please refer to Appendix 1.

Professors Kermode and Carroll, or other neurologists involved in the study, will be responsible for screening potential participants, gathering participant information, obtaining informed consent (or confirming it has been obtained by a member of the study team), determining eligibility for randomisation, clinical evaluation, clinical management of the participants during the course of the study, and review of all diagnostic blood tests and MRI results.

For those randomised to receive narrow band UVB phototherapy (and prior to phototherapy), Dr Cole will obtain the patient's sun exposure history, occupation, personal and family history of skin cancer, and medications used. Upon examination, sun damage and presence of skin disease including skin cancers will be documented.

10.1 Screening/Enrolment procedure (Consent Form)

All potential participants in this study must provide informed consent before any study related procedures are undertaken. The nature of the study will be explained by the investigator and any questions that the participant has should be addressed. If in agreement to proceed with the study, participants will then need to sign the Participant Informed Consent Form. Participants will be provided with a copy of the Participant Informed Sheet.

At the screening visit, Professors Kermode or Carroll, or other neurologists involved in the study will:

- Provide detailed study information
- Review eligibility check list

- Obtain signed informed consent (if participant already willing)
- Complete procedures that are part of patient best standard of care, namely:

(i) Review history of first demyelinating event (KFS, EDSS, and Multiple Sclerosis Functional Composite (MSFC)
(ii) Review medical history,
(iii) Review medication history,
(iv) Arrange a gadolinium-enhanced cerebral MRI (standard of care)(digital copy of films to be retained for PhoCIS), and
(v) Prescribe vitamin D supplementation to obtain a serum 25(OH) vitamin D level of approx. 100 nmol/L

If the participant wishes to discuss participation in the study with their family or friends, they may request that one of the project co-ordinators contact them within a week to further discuss participation in the trial. Verbal consent can be given over the telephone. A 'Baseline' visit with a member of the study team will be arranged and written consent obtained. This visit will confirm that eligibility to participate in this study and any questions that you may have will be answered. This visit will take about 1.5 – 2 hours.

The following will be performed at the Baseline visit (if not already done):

(1) Blood collected for baseline measurement of biological molecules (biomarkers) and collection of blood cells for studies of their biological activity,
(2) Questionnaires completed about your symptoms and its effect on your health and quality of life, including the Quality of Life Questionnaire (SF36v2), Fatigue Severity Scale, Lifestyle Questionnaire (see Appendix),
(3) A serum and urine pregnancy test (female subjects only),
(4) Anthropometric measurements (weight, height, waist and hip circumference), blood pressure. Participants will be asked to remove clothing to allow waist and hip measurement and placement of a blood pressure cuff on their arm
(5) Eye/skin/hair colour assessment
(6) Assessment of skin reflectance and preparation of a silicone cast of the back of the hand as a measure of past sun exposure
(7) Saliva collection for EBV analysis.

10.2 Post-screening

Upon successful completion of the screening process (pregnancy test that was negative and all inclusion and exclusion criteria confirmed), eligible participants will be enrolled into the study. Eligible participants will then be randomised into one of two treatment groups, namely to receive phototherapy or not to receive phototherapy.

10.3 Treatment schedule

Narrow band UVB phototherapy will be given three times/week for eight weeks (24 exposures in total). Narrow band UVB phototherapy will be delivered according to the Dundee protocol which is based on the participant's skin type. The starting dose of 20 mJ/cm^2 is chosen based on knowledge of the skin type and will be well below the likely erythema threshold. All participants will start with 40% increments on their initial dose, which will be reduced to 20% increments after 6 exposures. At each visit the dose given and any adverse effects will be recorded by Dr Cole, or her experienced study nurses.

Dr Cole will assess the skin of the participants before and 6 months after initiation of phototherapy, and during the trial if the participants have any concerns.

Narrow band UVB phototherapy will be initiated as soon as possible for those who are not prescribed a short course (few days) of glucocorticoids for treatment of their first demyelinating event.

If participants randomised to receive narrow band UVB phototherapy have been given a short course of glucocorticoids to treat their symptoms, the participants will be asked to commence UVB phototherapy in one month after completion of glucocorticoids. This will allow a drug-washout period and normalization of their immunological biomarkers. After this 'washout period' and immediately prior to the start of phototherapy, they will be asked to donate 50 ml blood for pre-therapy measurement of biomarkers and collection of peripheral blood mononuclear cells for functional assays.

All participants will be required to wear a UVB dosimeter for 8 weeks. The UVB dosimeters will be used to collect daily UVB exposure data for these participants.

10.3.1 Sun exposure

Participants will be asked to avoid tanning salons and sun beds. Reference material on the current sun exposure guidelines, as advised by the Cancer Council Australia, will be provided on request (www.cancerwa.asn.au/prevention/sunsmart). Participants should not stay in the sun for sufficient time to cause reddening of the skin. This trial is being performed in winter to avoid sun exposure.

A silicone skin cast of the back of the hand will be prepared from all participants. This will allow us to test whether past sun exposure modifies the immune response to phototherapy. This provides a reliable and validated estimate of actinic damage secondary to cumulative sun exposure [17,44].

10.4 Follow-Up Visits

There will be seven study time-points (Appendix 1, Study Schedule), namely (1) before phototherapy (see above), (2) after the first week of phototherapy, (3) after 1 month of

phototherapy (mid-intervention), (4) after 2 months of phototherapy (end of intervention), (5) after 3 months, (one month after termination of phototherapy), (6) 6 months, (four months after phototherapy, and (7) 12 months, (10 months after phototherapy).

10.4.1 The 1 week visit

Members of the Study Team will confirm that no adverse event has taken place due to narrow band UVB exposure. Blood will be collected for measurement of biomarkers and isolation of peripheral blood mononuclear cells for functional assays. Any change in symptoms or medications will be recorded.

10.4.2 Study visits at 1 month, 2 months, 3 months, and 6 months since start of phototherapy (or randomisation into the non-phototherapy group)

Participants will be reviewed as per the study schedule (Appendix 1).

Participants will have an appointment with their neurologist after 3 and 6 months. After 1 and 2 months, participants will meet one of the study team unless any symptoms require neurologist review.

- Blood collection for measurement of biomarkers and isolation of peripheral blood mononuclear cells for functional assays (1, 2, 3 and 6 months)
- Gadolinium-enhanced cerebral MRI (after 3 months if neurologist feels necessary, after 6 months for all participants)
- Clinical evaluations with review of any adverse events, intercurrent medical events and updated concomitant medications (1, 2, 3 and 6 months)
- Serial Questionnaires (6 months, see Appendices).
- KFS, MSFC (1, 2, 3 and 6 months).
- Measures of weight, blood pressure (1, 2, 3 and 6 months). Participants will be asked to remove clothing to allow placement of a blood pressure cuff on their arm
- Saliva collection for EBV measurement

10.4.3 Final Visit 12 months since start of phototherapy (or randomisation into the non-phototherapy group)

Participants will be reviewed by both a neurologist and a member of the study team as per study schedule (Appendix 1, Study schedule).

- Blood collection for measurement of biomarkers and isolation of peripheral blood mononuclear cells for functional assays
- Gadolinium-enhanced cerebral MRI
- Clinical evaluations with review of relapse history, adverse events, intercurrent medical events and updated concomitant medications
- EDSS, KFS, MSFC.
- Fatigue Severity Scale, SF-36, Exit questionnaires (See Appendices).

- Anthropometric measurements (weight, height, waist and hip circumference), blood pressure. Participants will be asked to remove clothing to allow waist and hip measurement and placement of a blood pressure cuff on their arm
- Eye/skin/hair colour assessment
- Assessment of skin reflectance and preparation of a silicone cast of the back of the hand
- Saliva collection for EBV measurement

10.4.4 Unscheduled Visits (Relapse or Adverse Event Visit)

Participants will be encouraged to report any new symptoms to the study team within 48 hours of occurrence. If significant new or worsening neurological symptoms suspicious for a relapse are present, or if a potential adverse event has occurred, then an unscheduled visit should be arranged as soon as possible (ideally within 4 days of symptom onset).

The following assessments should be undertaken at the unscheduled visit:

- History of new symptoms

If suspicious of a relapse:

- KFS/EDSS
- Relapse treatment as indicated

If suspicious of an adverse event:

- Initiation of appropriate investigations and management.
- Documentation of potential adverse event to be sent to the Co-ordinating Principal Investigator for review by the Data Safety Monitoring Board (if Serious AE).
- If a serious adverse event was managed by another doctor/hospital, then the Co-ordinating Principal Investigator should make all reasonable attempts to obtain relevant documentation.

10.4.5 Early Termination Visit

If a participant exits the study for any reason (including inability to complete 24 phototherapy sessions in 12 weeks), an early termination visit will be organised as soon as possible.

This visit will comprise

- Blood collection for measurement of biomarkers and isolation of peripheral blood mononuclear cells for functional assays
- Gadolinium-enhanced cerebral MRI (exit scan)
- Clinical evaluations with review of relapse history, adverse events, intercurrent medical events and updated concomitant medications
- EDSS, KFS, MSFC
- Fatigue Severity Scale, SF-36, Exit questionnaires
- Anthropometric measurements (weight, height, waist and hip circumference), blood pressure

- Eye/skin/hair colour assessment

Assessment of skin reflectance and preparation of a silicone cast of the back of the hand.

10.5 Safety Assessments

Professors Kermode and Carroll, together with Dr Cole and designated study personnel will monitor each participant for adverse events during the study. All adverse events reported between consent and final follow-up will be recorded in the Case Report Form (CRF). Members of the project team will ask the participant non-leading questions in an effort to detect adverse events. Examples of this are:

"How are you feeling?"

Or

"Since you were last asked, have you felt unwell or different from usual?"

In addition, participants should be encouraged to spontaneously report any medical illness, or new symptoms.

10.6 Biomarker Studies

All participants will be asked to donate blood at each follow-up. The blood samples will be principally used for assay of measures of the function of blood immune cells, as well as markers in serum such as 25(OH)D. Gene expression patterns in the blood cells will also be studied. The kinetics of changes in any of these biomarkers due to phototherapy will be analysed. In the healthy controls, gene expression patterns (transcriptome analyses of cells in whole blood) and vitamin D levels in serum will be measured.

Permission will be sought from the patients diagnosed with CIS to use samples of blood to create a serum, whole blood, DNA, and RNA bank for subsequent scientific studies related to MS progression.

11. Advertising

There will be no advertisements for participants of this study, except for the healthy controls who will donate blood 11 ml blood monthly for 12 months, or a larger donation of blood on a single occasion. Posters have been prepared to recruit the healthy controls from the Telethon Kids Institute, Subiaco, Western Australia.

12. Research involving ionizing radiation

Not applicable as narrow band UVB radiation is not ionizing radiation.

13. Inclusion Criteria

For inclusion in this study, a participant must meet the following criteria:

- Aged between 18 and 65 years old inclusive.
- Recently diagnosed (<120 days) with a first isolated, well-defined, uni- or multi-focal first demyelinating event (FDE).
- Able to receive their first phototherapy within 120 days of FDE symptom onset.
- An MRI brain scan that is supportive of demyelinating disease (Paty A or Paty B criteria, i.e. the presence of at least four T2 lesions greater than 3 mm, or at least three T2 lesions greater than 3 mm, one of which must be periventricular, respectively).
- An EDSS between 0 - 6.5 (inclusive)
- Must be able to give informed consent and sign the informed consent form
- Must be able to comply with all study procedures, and attend 24 phototherapy sessions and centres for venepuncture on multiple occasions during and after phototherapy
- If female of child-bearing age, must be willing to use effective contraception
- Must be willing to avoid use of sunbeds
- Must be able to stand in the phototherapy cubicle for up to 5 minutes at a time

14. Exclusion Criteria

Any of the following conditions will exclude a participant from the study:

- Known co-morbid illnesses that might be exacerbated by phototherapy, including lupus erythematosus and xeroderma pigmentosum
- A history of melanoma, multiple non melanoma skin cancers
- Previous prolonged courses of UVB or photochemotherapy (PUVA), or use of sunbeds
- Cardiovascular or respiratory disease that would prevent standing in the treatment cubicle
- Bullous disease
- Use of photosensitizing medications
- Very fair skin that burns with very minimal sun exposure (as judged by the dermatologist involved)
- Current immunosuppressive drug therapy (beta-interferon, glatiramer acetate, natalizumab, mitoxantrone, or other chemotherapy agent specifically for demyelinating disease) prior to CIS diagnosis. (*Note that requirement for immunomodulatory therapy in the course of MS disease management will not exclude patients during follow-up; treatment variables will be collected and analysed in both the intervention and control arms in the planned analysis).
- Current pregnancy, breastfeeding or planning to become pregnant in the next 12 months.
- A second clinical demyelinating event prior to randomisation
- Concurrent diagnosis of other neurological, psychiatric or other disease, which, in the opinion of the investigator, could impair capacity to provide informed consent or interfere with study compliance.
- Current enrolment in another interventional trial

- Any contraindication to MRI scanning or intravenous Gadolinium including:
    - Cardiac Pacemaker
    - Cardiac Defibrillator
    - Metal fragments in the eye
    - Any other non-MRI compatible medical device/implant or medical condition
    - Previous allergic reaction to Gadolinium
    - Severe claustrophobia

15. Withdrawal Criteria

Participants will be screened for adverse events during phototherapy, and will cease therapy if they experience a significant or serious adverse event, which, in the opinion of the treating neurologists (Professors Kermode and Carroll) or the dermatologist (Dr Cole), is related to the treatment.

15.1 Removal/withdrawal of subjects

Participants will be free to withdraw from the study at any time. If they wish to exit the study, an exit visit will be requested to assess any changes in the parameters measured. A cerebral MRI scan will be performed as part of the early termination visit and will substitute for the next protocol-specified MRI scan. Participants will be asked to exit the trial if there is more than one week between phototherapy sessions and they cannot complete 24 phototherapy sessions within 12 weeks. They will be asked to return to the clinic for an early withdrawal/Exit visit.

If a participant develops a confirmed second demyelinating event (confirmed relapse), the participant should be managed by Professors Kermode and Carroll. Subjects will be withdrawn from UVB phototherapy if they experience a significant or serious adverse event, which, in the opinion of Dr Cole or Professors Kermode or Carroll, is related to UVB phototherapy.

15.2 Early termination of the study

The study may be terminated prematurely by the Co-ordinating Principal Investigator or their designee, after consultation with the Steering committee and the Data Safety Monitoring Board if:

- The number and/or severity of adverse events justify discontinuation of the study
- New data become available which raise concern about the safety of UVB phototherapy, so that continuation might cause unacceptable risks to subjects.

In addition, the Co-ordinating Principal Investigator reserves the right to discontinue the trial prior to inclusion of the intended number of subjects, but intends only to exercise this right for valid scientific or administrative reasons.

After such a decision, the Co-ordinating Principal Investigator must contact all participating subjects within two weeks, and written notification must be sent to the Ethics Committee.

16. Other Participants

Not relevant

17. Efficacy

There are many patients with psoriasis who gain large clinical benefits from narrow band UVB phototherapy. The dermatologists talk about phototherapy 'junkies'. With no documented side effects for patients with psoriasis, we propose on the epidemiological data and the murine studies, that UVB phototherapy will benefit patients with CIS.

Efficacy Assessments:

- Fatigue Severity Score (FSS)
- EDSS, KFS, and MSFC
- SF-36v2 Quality of Life Questionnaire
- Lifestyle Questionnaires

18. Adverse Events (AE) and Serious Adverse Events (SAE)

Members of the investigator team are responsible for the detection and documentation of events meeting the criteria and definition of an adverse event (AE) or a serious adverse event (SAE) as provided in this protocol.

18.1 Definition of an Adverse Event (AE)

Any untoward medical occurrence in a participant, temporally associated with delivery of narrow band UVB phototherapy, whether or not considered related to the UVB phototherapy.

Examples of an AE include:

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after administration of narrow band UVB phototherapy even though it may have been present prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.

18.2 Definition of a Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence that as a result of UVB phototherapy:

a) results in death

b) is life threatening[b]

c) requires inpatient hospitalisation or prolongation of an existing hospitalisation.[c]

d) results in disability/incapacity[d], or

e) is a congenital abnormality / birth defect.

[b] *Note: The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.*

[c] *Note: In general, hospitalisation signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or out-patient setting. Complications that occur during hospitalisation are AEs. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious. When in doubt as to whether 'hospitalisation' occurred or was necessary, the AE should be considered serious.*
Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

[d] *Note: The term disability means a substantial disruption of a person"s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions, but do not constitute a substantial disruption*

Hospital admission for the purpose of treating an MS relapse will not be considered as a SAE, as it is an expected occurrence in participants with CIS. Medical and scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition.

18.3 Clinical Laboratory and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings (e.g. clinical chemistry, haematology, urinalysis) or other abnormal assessments (e.g. ECG, vital signs) that are judged by the investigators as clinically significant will be recorded as AEs or SAEs if they meet the definition of an AE, as defined in Section 18.1 or SAE as defined in Section 18.2. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal laboratory findings or other abnormal assessments that are associated with a disease reported in the medical history, unless judged by the investigators as more severe than expected for the subject's condition, or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The investigators will exercise their medical and scientific judgement in deciding whether an

abnormal laboratory finding or other abnormal assessment is clinically significant.

18.4 Time Period, Frequency, and Method of Detecting AEs and SAEs

All adverse events will be recorded between the time of consent and follow-up visits. Each participant will be monitored regularly by the investigators and study personnel for adverse events occurring throughout the study.

18.5 Recording of AEs and SAEs

When an AE/SAE occurs, it is the responsibility of the investigators to review all documentation (e.g. hospital progress notes, laboratory, and diagnostic reports) relative to the event. The investigators will then record all relevant information regarding an AE/SAE into the Case Report Form for that participant.

For each adverse event, start and stop dates, action taken, outcome, intensity (see Section 18.8.1) and relationship to narrow band UVB phototherapy (causality) (see Section 18.8.2) must be documented. If an AE changes in frequency or intensity, a new entry of the event must be made in the Case Report Form for that participant.

The investigators will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In the absence of a diagnosis, the individual signs/symptoms should be documented. All details of any treatments initiated due to the adverse event should be recorded in the Case Report Form for that participant.

18.6 Prompt Reporting of SAEs to the Data Safety Monitoring Board

Once the investigators and the Co-ordinating Principal Investigator become aware that an SAE has occurred in a study participant, they will immediately notify the Data Safety Monitoring Board. The SAE form must be completed as thoroughly as possible with all available details of the event, signed by the investigator (or appropriately qualified designee), and faxed to the independent neurologist on the Data Safety Monitoring Board (Dr Jason Burton) within 24 hours of first becoming aware of the event.

If the investigators do not have all information regarding an SAE, they will not wait to receive additional information before notifying the Co-ordinating Principal Investigator of the event and completing the form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 18.8.2, “Assessment of Causality”. If data obtained after reporting indicates that the assessment of causality is incorrect, then the SAE form may be appropriately amended, signed and dated, and resubmitted to the Co-ordinating Principal Investigator.

After notifying the Data Safety Monitoring Board, the Co-ordinating Principal Investigator must inform the Ethics Committee of any SAEs.

The investigators, and others responsible for participant care, should institute any supplementary investigations of serious adverse events based on their clinical judgement of the likely causative factors. This may include seeking further opinion from a specialist in the field of the adverse event. Members of the study team responsible for participant care may also request extra tests. If a subject dies, any post-mortem findings, including histopathology will be provided to the Co-ordinating Principal Investigator and the Data Safety Monitoring Board. No medical help, diagnosis, or advice should be withheld from the subject due to an inability to contact the Co-ordinating Principal Investigator.

18.7 Expeditable Events

Expeditable events are those adverse events that are **CAUSALLY** related to narrow band UVB phototherapy, **AND** that are both **SERIOUS** (see Section 18.2) and **UNEXPECTED (**SUSAR, Suspected Unexpected Serious Adverse Reaction**)**(see Section 18.8.3). Such events are subject to expedited reporting to regulatory authorities and will be reported within the stipulated timelines by the Co-ordinating Principal Investigator.

18.8 Evaluating AEs and SAEs

18.8.1 Assessment of Intensity

The investigators will make an assessment of intensity for each AE and SAE reported during the study.

The assessment will be based on the investigator's clinical judgement. The intensity of each AE and SAE recorded in the Case Report Forms should be assigned to one of the following categories:

- **Mild:** An event that is easily tolerated by the subject, causing minimal and not interfering with everyday activities.
- **Moderate:** An event that is sufficiently discomforting to interfere with normal activities.
- **Severe:** An event which is incapacitating and prevents normal everyday activity.

An AE that is assessed as severe should not be confused with a SAE. Severity is a category utilised for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. An event is defined as "serious" when it meets one of the pre-defined outcomes as described in Section 18.2 "Definition of an SAE".

18.8.2 Assessment of Causality

The Co-ordinating Principal Investigator is obligated to assess the relationship between the intervention and the occurrence of each AE/SAE, in consultation with Professors Kermode and Carroll, and Dr Cole. Alternative causes, such as natural history of the underlying diseases,

concomitant therapy, other risk factors, and the temporal relationship of the event to the administration of narrow band UVB phototherapy will be considered and investigated.

The causal relationship to UVB phototherapy should be assessed using the following classifications:

Not Related In the Investigator's opinion, there is not a causal relationship between UVB phototherapy and the adverse event.

Unlikely The temporal association between the adverse event and UVB phototherapy is such that UVB phototherapy is not likely to have any reasonable association with the adverse event.

Possible The adverse event could have been caused by the study participants's clinical state or UVB phototherapy.

Probable The adverse event follows a reasonable temporal sequence from the time of UVB phototherapy, abates upon discontinuation of UVB phototherapy and cannot be reasonably explained by the known characteristics of the study participants's clinical state.

Definitely The adverse event follows a reasonable temporal sequence from the time of UVB phototherapy or reappears when UVB phototherapy is reintroduced.

There may be situations when an SAE has occurred and a member of the study team has minimal information to include in the initial report to the Co-ordinating Principal Investigator, and the Data Safety Monitoring Board. However, it is very important that the member of the study team always makes an assessment of causality for every event prior to transmission of the SAE form to the Co-ordinating Principal Investigator. Investigators may change their opinion of causality in light of follow-up information, amending the SAE form accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

18.8.3 Assessment of Expectedness

Expected An adverse reaction, the nature or severity of which is consistent with the Participant Information Sheet for narrow band UVB phototherapy.

Unexpected An adverse reaction, the nature or severity of which is not consistent with information in the Participant Information Sheet for narrow band UVB phototherapy.

18.9 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigators are required to proactively follow each subject and provide further information to the Co-ordinating Principal Investigator on the participant's condition. All AEs and SAEs documented at a previous visit/contact and are designated as ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilises, until the event is otherwise explained, or until the participant is lost to follow-up. Once resolved, the appropriate AE/SAE Case Report Form page(s) will be updated. Members of the study team will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.

New or updated information will be recorded on the originally completed SAE form, with all changes signed and dated by the investigator. The updated SAE form should be resent to the Co-ordinating Principal Investigator.

19. Data Analysis and Statistical Considerations

19.1 Intention to treat-definition

Participants who have undergone 2 weeks (6 sessions) of narrow band UVB phototherapy will qualify for intention-to-treat analysis.

19.2 Safety monitoring and analysis

The independent Data Safety Monitoring Board will review all serious adverse events individually and unblinded, all reported adverse events in summary format and all study withdrawals. The Data Safety Monitoring Board may recommend cessation of the study due to safety concerns at any time. It is envisaged that the Data Safety Monitoring Board will meet 6-monthly by teleconference (or as required), to be convened by the Co-ordinating Principal Investigator. The Data Safety Monitoring Board will consist of an independent neurologist (Dr Jason Burton), a dermatologist and an endocrinologist.

19.3 Sample size

Our power calculations assume recruitment of 30 subjects to receive UVB phototherapy and 30 patients to not receive phototherapy (but allow study of seasonal effects). If new MRI lesions are expected in 90% of CIS patients over 1.5-2 years (CHAMPS, ETOMS, BENEFIT, PRECISE studies), then a treatment effect (ie reduction of 10%) should be discernible with a sample size of 30 patients. Power calculations for analysis of a biomarker (transcriptome) change based on standard deviation and means for each gene in winter indicated that between 11 and 27 patients need to be compared for a $P<0.05$.

19.4 Analysis Plan

19.4.1 Time to Event Analysis

For all time-to-event analyses (time to recurrent demyelinating event, recurrent clinical relapse,

three- month confirmed disease progression, 12 month recurrent disease activity rates), we will determine the hazard ratio of their development at 12 months, adjusted for known important covariates, namely age, sex, multifocal/unifocal onset, T2 lesion number at baseline (<9, 9+), Gadolinium-enhanced lesion number at baseline (0,1,2+), and use of intravenous methylprednisolone to treat first demyelinating event. This analysis will utilise a proportional hazard regression model. Additionally, Kaplan-Maier plots will be constructed and difference between treatment assignations tested by log-rank test for trend. Analyses will also be adjusted for variables we are collecting in the study questionnaires (eg. estimated dietary calcium and vitamin D intake, recent sun exposure, remote sun exposure, skin type), and baseline 25(OH)D.

19.4.2 Temporal patterns between biomarker measures and relapse

Blood will be taken at baseline, 1 week, 1 month, 2 months, 3 months, 6 months and 12 months after initiation of UVB phototherapy. Other than immunophenotyping of cells in freshly collected blood, all other preparations of blood, serum and peripheral blood mononuclear cells will be frozen and analysed at the end of the study. Differences in continuous responses between groups will be tested for significance using one-way ANOVA/t-tests or Kruskal-Wallis/Mann-Whitney tests as appropriate to the characteristics of the data. Covariate adjustment will be accommodated via general linear models. Comparisons of binary or categorical variables will be based on Fisher exact or Chi-squared tests, or logistical regression models to incorporate covariate adjustment. Repeated measurements over time will be analysed by longitudinal mixed models.

20. Data Management

20.1 Case Report Form (CRF)

A Case Report Form will be used to collect data for each Study Subject. Each Case Report Form (folders established for each participant) will allow the collection of records of all clinical encounters and investigation results as the raw data/source data. Participant privacy will be respected at all times and all centrally held data will only identify participants by a unique identification number and participant initials. Completed Case Report Forms will be checked for completeness and accuracy by a monitor, against the sourced data.

In compliance with Notes for Guidance on Good Clinical Practice, Professors Kermode and Carroll will allow the Co-ordinating Principal Investigator, and the other Project Officers, access to participant data including raw data. This will include all study-relevant information including, but not limited to, case notes, laboratory investigation results, clinic letters, discharge summaries and autopsy reports.
Completed Case Report Forms will be retained by the Co-ordinating Principal Investigator.

20.2 Data Capture

The data capture will be electronically (sometimes scanned from written case notes). Data entry will be the responsibility of the Co-ordinating Principal Investigator and the Project Officer(s). Original Case Report Forms will be used when entering information into the computer

database. The database will be checked against the Case Report Forms for accuracy.

All information collected for the study will have identifying information removed and be kept private, confidential and secure. Data will be designated as complete when all visit-related data have been recorded electronically and the database is deemed to be error free and accuracy assured.

21. Monitoring and Quality Assurance

The study will be reviewed by a Data Safety Monitoring Board. The independent neurologist on this Board (Dr Jason Burton) will meet 6-monthly with the Co-ordinating Principal Investigator and the other and the other Project Officers, for the purpose of facilitating the work and fulfilling the objectives of the study. In order to ensure the accuracy of data, direct access to source documents by the representatives of both the Data Safety Monitoring Board and any regulatory authority is mandatory. Anonymity of the participant data will be maintained at all times.

21.1 Curriculum Vitae and Other Documentation

To comply with regulatory requirements in some countries, all Investigators signing the Protocol and all trial staff will provide a current Curriculum Vitae (CV) to be filed by Co-ordinating Principal Investigator. The CV should include name, title, occupation, education, research experience and present and former positions. All CVs must be signed and dated. A Staff Duties Delegation and Signature List of all personnel involved in the conduct of the study are also required.

21.2 EDSS certification for the examining neurologists/physicians

Examining physicians will provide a current Neurostatus EDSS competency certificate (within 2 years) or must conduct the EDSS certification prior to performing any EDSS examinations for the trial.

22. Investigator Responsibility

'Investigators' as used in this Protocol and on the Case Report Forms refer to the members of the Steering Committee, or an appropriately qualified member of the staff that Professors Kermode or Carroll, or the Co-ordinating Principal Investigator, designate to perform specified duties of the Protocol. The Co-ordinating Principal Investigator is ultimately responsible for the conduct of all aspects of the study. Each member of the investigator team will comply with the local regulations regarding clinical trials and the Investigator responsibilities outlined in the ICH GCP guidelines [45]. All study investigators will be responsible for ensuring that they and all study personal are familiar with and practice in accordance with these guidelines.

23. Publication of Study Outcomes

All data generated by this study will remain the property of the Steering Committee. All data

collected are confidential and must not be released to any third party without prior permission of the Steering Committee and where relevant the participant to which the data pertains (excepting release of information required under regulatory requirements e.g. HREC reporting).

It is intended that the results of this study will be published in a leading medical journal. All data will be de-identified and published in aggregate form only.

24. Administrative Procedures

24.1 Ethical Considerations

The amount of blood to be sampled in the study is not considered to be excessive in adult subjects. This study will be conducted in accordance with the requirements of the Declaration of Helsinki, the NHMRC National Statement on Ethical Conduct in Research Involving Humans (1999) and the Notes for Guidance on Good Clinical Practice as adopted by the Australian Therapeutic Goods Administration (2000) (CPMP/ICH/135/95) and the ICH GCP Guidelines [45].

24.2 Ethical Review Committee

The Protocol, participant information and consent form, and all participant recruitment documentation for this study will be submitted for approval to the Belberry Ltd Human Research Ethics Committee (HREC) and written approval obtained.

The Co-ordinating Principal Investigator will be responsible for reporting any SAEs to the Belberry Ltd Human Research Ethics Committee as soon as possible, and in accordance with the guidelines of the HREC.

Any amendments to the study protocol, participant information and consent form, and any recruitment documentation must also receive HREC approval before being implemented (See Protocol Amendments below).

24.3 Trial Registration

This study has been registered with the Australian New Zealand Clinical Trials Register hosted by the National Health and Medical Research Council (www.anzctr.org.au). It has been allocated the ACTRN: ACTRN12614000185662

Web address of the trial**:** http://www.ANZCTR.org.au/ACTRN12614000185662.aspx
Date registered: 19/02/2014 **Registered by**: Prue Hart

The trial will also be registered under the Clinical Trial Notification (CTN) scheme.

24.4 Emergency Contact with Investigators

All participants will be provided with contact details of whom to contact in the case of an emergency.

24.5 Notification of Primary Care Physician

With the consent of the participant, it is the responsibility of the recruiting neurologist to notify the primary care physician of the subject's participation in the study, provided that such a physician can be identified. A letter will be sent to the physician stating the nature of the study, treatments, expected benefits or adverse events and concomitant drugs to be avoided. A copy shall be retained by the neurologist and the Co-ordinating Principal Investigator.

24.6 Financial Aspects

This trial is funded by a project grant from the National Health and Medical Research Council of Australia (ID 1067209).

24.7 Protocol Amendments

No amendments to the Protocol may be implemented without prior approval from the Co-ordinating Principal Investigator and the appropriate Ethics Committee. If a Protocol amendment requires changes to the Informed Consent Form, the revised Informed Consent Form must be approved by the HREC. Protocol modifications that impact on participant safety or the validity of the study will be approved by the HREC.

Once the final Protocol has been issued and signed by the Co-ordinating Principal Investigator and the authorised signatories, it shall not be informally altered. Protocol amendments are alterations to a legal document and have the same legal status. Therefore, they must pass through appropriate steps before being implemented.

It is the responsibility of the Co-ordinating Principal Investigator to submit the amendment to the Ethics Committee for their approval. The original signed copy of amendments will be kept by the Co-ordinating Principal Investigator with the original Protocol. It should be noted that where an amendment to the Protocol substantially alters the study design or the potential risks to the participants, each participant's consent to continue participation should be obtained.

24.8 Protocol Compliance

The instructions and procedures specified in this Protocol require diligent attention to their execution. Any participant treated in a manner that deviates from the Protocol, or who is admitted into the study but is not qualified according to the Protocol may be ineligible for analysis and thereby compromise the study.

Only when an emergency occurs that requires a departure from the Protocol for an individual will there be such a departure. The nature and reasons for the Protocol violation shall be recorded in the Case Report Form for that participant.

24.9 Archives: Retention of Study Records

The Co-ordinating Principal Investigator will be responsible for ensuring all source documents,

Case Report Forms and essential documents will be kept for the appropriate retention period as stipulated by local regulations and ICH-GCP [45].

24.10 Archives: Retention of Study Specific Samples

The blood of participants collected for studies as outlined in the biomarker section of this protocol will be stored and used for the purposes of biomarker analyses as consented by the participant. The participant's samples will only identify participants by a unique identification number and participant initials. The master code list will be held by the Co-ordinating Principal Investigator in a secure and locked environment.

24.11 Steering Committee

The study protocol and conduct of the study has been reviewed and monitored by the steering committee comprising all the principal investigators listed in Section 1.

25. Other Ethics Committees to which this study has been submitted

Ethical approval for this trial has not been submitted to any other ethics committee. The University of Western Australia will recognize approval by Belberry Ltd Human Research Ethics Committee.

26. References

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Appendix 1: Study Schedule

Action	Initial Screen/ Baseline	After confirmation of participation: Randomised to UVB phototherapy or No phototherapy								
		0	1 wk	1 mth	2 mth	3 mth	6 mth	12 mth	Early withdrawal/ Exit	Unscheduled Visit
Informed consent	N									
Selection Criteria	N	N Only if >1 month since screening bloods (due to steroids)								
Urine and serum Pregnancy Test	N[1]									
Imaging by MRI	N					$\pm^{N}$	N	N	N	$\pm^{N}$
Neurological Review (incl EDSS)	N					N	N	N	N	N
Report adverse events			N	N	N	N	N	N	N	N
Medical Review	N					N	N	N	N	N
Discuss any symptom changes	-		ST	ST	ST	N	N	N	N	N
Concomitant medications	N		ST	ST	ST	N	N	N	N	N
Neurological Tests (incl KFS, MSFC)	ST			ST	ST	ST	ST	ST	ST	ST
Anthropometric measures, blood pressure	ST							ST	ST	
Weight, blood pressure				ST	ST	ST	ST			
Eye/skin/hair colour, Skin reflectance,	ST							ST	ST	

Silicon cast										
Questionnaires (Lifestyle, SF36QoL, FSS)	ST						ST	ST	ST	
Skin assessment by consultant dermatologist	√√						√√			
Saliva collection for EBV analysis	X		X	X	X	X	X	X	X	
Blood taken for assessment of the following:										
Blood Transcriptome	X	X	X	X	X	X	X	X	X	
Serum 25(OH)D	X	Only if >1 month since screening bloods (due to steroids)					X		X	
Immunophenotyping	X		X	X	X	X	X	X	X	
PBMC (FoxP3 assay)	X		X	X	X	X	X	X	X	
PBMC (DC assay)	X		X	X	X	X	X	X	X	

Narrow band UVB Phototherapy

[1] For child bearing potential females only

N = As assessed by the investigator Neurologist

ST = As assessed by member of the Study Team (dark shading)

X = Blood taken for assessment of biomarkers

Appendix 2 Relapse and Progression Definitions

Relapse Definition:

A clinical relapse is defined as any new or worsening neurological symptom which lasts for at least 24 hours and is associated with a deterioration of EDSS of at least 1 point and/or an increase in one of the following KFS scores of at least 1 point: pyramidal, sensory, visual, brainstem, cerebellar. Isolated increases of bladder and bowel or cognitive/mental KFS scores will not constitute a relapse confirmation. New or worsening symptoms will not be considered as a new relapse if their onset occurs within 30 days of the onset of a previous relapse, or if they occur in the presence of infection or fever, and are described by the treating physician as a pseudo-relapse.

Progression Definition:

Confirmed EDSS progression is defined as an increase in at least one point on the EDSS scale from the baseline value, confirmed on a second visit at least three months after the visit during which the initial increase was noted. Exceptions: If baseline EDSS is 0, the value for confirmed progression is 1.5. If the baseline EDSS value is 5.5, 6.0 or 6.5, the disease step required for confirmed progression is an EDSS increase of 0.5. The EDSS value that led to confirmed progression must not regress at any subsequent EDSS assessment during the course of the study. The confirmation visit must not occur at the time of a new relapse.

Lifestyle Questionnaire - Baseline

Participant Name _____ **Participant Number** _____ **Date Completed** _____

We want to know about your recent sun exposure (in the PAST MONTH)

1. On average, for each day of the week listed in the Table below , please write the number of minutes you spent in the sun for each of the 3 times of day listed in the left hand column.

To save you time, you will see from the questions just above the Table that if most weekdays are the same, just fill in one weekday and if most weekend days are the same, then just fill in one weekday.

1a. In general, are all weekdays the same for sun exposure? Yes ☐ No ☐
If yes, please complete one weekday only in the table below.

1b. In general, are weekend days the same for sun exposure? Yes ☐ No ☐
If yes, please complete one weekend day only in the table below.

When you write in the minutes you spend in the sun, in the adjacent column, circle the type of clothing you wear.
The choices for clothing are:
Long-sleeved top (LSTop) that covers the arms, e.g. long-sleeved shirt
Short-sleeved top (SSTop) that expose the forearms e.g. t-shirt
Long-Leg (LLeg) that covers the legs, e.g. long trousers, long skirt
Short-Leg (SLeg) that exposes up to the knees e.g. skirt, shorts

1c In general, are all weekdays much the same for clothing? Yes ☐ No ☐
If yes, please complete usual clothing for one weekday only in the table below.

1d. In general, are weekend days much the same for clothing? Yes ☐ No ☐
If yes, please complete usual clothing for one weekend day only in the table below.

	Monday		**Tuesday**		**Wednesday**		**Thursday**		**Friday**		**Saturday**		**Sunday**	
Time of day	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes
6am-10am	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg
10am-2pm	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg
2pm-6pm	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg

Site Use only: Participant ID_____ Date completed _____

Lifestyle Questionnaire - Baseline

2a Have you lived away from your usual home in the past month, e.g. on holiday or, away for work?

☐ Yes (If yes go to Q2b) ☐ No (go to Q3)

2b. Where did you go? _____(town, state, country)

2c. And how long were you there for?_____

2d. Was this to a waterside location?

☐ Yes ☐ No

2e. While away, was your sun exposure: more, less or the same as your usual sun exposure when living at home.

☐ More ☐ Less ☐ Same

3 Did you wear glasses to see properly as a child, teenager or young adult?

☐ Yes ☐ No (Go to Question 4a)

3a. If yes, at what age did you start wearing glasses? _____years

3b. Why did you start wearing glasses?

☐ Short-sightedness (*this means you can't see things far away without glasses*)

☐ Squint

☐ Long-sightedness (*this means that you can't see near things without glasses*)

☐ Other, please specify_____

We would like to record your sun exposure from when you were growing up. For each age range in the table below, please tick a box to record how many hours a day you would normally have spent in the sun during weekends and holidays.

4a. In summer, during weekends and holidays, how much time would you normally have spent in the sun in the following age periods? (please tick one box for each age period)

Summer					
Age	<1 hr a day*	1 to 2 hrs per day	2 to 3 hrs per day	3 to 4 hrs per day	≥ 4 hrs a day
6 – 10 yrs	☐1	☐2	☐3	☐4	☐5
11 – 15 yrs	☐1	☐2	☐3	☐4	☐5
16 – 20 yrs	☐1	☐2	☐3	☐4	☐5
The last 3 years	☐1	☐2	☐3	☐4	☐5

Site Use only: Participant ID_____ Date completed _____

Lifestyle Questionnaire - Baseline

*If you answered 'less than 1 hr a day', was it usually: *(please tick one box for each relevant age period)*

Age	None	Some, but less than ½ hr	½ to 1 hr
6 – 10 yrs	☐1	☐2	☐3
11 – 15 yrs	☐1	☐2	☐3
16 – 20 yrs	☐1	☐2	☐3
The last 3 years	☐1	☐2	☐3

4b. In winter, during weekends and holidays, how much time would you normally have spent in the sun in the following age periods? *(please tick one box for each age period)*

Winter					
Age	< 1 hr a day*	1 to 2 hrs per day	2 to 3 hrs per day	3 to 4 hrs per day	≥4 hrs a day
6 – 10 yrs	☐1	☐2	☐3	☐4	☐5
11 – 15 yrs	☐1	☐2	☐3	☐4	☐5
16 – 20 yrs	☐1	☐2	☐3	☐4	☐5
The last 3 years	☐1	☐2	☐3	☐4	☐5

*If you answered 'less than 1 hr a day', was it usually: *(please tick one box for each relevant age period)*

Age	None	Some, but less than ½ hr	½ to 1 hr
6 – 10 yrs	☐1	☐2	☐3
11 – 15 yrs	☐1	☐2	☐3
16 – 20 yrs	☐1	☐2	☐3
The last 3 years	☐1	☐2	☐3

5. In the LAST MONTH how often did you consume each of these foods/drinks?
(Put a cross in one box for each food. Each row MUST have a cross in it)

Food/Drink	One time or never	2-3 times in the month	1-2 a week	3-4 a week	5-6 a week	1 a day	2-3 a day	4 or more a day
a. Fresh salmon	☐	☐	☐	☐	☐	☐	☐	☐
b. Fresh tuna	☐	☐	☐	☐	☐	☐	☐	☐
c. Canned red salmon	☐	☐	☐	☐	☐	☐	☐	☐
d. Canned pink salmon	☐	☐	☐	☐	☐	☐	☐	☐
e. Canned tuna	☐	☐	☐	☐	☐	☐	☐	☐
f. Canned sardines	☐	☐	☐	☐	☐	☐	☐	☐
g. Canned mackerel	☐	☐	☐	☐	☐	☐	☐	☐
h. Margarine (exclude butter)	☐	☐	☐	☐	☐	☐	☐	☐
i. Dairy blend spread (exclude butter)	☐	☐	☐	☐	☐	☐	☐	☐

Site Use only: Participant ID_____ Date completed _____

Lifestyle Questionnaire - Baseline

6. On average, how many eggs do you usually eat per week?

I don't eat eggs	Less than 1 per week	1 - 2 a week	3 - 5 a week	6 or more a week
☐	☐	☐	☐	☐

7. On average, how often do you eat mushrooms?

One time or less in the month	2 – 3 times in the month	1 – 2 times a week	3 – 4 times a week	5 – 6 times a week	1 time a day	2 – 3 times a day	4 or more times a day
☐	☐	☐	☐	☐	☐	☐	☐

8. We are interested in your calcium intake. Please mark how often you eat these foods:

Food	One time or never	2-3 times in the month	1-2 a week	3-4 a week	5-6 a week	1 a day	2-3 a day	4 or more a day
8a. Cheese – Prepacked slice (20g)	☐	☐	☐	☐	☐	☐	☐	☐
Cheese – Hard/tasty 1 slice (20g)	☐	☐	☐	☐	☐	☐	☐	☐
Cheese – Cream 1 tablespoon	☐	☐	☐	☐	☐	☐	☐	☐
Cheese – Cottage 1 tablespoon	☐	☐	☐	☐	☐	☐	☐	☐
8b. Yoghurt – Natural, small carton (200g)	☐	☐	☐	☐	☐	☐	☐	☐
Yoghurt – Fruit, small carton (200g)	☐	☐	☐	☐	☐	☐	☐	☐
Yoghurt – Fruche, small carton (200g)	☐	☐	☐	☐	☐	☐	☐	☐
Le Rice, small carton (180g)	☐	☐	☐	☐	☐	☐	☐	☐
Creamed rice, 1 serve (150g)	☐	☐	☐	☐	☐	☐	☐	☐
Crème caramel, 1 serve (150g)	☐	☐	☐	☐	☐	☐	☐	☐
Custard, 1 serve (1/2 cup)	☐	☐	☐	☐	☐	☐	☐	☐
Rice pudding, 1 serve (1/2 cup)	☐	☐	☐	☐	☐	☐	☐	☐
Sago/semolina/tapioca (1/2 cup)	☐	☐	☐	☐	☐	☐	☐	☐
8c. Ice cream – Tub (2 scoups)	☐	☐	☐	☐	☐	☐	☐	☐
Ice cream – On stick/cone	☐	☐	☐	☐	☐	☐	☐	☐

Site Use only: Participant ID_____ Date completed _____

Lifestyle Questionnaire - Baseline

8d. How much milk would you usually add to cereal

None	About ½ a cup	About 1 cup	About 2 cups or more (please state how much)
☐	☐	☐	____

8e. How much milk in all forms would you drink in a day?

_____ml OR _____cups

The following questions are about your intake of milk that has been FORTIFIED BY VITAMINS (e.g. PhysiCAL or Anlene, See Appendix A). Do NOT include milk you use that does not have added vitamins.

9a. Did you use milk FORTIFIED BY VITAMINS in the LAST MONTH?

☐ Yes ☐ No (If No then skip to question 10)

If YES, what brand did you usually use? _____

9b. How often in the last month did you drink milk FORTIFIED BY VITAMINS as a BEVERAGE? (NOT in tea or coffee, NOT on cereal)

One time or less in the month Go to Q9d	2 – 3 times in the month	1 – 2 times a week	3 – 4 times a week	5 – 6 times a week	1 time a day	2 – 3 times a day	4 or more times a day
☐	☐	☐	☐	☐	☐	☐	☐

9c. Each time you drank milk FORTIFIED BY VITAMINS as a beverage, how much did you usually drink?

Less than 1 cup	1 to 1 ½ cups	More than 1 ½ cups
☐	☐	☐

9d. How often in the last month did you put milk FORTIFIED BY VITAMINS in TEA or COFFEE?

One time or less in the month Go to Q9f	2 – 3 times in the month	1 – 2 times a week	3 – 4 times a week	5 – 6 times a week	1 time a day	2 – 3 times a day	4 or more times a day
☐	☐	☐	☐	☐	☐	☐	☐

Site Use only: Participant ID_____ Date completed _____

Lifestyle Questionnaire - Baseline

9e. Each time you put milk FORTIFIED BY VITAMINS in tea or coffee, approximately how much did you usually add?

Less than 1 tablespoon	1 to 3 tablespoons	More than 3 tablespoons
☐	☐	☐

9f. How often in the last month did you put milk FORTIFIED BY VITAMINS on CEREAL?

One time or less in the month <u>Go to Q10</u>	2 – 3 times in the month	1 – 2 times a week	3 – 4 times a week	5 – 6 times a week	1 time a day	2 – 3 times a day	4 or more times a day
☐	☐	☐	☐	☐	☐	☐	☐

9g. When you used milk FORTIFIED BY VITAMINS on your cereal how much did you usually add?

Less than 1 cup	1 to 1 ½ cups	More than 1 ½ cups
☐	☐	☐

10. Physical activity

10a. In the LAST WEEK, how many times did you walk continuously for at least 10 minutes? (for recreation, exercise or to get to or from places)

Times in the last week _____

10b. What do you estimate was the total time you spent walking in this way in the LAST WEEK?

Hours _____ minutes _____

10c. In the LAST WEEK, how many times did you do any vigorous gardening or heavy work around the yard that made you breathe harder or puff and pant?

Times in the last week _____

10d. What do you estimate was the total time you spent doing vigorous gardening or heavy work around the yard in the LAST WEEK?

Hours _____ minutes _____

The next questions EXCLUDE household chores, gardening, or yard work.

10e. In the LAST WEEK how many times did you do any vigorous physical activity that made you breathe harder or puff and pant? (e.g. jogging, cycling, aerobics, competitive tennis)

Times in the last week _____

Site Use only: Participant ID_____ Date completed _____

10f. What do you estimate was the total time you spent doing this vigorous physical activity in the LAST WEEK?
Hours _____ minutes _____

10g. In the LAST WEEK, how many times did you do any other more moderate physical activities that you have not already mentioned? (e.g. gentle swimming, social tennis, golf)
Times in the last week _____

11. Smoking, Alcohol and Marijuana

11a. Have you ever been a regular tobacco smoker?
(That is, you smoked tobacco daily or almost daily for at least 6 months)
☐ Yes ☐ No (go to Q12a)

11b. How old were you when you first started smoking regularly?
_____ Years

11c. Are you a regular smoker now?
☐ Yes (Go to 11d) ☐ No (Go to 11e)

11d. If yes: how much do you smoke on average each day, currently?
_____ cigarettes a day _____ pipes/cigars a day (Go to question 12a)

11e. If no: How old were you when you stopped smoking permanently?
_____ Years

11f. About how much did you smoke on average each day when you smoked?
_____ cigarettes a day _____ pipes/cigars a day

12a. Do you smoke any other substances regularly (at least once per week)?
☐ Yes ☐ No

12b. If yes, please specify
_____

Site Use only: Participant ID_____ Date completed _____

Lifestyle Questionnaire - Baseline

13a. About how many alcoholic drinks do you usually have each week?
(one drink = a glass of wine, a glass of beer or nip of spirits; put "0" if you do not drink, or have less than one drink each week)
_____ number of alcoholic drinks each week

13b. On how many days each week do you usually drink alcohol?
_____ days each week

14. Please refer to the list of health conditions given to you (see Appendix B).

14a Have you personally definitely had any of these conditions? If so, please write them down.
(NB: Definitely means a doctor has diagnosed the condition).

_____

_____

_____

_____

14b Please again refer to the list of health conditions (see Appendix B)..
If any living or deceased blood relative definitely had any of these conditions, please write the conditions down.
(NB: Definitely means a doctor has diagnosed the condition).

_____

_____

_____

_____

14c Do you have a blood relative with multiple sclerosis?

☐ Yes ☐ No (thank you for completing this questionnaire)

If yes, please specify relative and which side of the family they come from:

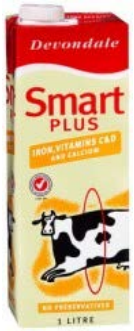
e.g. uncle on mother's side; cousin on father's side.

_____

Thank you for your time ☺

Site Use only: Participant ID_____ Date completed _____

Lifestyle Questionnaire Appendix A: Vitamin D Fortified Dairy Products Guide

Vitamin D Fortified Dairy Products Guide-Australian Examples				
				
Anlene (5ug/250ml)	Anlene no fat (5ug/ml)	Physical Low Fat with Vitamin D (1.25ug/250g)	Yoplait Cal-tivate (1.1ug/175ml)	Devondale Smart plus Iron and Vitamins A & D (1.3ug/250ml)
				
Pura Boost (1.25ug/250ml)	Jalna Vitalise with Vitamins (2.5ug/250g)	Physical No Fat with Vitamin D (1.25ug/250g)	VitaSoy CalciPlus (5ug/250ml)	Kraft Singles (0.8ug/slice)

e.g. AUST Products guide 22 Aug 2012

Lifestyle Questionnaire Appendix A: Vitamin D Fortified Dairy Products Guide

Vitamin D Fortified Dairy Products Guide NZ Examples				
				
Vita Soy Calci plus (5ug/250ml)	Meadow Fresh Calci-trim longlife milk (1.0ug/200ml)	Anchor Calci+ milk (1.25ug/250ml)	Fresh & Fruity yogurts (1.0ug/150g)	Anchor Fast start liquid breakfast (2.5ug/250ml)
				
Kraft Singles (0.8ug/slice)	Flora spreads (10ug/100g)	Meadow Fresh Calci strong original and flavoured milk (1.25ug/250ml)	Meadow Fresh Calci-trim milk (1.25ug/250ml)	Meadowlea spreads (10ug/100g)

e.g. NZ Products guide 07 Nov 2012

Lifestyle Questionnaire Appendix B: List of Health Conditions

Please read this list of health conditions to answer question 14. Some of these are rare and you may not have heard of them but please read each one carefully.

Hashimoto's thyroid disease
Graves' thyroid disease
Overactive thyroid or hyperthyroidism
Underactive thyroid or hypothyroidism
Thyroid lumps or thyroid nodules
Thyroid cancer
Other thyroid disease
Coeliac disease
Type 1 (ONE) juvenile diabetes
Vitamin B12 deficiency
Pernicious anaemia (not regular anaemia but the special anaemia called pernicous anaemia)
Psoriasis
Vitiligo
Lupus
Rheumatoid arthritis (not any arthritis but definite rheumatoid arthritis)
Ulcerative colitis
Crohn's disease
Haemochromatosis
Alopecia
Thrombocytopaenia or low platelets
Addison's disease
Sjogren's syndrome
Scleroderma or a condition called CREST
Polymyositis
Dermatomyositis
Myaesthenia gravis
Polymyalgia
Polymyalgia rheumatica
Mixed connective tissue disease
Primary biliary cirrhosis (not regular cirrhosis but the special primary biliary cirrhosis)
Glomerulonephritis
Vasculitis
Asperger's syndrome
Anti-Phospholipid syndrome
Narcolepsy

PhoCIS Lifestyle Questionnaire – Serial

Participant Name _____ **Participant Number** _____ **Date Completed** _____

We want to know about your recent sun exposure (in the PAST MONTH)

1. On average, for each day of the week listed in the Table below , please write the number of minutes you spent in the sun for each of the 3 times of day listed in the left hand column.

To save you time, you will see from the questions just above the Table that if most weekdays are the same, just fill in one weekday and if most weekend days are the same, then just fill in one weekday.

1a. In general, are all weekdays the same for sun exposure? Yes ☐ No ☐
If yes, please complete one weekday only in the table below.

1b. In general, are weekend days the same for sun exposure? Yes ☐ No ☐
If yes, please complete one weekend day only in the table below.

When you write in the minutes you spend in the sun, in the adjacent column, circle the type of clothing you wear.
The choices for clothing are:
Long-sleeved top (LSTop) that covers the arms, e.g. long-sleeved shirt
Short-sleeved top (SSTop) that expose the forearms e.g. t-shirt
Long-Leg (LLeg) that covers the legs, e.g. long trousers, long skirt
Short-Leg (SLeg) that exposes up to the knees e.g. skirt, shorts

1c In general, are all weekdays much the same for clothing? Yes ☐ No ☐
If yes, please complete usual clothing for one weekday only in the table below.

1d. In general, are weekend days much the same for clothing? Yes ☐ No ☐
If yes, please complete usual clothing for one weekend day only in the table below.

	Monday		**Tuesday**		**Wednesday**		**Thursday**		**Friday**		**Saturday**		**Sunday**	
Time of day	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes
6am-10am	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg
10am-2pm	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg
2pm-6pm	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg

PhoCIS Lifestyle Questionnaire – Serial

2a Have you lived away from your usual home in the past month, e.g. on holiday or, away for work?

☐ Yes (If yes go to Q2b) ☐ No (thank you for completing the questionnaire)

If Yes:

2b. Where did you go? _____(town, state, country)

2c. And how long were you there for?_____

2d. Was this to a waterside location?

☐ Yes ☐ No

2e. While away, was your sun exposure: more, less or the same as your usual sun exposure when living at home.

☐ More ☐ Less ☐ Same

Thank you for your time ☺

PhoCIS Lifestyle Questionnaire – Exit/Final Study Visit

Participant Name _____ **Participant Number** _____ **Date Completed** _____

We want to know about your recent sun exposure (in the PAST MONTH)

1. On average, for each day of the week listed in the Table below , please write the number of minutes you spent in the sun for each of the 3 times of day listed in the left hand column.

To save you time, you will see from the questions just above the Table that if most weekdays are the same, just fill in one weekday and if most weekend days are the same, then just fill in one weekend day.

1a. In general, are all weekdays the same for sun exposure? Yes ☐ No ☐
If yes, please complete one weekday only in the table below.

1b. In general, are weekend days the same for sun exposure? Yes ☐ No ☐
If yes, please complete one weekend day only in the table below.

When you write in the minutes you spend in the sun, in the adjacent column, circle the type of clothing you wear.
The choices for clothing are:
Long-sleeved top (LSTop) that covers the arms, e.g. long-sleeved shirt
Short-sleeved top (SSTop) that expose the forearms e.g. t-shirt
Long-Leg (LLeg) that covers the legs, e.g. long trousers, long skirt
Short-Leg (SLeg) that exposes up to the knees e.g. skirt, shorts

1c In general, are all weekdays much the same for clothing? Yes ☐ No ☐
If yes, please complete usual clothing for one weekday only in the table below.

1d. In general, are weekend days much the same for clothing? Yes ☐ No ☐
If yes, please complete usual clothing for one weekend day only in the table below.

	Monday		**Tuesday**		**Wednesday**		**Thursday**		**Friday**		**Saturday**		**Sunday**	
Time of day	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes	Time in the sun (mins)	Clothes
6am-10am	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg
10am-2pm	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg
2pm-6pm	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg	mins	LSTop SSTop LLeg SLeg

PhoCIS Lifestyle Questionnaire – Exit/Final Study Visit

2a Have you lived away from your usual home in the past month, e.g. on holiday or, away for work?

☐ Yes (If yes go to Q2b) ☐ No (go to Q3)

2b. Where did you go? _____(town, state, country)

2c. And how long were you there for?_____

2d. Was this to a waterside location?

☐ Yes ☐ No

2e. While away, was your sun exposure: more, less or the same as your usual sun exposure when living at home.

☐ More ☐ Less ☐ Same

3. In the LAST MONTH how often did you consume each of these foods/drinks?

(Put a cross in one box for each food. Each row MUST have a cross in it)

Food/Drink	One time or never	2-3 times in the month	1-2 a week	3-4 a week	5-6 a week	1 a day	2-3 a day	4 or more a day
a. Fresh salmon	☐	☐	☐	☐	☐	☐	☐	☐
b. Fresh tuna	☐	☐	☐	☐	☐	☐	☐	☐
c. Canned red salmon	☐	☐	☐	☐	☐	☐	☐	☐
d. Canned pink salmon	☐	☐	☐	☐	☐	☐	☐	☐
e. Canned tuna	☐	☐	☐	☐	☐	☐	☐	☐
f. Canned sardines	☐	☐	☐	☐	☐	☐	☐	☐
g. Canned mackerel	☐	☐	☐	☐	☐	☐	☐	☐
h. Margarine (exclude butter)	☐	☐	☐	☐	☐	☐	☐	☐
i. Dairy blend spread (exclude butter)	☐	☐	☐	☐	☐	☐	☐	☐

4. On average, how many eggs do you usually eat per week?

I don't eat eggs	Less than 1 per week	1 - 2 a week	3 - 5 a week	6 or more a week
☐	☐	☐	☐	☐

Site Use only: Participant ID_____ Date completed _____

PhoCIS Lifestyle Questionnaire – Exit/Final Study Visit

5. On average, how often do you eat mushrooms?

One time or less in the month	2 – 3 times in the month	1 – 2 times a week	3 – 4 times a week	5 – 6 times a week	1 time a day	2 – 3 times a day	4 or more times a day
☐	☐	☐	☐	☐	☐	☐	☐

6. We are interested in your calcium intake. Please mark how often you eat these foods:

Food	One time or never	2-3 times in the month	1-2 a week	3-4 a week	5-6 a week	1 a day	2-3 a day	4 or more a day
6a. Cheese – Prepacked slice (20g)	☐	☐	☐	☐	☐	☐	☐	☐
Cheese – Hard/tasty 1 slice (20g)	☐	☐	☐	☐	☐	☐	☐	☐
Cheese – Cream 1 tablespoon	☐	☐	☐	☐	☐	☐	☐	☐
Cheese – Cottage 1 tablespoon	☐	☐	☐	☐	☐	☐	☐	☐
6b. Yoghurt – Natural, small carton (200g)	☐	☐	☐	☐	☐	☐	☐	☐
Yoghurt – Fruit, small carton (200g)	☐	☐	☐	☐	☐	☐	☐	☐
Yoghurt – Fruche, small carton (200g)	☐	☐	☐	☐	☐	☐	☐	☐
Le Rice, small carton (180g)	☐	☐	☐	☐	☐	☐	☐	☐
Creamed rice, 1 serve (150g)	☐	☐	☐	☐	☐	☐	☐	☐
Crème caramel, 1 serve (150g)	☐	☐	☐	☐	☐	☐	☐	☐
Custard, 1 serve (1/2 cup)	☐	☐	☐	☐	☐	☐	☐	☐
Rice pudding, 1 serve (1/2 cup)	☐	☐	☐	☐	☐	☐	☐	☐
Sago/semolina/tapioca (1/2 cup)	☐	☐	☐	☐	☐	☐	☐	☐
6c. Ice cream – Tub (2 scoups)	☐	☐	☐	☐	☐	☐	☐	☐
Ice cream – On stick/cone	☐	☐	☐	☐	☐	☐	☐	☐

6d. How much milk would you usually add to cereal

None	About ½ a cup	About 1 cup	About 2 cups or more (please state how much)
☐	☐	☐	____

Site Use only: Participant ID_____ Date completed _____

PhoCIS Lifestyle Questionnaire – Exit/Final Study Visit

6e. How much milk in all forms would you drink in a day?

_____ml OR _____cups

The following questions are about your intake of milk that has been FORTIFIED BY VITAMINS (e.g. PhysiCAL or Anlene, See Appendix A). Do NOT include milk you use that does not have added vitamins.

7a. Did you use milk FORTIFIED BY VITAMINS in the LAST MONTH?

☐ Yes ☐ No (If No then skip to question 7)

If YES, what brand did you usually use? _____

7b. How often in the last month did you drink milk FORTIFIED BY VITAMINS as a BEVERAGE? (NOT in tea or coffee, NOT on cereal)

One time or less in the month Go to Q7d	2 – 3 times in the month	1 – 2 times a week	3 – 4 times a week	5 – 6 times a week	1 time a day	2 – 3 times a day	4 or more times a day
☐	☐	☐	☐	☐	☐	☐	☐

7c. Each time you drank milk FORTIFIED BY VITAMINS as a beverage, how much did you usually drink?

Less than 1 cup	1 to 1 ½ cups	More than 1 ½ cups
☐	☐	☐

7d. How often in the last month did you put milk FORTIFIED BY VITAMINS in TEA or COFFEE?

One time or less in the month Go to Q7f	2 – 3 times in the month	1 – 2 times a week	3 – 4 times a week	5 – 6 times a week	1 time a day	2 – 3 times a day	4 or more times a day
☐	☐	☐	☐	☐	☐	☐	☐

Site Use only: Participant ID_____ Date completed _____

PhoCIS Lifestyle Questionnaire – Exit/Final Study Visit

7e. Each time you put milk FORTIFIED BY VITAMINS in tea or coffee, approximately how much did you usually add?

Less than 1 tablespoon	1 to 3 tablespoons	More than 3 tablespoons
☐	☐	☐

7f. How often in the last month did you put milk FORTIFIED BY VITAMINS on CEREAL?

One time or less in the month <u>Go to Q8</u>	2 – 3 times in the month	1 – 2 times a week	3 – 4 times a week	5 – 6 times a week	1 time a day	2 – 3 times a day	4 or more times a day
☐	☐	☐	☐	☐	☐	☐	☐

7g. When you used milk FORTIFIED BY VITAMINS on your cereal how much did you usually add?

Less than 1 cup	1 to 1 ½ cups	More than 1 ½ cups
☐	☐	☐

Site Use only: Participant ID_____ Date completed _____

PhoCIS Lifestyle Questionnaire – Exit/Final Study Visit

8. Physical activity

8a. In the LAST WEEK, how many times did you **walk continuously** for at least 10 minutes? (for recreation, exercise or to get to or from places)

Times in the last week _____

8b. What do you estimate was the total time you spent **walking** in this way in the LAST WEEK?

Hours _____ minutes _____

8c. In the LAST WEEK, how many times did you do any **vigorous gardening or heavy work around the yard** that made you breathe harder or puff and pant?

Times in the last week _____

8d. What do you estimate was the total time you spent doing **vigorous gardening or heavy work around the yard** in the LAST WEEK?

Hours _____ minutes _____

The next questions EXCLUDE household chores, gardening, or yard work.

8e. In the LAST WEEK how many times did you do any **vigorous physical activity** that made you breathe harder or puff and pant? **(e.g. jogging, cycling, aerobics, competitive tennis)**

Times in the last week _____

8f. What do you estimate was the total time you spent doing this **vigorous physical activity** in the LAST WEEK?

Hours _____ minutes _____

8g. In the LAST WEEK, how many times did you do any other more **moderate physical activities** that you have not already mentioned? (e.g. gentle swimming, social tennis, golf)

Times in the last week _____

Site Use only: Participant ID_____ Date completed _____

PhoCIS Lifestyle Questionnaire – Exit/Final Study Visit

9. Smoking, Alcohol and Marijuana

9a. Are you a regular smoker now?

Yes ☐ ☐ No (go to Q10a)

9b. If yes, how much do you smoke on average each day currently?

_____ cigarettes a day _____ pipes/cigars a day

9c. Do you smoke any other substances regularly (at least once per week)?

☐ Yes ☐ No

9d. If yes, please specify _____

10a. About how many alcoholic drinks do you usually have each week?

(one drink = a glass of wine, a glass of beer or nip of spirits; put "0" if you do not drink, or have less than one drink each week)

_____ number of alcoholic drinks each week

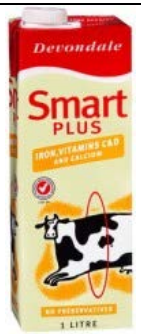
10b. On how many days each week do you usually drink alcohol?

_____ days each week

Thank you for your time ☺

Site Use only: Participant ID_____ Date completed _____

Lifestyle Questionnaire Appendix A: Vitamin D Fortified Dairy Products Guide

Vitamin D Fortified Dairy Products Guide-Australian Examples				
				
Anlene (5ug/250ml)	Anlene no fat (5ug/ml)	Physical Low Fat with Vitamin D (1.25ug/250g)	Yoplait Cal-tivate (1.1ug/175ml)	Devondale Smart plus Iron and Vitamins A & D (1.3ug/250ml)
				
Pura Boost (1.25ug/250ml)	Jalna Vitalise with Vitamins (2.5ug/250g)	Physical No Fat with Vitamin D (1.25ug/250g)	VitaSoy CalciPlus (5ug/250ml)	Kraft Singles (0.8ug/slice)

e.g. AUST Products guide 22 Aug 2012

Lifestyle Questionnaire Appendix A: Vitamin D Fortified Dairy Products Guide

Vitamin D Fortified Dairy Products Guide NZ Examples				
				
Vita Soy Calci plus (5ug/250ml)	Meadow Fresh Calci-trim longlife milk (1.0ug/200ml)	Anchor Calci+ milk (1.25ug/250ml)	Fresh & Fruity yogurts (1.0ug/150g)	Anchor Fast start liquid breakfast (2.5ug/250ml)
				
Kraft Singles (0.8ug/slice)	Flora spreads (10ug/100g)	Meadow Fresh Calci strong original and flavoured milk (1.25ug/250ml)	Meadow Fresh Calci-trim milk (1.25ug/250ml)	Meadowlea spreads (10ug/100g)

e.g. NZ Products guide 07 Nov 2012

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Your Health and Well-Being

This questionnaire asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. ***Thank you for completing this survey!***

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. <u>Compared to one week ago</u>, how would you rate your health in general <u>now</u>?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse now than one week ago	Much worse now than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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3. The following questions are about activities you might do during a typical day. Does <u>your health now limit you</u> in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a	<u>Vigorous activities</u>, such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b	<u>Moderate activities</u>, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐ 1	☐ 2	☐ 3
c	Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d	Climbing <u>several</u> flights of stairs	☐ 1	☐ 2	☐ 3
e	Climbing <u>one</u> flight of stairs	☐ 1	☐ 2	☐ 3
f	Bending, kneeling, or stooping	☐ 1	☐ 2	☐ 3
g	Walking <u>more than a kilometre</u>	☐ 1	☐ 2	☐ 3
h	Walking <u>several hundred metres</u>	☐ 1	☐ 2	☐ 3
i	Walking <u>one hundred metres</u>	☐ 1	☐ 2	☐ 3
j	Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

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4. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Cut down on the <u>amount of time</u> you spent on work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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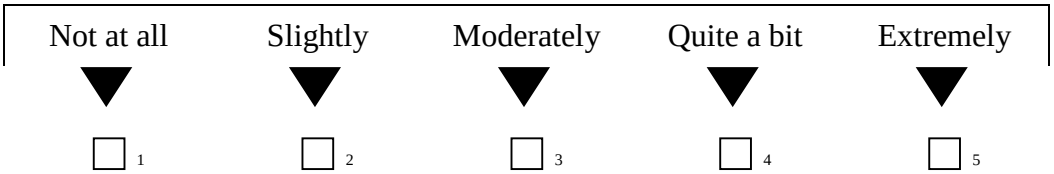
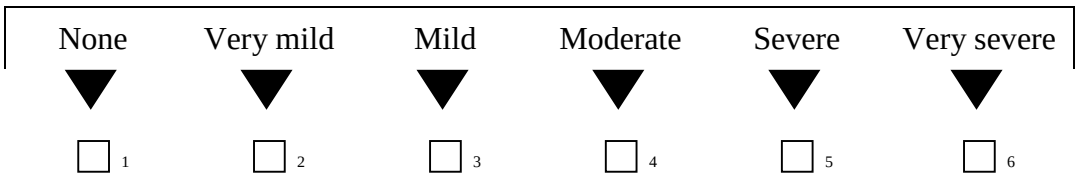
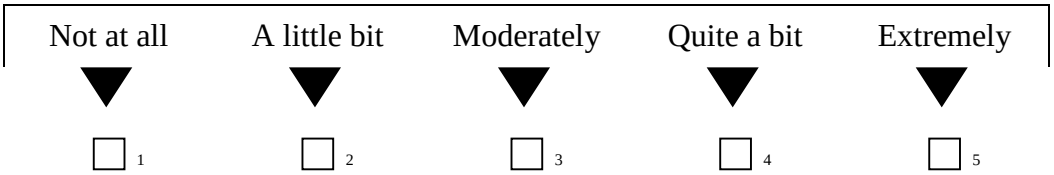
6. During the <u>past week</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?



7. How much <u>bodily</u> pain have you had during the <u>past week</u>?



8. During the <u>past week</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?



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9. These questions are about how you feel and how things have been with you <u>during the past week</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past week</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
e Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
f Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
g Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
h Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
i Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

10. During the <u>past week</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities (like visiting with friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a	I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b	I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c	I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
d	My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Thank you for completing these questions!

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PhoCIS – Fatigue Severity Scale

Participant Name _____ **Participant Number** _____ **Date Completed** _____

The Fatigue Severity Scale (FSS) is a method of evaluating the impact of fatigue on you and requires you to rate your level of fatigue.

There are nine statements that rate the severity of your fatigue symptoms.

Read each statement and circle a number from 1 to 7, based on how accurately it reflects your condition during the past week and the extent to which you agree or disagree that the statement applies to you. It is important that you circle a number (1 to 7) for every question.

- A low value (e.g., 1) indicates strong disagreement with the statement, whereas a high value (e.g., 7) indicates strong agreement.

Fatigue Severity Scale Questionnaire		Strongly **Disagree** → Strongly **Agree**						
1	My motivation is lower when I am fatigued	1	2	3	4	5	6	7
2	Exercise brings on my fatigue	1	2	3	4	5	6	7
3	I am easily fatigued	1	2	3	4	5	6	7
4	Fatigue interferes with my physical functioning	1	2	3	4	5	6	7
5	Fatigue causes frequent problems for me	1	2	3	4	5	6	7
6	My fatigue prevents sustained physical functioning	1	2	3	4	5	6	7
7	Fatigue interfered with carrying-out certain duties and responsibilities	1	2	3	4	5	6	7
8	Fatigue is among my three most disabling symptoms	1	2	3	4	5	6	7
9	Fatigue interferes with my work, family and social life	1	2	3	4	5	6	7
FSS Score (Total)		☐☐						

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Reference: Krupp L et al. The Fatigue Severity Scale: Application to Patients With Multiple Sclerosis and Systemic Lupus Erythematosus. Arch Neurol 1989;46(10):1121-1123

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