# THE ROLE OF VITAMIN D IN CONTROLLING AND REDUCING DM RISKS (D4D)

Version IV

November 2018

**SYNOPSIS**

Protocol title: The Role of Vitamin D in Controlling and Reducing DM Risks (D4D)

Protocol version: Version IV

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**Summary**


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|---|---|
| **Study title** | The Role of Vitamin D in Controlling and Reducing DM Risks (D4D) |
| **Protocol version** | Version IV |
| **Objectives** | To determine if vitamin D can benefit DM and the impacts from different heterogeneous vitamin D sources. |
| **Study design** | The D4D trial is designed as a multi-centre, single-blind, randomized, parallel group, superiority study to determine the role of Vitamin D from the oral supplement, sun exposure and dietary invention in controlling and reducing DM risks. |
| **Planned sample size** | 120-140 participants |
| **Selection criteria** | 1) Aged ≥ 18 years old; 2) Diagnosed with DM in the preceding 12 months, and not on diabetic medication or insulin treatment; 3) Serum 25OHD is between 28 nmol/l and 85 nmol/l and not on vitamin D supplements or any relevant medications; 4) Do not have thyroid diseases, liver impairment, renal failure, cancer, osteoporosis, dementia, mental diseases or taking relevant medications; 5) Not pregnant or breastfeeding women. |
| **Study procedures** | Eligible participants will be randomized in equal proportion into one of 4 groups: vitamin D supplement, dietary intervention, sun exposure and wait list control.<br>The vitamin D supplement group will be given an oral vitamin D supplement to ingest, dosage set as 500 IU per day. The dietary intervention group will be asked to follow a 'vitamin D food resources' list to obtain 10-15 μg/d of vitamin D from food. The sun exposure group will be required to expose about 15% of body surface (hands, face and arms) to natural sunlight anytime from 10am to 4pm for 3-4 minutes/d from December to January, or 8 minutes/d from July to August or 10– 11 min/d from February to June or September to November, to get approximately 12.5 μg/d of vitamin D per day. No interventions will be given to the wait list control group.<br>The total study period of the trial is 9 months. A face-to-face adherence reminder and examination session will occur at baseline and on a monthly basis. A blood test of vitamin D level and DM biomarkers will be obtained at baseline, and at the 3rd month and 9th month session. Participants who report with any side effects or upset symptoms will be assessed by study therapists and excluded from the trial once being confirmed. |
| **Statistical considerations** | Sample size calculation: By setting the significance level $\alpha=0.05$, the power $1-\beta = 0.8$ based on Campbell & Machin (1993) formula: $m=(Z\alpha + Z2\beta)2\{\pi1(1-\pi1)+\pi2(1-\pi2)\}/\delta2$, $(Z\alpha + Z2\beta)2 = 7.849$, $\delta=\pi2-\pi1=0.7-0.35= 0.35$; $m=28$. Therefore for the current study, the sample size of each group is calculated as at least 28, hence it requires at least 112 participants in total. With the consideration of a dropout rate 10%-20%, it is planned to recruit 31-34 participants per group with 123-134 participants in total.<br>Analysis plan: Data are expressed as means ± SDs. Initially, the Kolmogorov–Smirnov goodness-of-fit test will be used to assess the normal distribution of variables. Secondly, two-factor repeated-measures analysis of variance (ANOVA) will be used with Bonferroni correction in the current trial with time stages and |

| | |
|---|---|
| | interventions as factors. A Tukey's post-hoc comparison will be applied to identify the differences between four intervention groups at 3 months and 9 months in the case of significant interaction findings in the ANOVA. Thirdly, correlations between variables were evaluated by using either Pearson (r) (for data with normal distribution) or Spearman (rs) (for data with no normal distribution) correlations. A p-value <0.05 is considered statistically significant. All statistical analyses will be computed using the Statistical Package for Social Science version 17 (SPSS, Chicago, IL, USA). Missing values are treated according to the last observation carried forward (LOCF) method and will be assessed via a sensitivity analysis. |
| **Study duration** | The whole study period including research preparation, participants recruitment, intervention, report writing is designed as 3 years; participants are required to be involved in current research for 9 months. |

## 1.BACKGROUND

### 1.1. DISEASE BACKGROUND*

Diabetes has become a major health issue for many developed and developing countries. There are 347 million people affected by Diabetes globally, and this number is expected to increase to 366 million by 2030 (Wild et al. 2004). Among those affected by Diabetes, over 90% people are diagnosed with Type 2 Diabetes (T2DM) (World Health Organization 2015). There were 999,000 Australians (4.6%) reported to have diabetes in 2012, the majority (85.3%) of which were T2DM (Australian Bureau of Statistics 2012). The prevalence of diabetes in Australia is expected to grow to 3.5 million by 2033 (Magliano et al. 2009).

Diabetes mellitus is a chronic disease characterized by hyperglycaemia resulting from defects in insulin secretion, insulin function, or both. It significantly affects people's health and is associated with many complications, including damage to several organs, especially the eyes, kidneys, heart, nerves and blood vessels.

The treatment of T2DM involves achieving optimal blood glucose level and of other known risk factors that damage blood vessels or organs (Australia Bureau of Statistics 2012). The management can be very challenging (Wallace & Matthews 2004), as it requires medication and insulin use as well as lifestyle changes such as a healthy diet (Kastorini & Panagiotakos 2009; Rahati et al. 2014) and increased physical exercise (Anders & Schroeter 2015).

There is growing evidence indicating an association between vitamin D levels and T2DM, and the association between 25 (OH) D and insulin resistance is currently classified as evidence level II by the NMHRC (Nowson et al. 2012). A large observational study from Finland found that males with the highest serum vitamin D level had the lowest risk of developing diabetes (Knekt et al. 2008). A similar result was found in women in a nested case-control study (Pittas et al. 2010).

A randomised trial conducted among non-diabetic but insulin-resistant South Asian women in New Zealand indicated that there was a significant improvement in insulin resistance by supplementing with vitamin D (von Hurst, Stonehouse & Coad 2010). This study suggested the importance of keeping a good 25(OH)D level (50-80 nmol/l) as a long-term maintenance, as it can benefit both insulin resistance and insulin sensitivity however not the secretion. Another randomized clinical trial suggested that vitamin D slowed down the increase in fasting glucose that may benefit T2DM patients (Pittas et al. 2007).

In our recent published review (Yu et al. 2018), we had assessed the association between vitamin D and glycaemia control among T2DM patients from eligible sixteen Randomised Controlled Trials (RCTs) and had concluded that the current reviewed RCTs did not support the association, considering with study limitations we suggest that more large, long-term and better-designed RCTs using heterogeneous vitamin D sources are required in the future.

### 1.2. RATIONALE FOR PERFORMING THE STUDY*

The current study hypothesized that adequate vitamin D level will help with correcting blood sugar level and HbA1c. It is aimed to determine the prevalence of vitamin D deficiency among DM patients; whether DM patients have low vitamin D intake in daily life; and whether corrected vitamin D level will benefit DM patients. This study will help to understand and explain the possible association between vitamin D and Diabetes Mellitus, help to reduce the cost of clinical care; the cost of medicine; reduce the compliance of DM and reduce the incidence of hospitalization.

## 2. STUDY OBJECTIVES*

### 2.1. PRIMARY OBJECTIVE*

To determine the role of vitamin D (through vitamin D oral supplementation, sun exposure, dietary intervention compare to wait list control) in controlling and reducing DM risks (as measured by HbA1c).

### 2.2. SECONDARY OBJECTIVES

To determine the prevalence of vitamin D deficiency among T2DM patients and,
To determine the differences of heterogeneous vitamin D sources and its impact on DM control.

## 3. STUDY DESIGN*

### 3.1. DESIGN*

The D4D trial is designed as a multi-centre, single-blind, randomized, parallel group, superiority study, to determine the role of vitamin D from the oral supplement, sun exposure and dietary invention in controlling and reducing DM risks. Randomisation will be performed as block randomisation with an equal ratio allocation through MINUM, a computer program that randomises and stratifys participants equally into the different arms of the study.

### 3.2. STUDY GROUPS

Eligible participants will be randomised in equal proportion into 4 groups: vitamin D supplement, dietary intervention, sun exposure and wait list control.

### 3.3. NUMBER OF PARTICIPANTS*

By setting the significance level $\alpha=0.05$, the power $1-\beta = 0.8$. Based on Campbell & Machin (1993) formula: $m=(Z\alpha + Z2\beta)2\{\pi1(1-\pi1)+\pi2(1-\pi2)\}/\delta2$, $(Z\alpha + Z2\beta)2 = 7.849$, $\delta=\pi2-\pi1=0.7-0.35= 0.35$; $m=28$. Therefore the sample size for each group in the current study is calculated to be at least 28, total recruit participants required to be at least 112. With the consideration of a dropout rate 10%-20%, it is planned to recruit 123-134 participants in total with 31-34 participants in each group.

### 3.4. NUMBER OF CENTRES

Participants are to be recruited primarily from the Earlwood Medical Centre (EMC), which is a community medical centre located in south central Sydney. Participants are also to be recruited from the Bangor Medical Centre located in south Sydney. All the following research visits including assessment and data collection will only be conducted in the Earlwood Medical Centre.

### 3.5. DURATION

The D4D research is planned to commence in late-2018 and expected to complete by 2021. The participants will be involved during the intervention phase for 9 months. The expected duration of the recruitment phase is 10-12 months.

## 4. PARTICIPANT SECTION

### 4.1. INCLUSION CRITERIA*

Participants eligible for the trial should comply with all of the following criteria:

1) Aged ≥ 18 years old; 2) Diagnosed with DM in the preceding 12 months, and not on diabetic medication or insulin treatment; 3) Serum 25OHD is between 28 nmol/l and 85 nmol/l and not on vitamin D supplements or any relevant medications; 4) Do not have thyroid diseases, liver impairment, renal failure, cancer, osteoporosis, dementia, mental diseases or taking relevant medications; 5) Not pregnant or breastfeeding women.

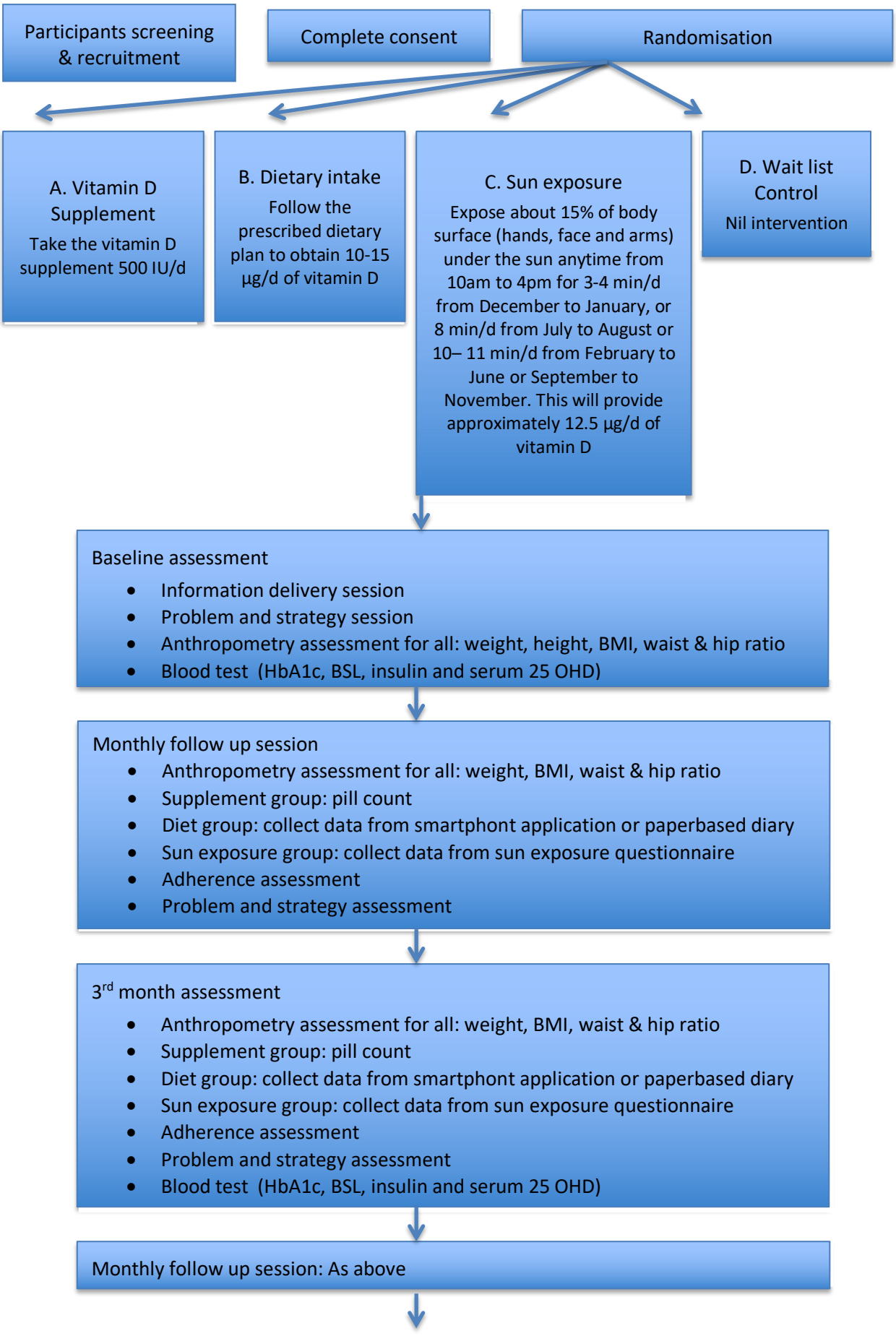
### 4.2. EXCLUSION CRITERIA*

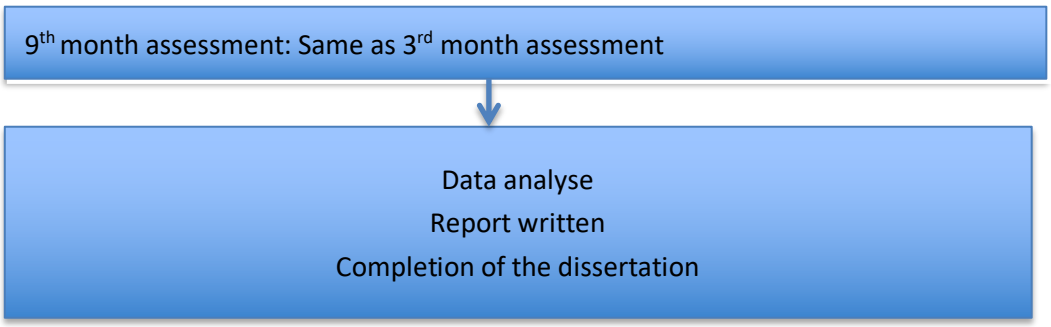
Participants are not eligible for the trial if they are:

1) Unable to give written informed consent or follow the instructions in current trial; 2) are already on vitamin D supplementation or relevant medications; 3) have liver impairment, renal failure (eGFR <50 ml/min), cancer, osteoporosis, dementia, mental disease, and thyroid diseases including hyperparathyroidism, hypercalcaemia, or taking any relevant medications; 4) are < 18 years old or are pregnant or breastfeeding women. 5) are vegen and can not ingest any animal product.

## 5. STUDY OUTLINE*

### 5.1. STUDY FLOW CHART


Participants screening & recruitment
Complete consent
Randomisation
A. Vitamin D Supplement
Take the vitamin D supplement 500 IU/d
B. Dietary intake
Follow the prescribed dietary plan to obtain 10-15 µg/d of vitamin D
C. Sun exposure
Expose about 15% of body surface (hands, face and arms) under the sun anytime from 10am to 4pm for 3-4 min/d from December to January, or 8 min/d from July to August or 10– 11 min/d from February to June or September to November. This will provide approximately 12.5 µg/d of vitamin D
D. Wait list Control
Nil intervention
Baseline assessment
Information delivery session
Problem and strategy session
Anthropometry assessment for all: weight, height, BMI, waist & hip ratio
Blood test (HbA1c, BSL, insulin and serum 25 OHD)
Monthly follow up session
Anthropometry assessment for all: weight, BMI, waist & hip ratio
Supplement group: pill count
Diet group: collect data from smartphont application or paperbased diary
Sun exposure group: collect data from sun exposure questionnaire
Adherence assessment
Problem and strategy assessment
3rd month assessment
Anthropometry assessment for all: weight, BMI, waist & hip ratio
Supplement group: pill count
Diet group: collect data from smartphont application or paperbased diary
Sun exposure group: collect data from sun exposure questionnaire
Adherence assessment
Problem and strategy assessment
Blood test (HbA1c, BSL, insulin and serum 25 OHD)
Monthly follow up session: As above




## 5.2. INVESTIGATION PLAN*

| List Interventions | Baseline assessment | 3rd month visit | 9th month visit | Other monthly visits |
|---|---|---|---|---|
| Training plans | Prior to baseline assessment | N/A | N/A | N/A |
| Information delivery session & Informed Consent | ✓ | N/A | N/A | N/A |
| Inclusion / Exclusion criteria | Prior to the initial visit | N/A | N/A | N/A |
| Anthropometry assessment | ✓ | ✓ | ✓ | ✓ |
| Dietary intake exam | ✓ | ✓ | ✓ | ✓ |
| Sun exposure exam | ✓ | ✓ | ✓ | ✓ |
| Pill count | N/A | ✓ | ✓ | ✓ |
| Adherence assessment with Problem & strategies session | ✓ | ✓ | ✓ | ✓ |
| Adverse Event Assessment | ✓ | ✓ | ✓ | ✓ |
| Blood test | ✓ | ✓ | ✓ | X |

**Training and certification plans**

*(Prior to baseline assessment, Earlwood medical centre, approx. 50 min)*

We will have the General Practitioners (GPs) who believed to meet GCP requirement with appropriate qualification and skill to conduct the trial and will have the 'study therapists' to assist them. 'Study therapists' must attend the compulsory training session for this research only prior to the commencement of the study, which will facilitate their understanding of the trial and their roles.

**Information delivery session**

*(Baseline assessment only; Earlwood medical centre; approx. 30min)*

- The importance of following study guidelines for adherence to daily study intervention;
- Instructions about taking supplements including dosage, storage and what to do in the event of a missed dose; notification there will be a pill count at every study visit;
- Instructions about how to apply the food list into real life and how to record daily dietary intake by using the smartphone application - 'East Diet Diary' or by a paper-based food diary and what to do if miss to record; notification there will be a dietary diary examination at monthly study visit;

- Instructions about clothing, timing, weather condition for sun exposure and how to record daily sun exposure time on the paper-based diary and what to do if miss to record; notification there will be a sun exposure diary exam at monthly study visit;
- The importance of notifying the clinic if experiencing problems possibly related to study products such as side effects, upset symptoms, lost pills or food lists or diary books.

**Anthropometry assessment**

*(Each visit; Earlwood Medical Centre; approx. 10min)*

- Weight (kg) is measured by a digital scale (Tanita UM-051).
- BMI is calculated out based on equation: BMI=weight (kg)/height$^2$ (m$^2$).
- Waist and hip ratio is measured by a measuring tape and calculated.

**Data collection: dietary data exam / sun exposure exam/ pill count**

*(Each visit; Earlwood Medical Centre; approx. 20min)*

- Pill count- Participants will return the unused tablets and bottle at each follow-up visit. Unused tablets will be counted and recorded on the appropriate CRF (case report form).
- A 24-hour food recall and a Food Frequency Questionnaire (FFQ) will be used at baseline to collect nutritional information of energy, protein, fat, carbohydrate and vitamin D. A 3-day food diary (2 workdays and 1 weekend day per week, hence four copies per month) is used for each follow-up visit. Diary can be completed through either paper-based diary or the smartphone application 'EasyDietDiary'. If participants failed to complete the diary, a 24 hr recall and a FFQ will be used to collect the missing information. An Accredited Practicing Dietitian (APD) will be appointed to design the dietary guideline and provide training to study therapists who conduct the nutritional information collection; data will be later processed through 'FOODWORK 8' database.
- Sun exposure time will be evaluated by the Sun exposure questionnaire (adapted from 45 and up Questionnaire) at baseline. Research staff will check the Sun exposure diary at each follow-up visit. Participants will be asked to do extra diary entries to compensate if they missed recording the information. We use the scoring from weekly sun exposure recall questionnaire (Hanwell et al. 2010) to assess the sun exposure status.

**Adherence session**

*(During the whole trial)*

- Maintain interest in the study through mailings and phone calls;
- Send letters to participants prior to the monthly follow up assessment, and ring on the previous day to remind the next day assessment;
- Provide assistance if participants have questions of the diet menu, or participants who experience food intolerance and allergy symptoms;
- Provide participants with information about the current status of the study, and plans for the next phase, as well as to acknowledge their support

**Problem and strategy session**

*(Each visit; Earlwood Medical Centre; approx. 5min)*

- Participants will be asked about any problems they have regarding taking their study supplements or use of the diaries. There will be a brief discussion of reasons for missed doses and simple strategies for enhancing adherence, eg, linking supplement taking to meals or other daily activities; schedule an outdoor time in noon; update the diet intake daily through phone applications.

**Adverse event assessment**

*(Each visit, Earlwood medical centre, approx. 5min)*

- Adverse events will be collected after the participant has provided consent and enrolled

in the study. There is the possibility that in the dietary intervention group, some subjects may report food intolerance and/or allergy symptoms to seafood or dairy products. We will record the incidences; APD will provide dietetics consultation and appropriate suggestion to minimize the risks. If the adverse effects continue, participants will be excluded from the trial, allergy test and related medical treatment will be provided if necessary.

**Blood test**

**(***Baseline assessment, 3rd month and 9th month only; Earlwood medical centre; approx. 10 min)*

- A government accredited Pathology Collection point or the Registered Nurses at Earlwood Medical Centre will collect the blood samples and forward the sample to the NATA accredited pathology laboratory to conduct the blood test for the Diabetes biomarker and serum 25OH D.

### 5.3. Study Procedure Risks*

Adverse events will be collected after the participant has provided consent and enrolled in the study. In the current trial, the dosage of vitamin D (500 IU) provided through supplementary, dietary or sun exposure is considered to be safe and it is unlikely to cause adverse effects. However, if participants report with any adverse effects, they will be provided with medical treatment if necessary and excluded from the trial.

Other than that, there is the possibility that in the dietary intervention group, some subjects may report with food intolerance and allergy symptoms to seafood or dairy products. Research staff will record the incidences. Participants will be asked to attend a dietitian review for appropriate suggestion to minimize the risks. If the adverse effects are continued, participants will be excluded from the trial, related test or medical treatment will be provided if necessary.

### 5.4. Recruitment and Screening*

Trial information will be provided through website, flyer and local advertising. The trial will also be introduced to GPs and allied health professionals for cross-referral recruitment. Participants who express an interest through email, phone calls and personal attendance at clinics will be recruited. These include self-referred participants and participants who are referred by a GP or health professional. Diabetic patients' lists (name only) in both clinic centres will be used to contact for an EOI (expression of interest) as well. Responses to any inquiries about participation in the research study are to be answered by a phone that is manned during business hours and answered by voicemail at all other times. A research assistant will respond to each inquiry immediately, using a screening instrument to identify eligible participants and provide the following instructions.

### 5.5. Informed Consent Process*

Once patients identify an interest in the trial, they will be directed to read the website information or information package and eventually sign the consent form and prepare to attend for the baseline assessment.

### 5.6. Enrolment Procedure*

The research staff will enrol the participants following the confirmation of the consent form and eligibility.

### 5.7. Randomisation Procedure

**Allocation: Sequence generation**

Participants will be randomly assigned to one of four different groups with an equal ratio referring to the permuted block randomisation. The software randomisation package MINUM will be used for sequence generation. The block sizes will not be disclosed, to ensure concealment.

**Allocation concealment mechanism**

Allocation concealment will be ensured, as the centre will not release the randomisation code until

the participants have been recruited into the trial. The randomisation will be conducted by an independent investigator (not the research student) and send the sequence to study therapists who are only responsible for implementing the randomisation.

**Implementation**

All participants who give consent for participation, and who fulfil the inclusion criteria, will be randomized. An independent investigator (not the research student) will send the randomisation instruction to the study therapist who is not involved in recruitment or outcome assessment. Follow the randomisation instrument, eligible study therapist prepares closed envelopes with printed randomisation numbers and are available in both recruitment centres. For every randomisation number, the corresponding code for the intervention group will be found inside the envelope. Only the study therapist will open the envelope and will find the treatment to be conducted for this participant. The therapist then gives the information about treatment that allocated to the patient. The randomisation list will be stored in the two centres for the whole time period of study.

## 6.SAFETY*

### 6.1. ADVERSE EVENT REPORTING*

**Adverse event**

Adverse events will be collected after the participant has provided consent and enrolled in the study. In the current trial, the dosage of vitamin D (500 IU) provided through supplement, dietary or sun exposure is considered to be safe and it is unlikely to cause adverse effects. However, if participants report any adverse effects, they will be provided with medical treatment if necessary and excluded from the trial.

In addition, there is the possibility that in the dietary intervention group, some participants may report food intolerance and allergy symptoms to seafood or dairy products. Research staff will record the incidence. Participants will be asked to attend a dietitian review for appropriate suggestions to minimize the risk of further food intolerances/allergies. If the adverse effects continue, participants will be excluded from the trial and provided with relevant test and medical treatment if necessary.

### 6.2. EARLY TERMINATION

The vitamin D dosage used in this study is considered to be of a safe level for daily intake and is currently recommended as the AI for vitamin D in Australia. It is unlikely to cause any side effects or symptoms by obtaining this dosage level through sun exposure, dietary change or supplementary intake. However, some participants may experience allergy or food intolerance risks by adding seafood or eggs into their daily meals even if cleared from allergy history at the initial screening. Participants with any severe allergic reaction or food intolerance will be excluded from current study, relevant medical treatment including allergy test would be arranged for participants if necessary.

## 7. BLINIDING AND UNBLINDING

The study therapist blind to treatment allocation will conduct the baseline assessment/monthly assessment for the anthropometry, dietary and sun exposure data collection. The pathology technician who is blind to treatment allocation will conduct the blood test. Due to the nature of the intervention, neither participants nor assessors will be blinded to the intervention but will be informed not to disclose the allocation status or status of the participant at the follow-up assessments. An employee outside the research team will input data into the computer in separate datasheets so that the research team can analyse data without having access to information about the allocation.

## 8. STATISTICAL CONSIDERATIONS*

By setting the significance level $\alpha$=0.05, the power 1-$\beta$ = 0.8 based on Campbell & Machin (1993) formula: $m=(Z\alpha + Z2\beta)2\{\pi1(1-\pi1)+\pi2(1-\pi2)\}/\delta2$, $(Z\alpha + Z2\beta)2 = 7.849$, $\delta=\pi2-\pi1=0.7-0.35= 0.35$; therefore m=28. Therefore the sample size for each group in the current study was calculated to be

at least 28, with at least 112 in total. With the consideration of a dropout rate 10%-20%, it is planned to recruit 123-134 participants in total hence 31-34 participants for each group.

Data are expressed as means ± SDs. Initially, the Kolmogorov–Smirnov goodness-of-fit test will be used to assess the normal distribution of the values. Secondly, two-factor repeated-measures analysis of variance (ANOVA) with a Bonferroni correction will be used in the current trial with time stages and interventions as factors. Tukey's post-hoc comparison will be applied to identify the differences between four intervention groups at 3 months and 9 months in the case of significant interaction finding in ANOVA. Thirdly, correlations between variables will be evaluated by using either a Pearson (r) (for data with normal distribution) or a Spearman (rs) (for data with no normal distribution) correlation. A p-value <0.05 is considered to be statistically significant. All statistical analyses will be computed using the Statistical Package for Social Science version 17 (SPSS, Chicago, IL, USA). Missing values are to be treated according to the last observation carried forward (LOCF) method and will be assessed via sensitivity analysis.

**9. CONFIDENTIALITY AND STORAGE AND ARCHIVING OF STUDY DOCUMENTS***

All reports, data collections, process and administrative forms and documents will be re-identified by a code ID number only to maintain participant confidentiality. Study data will be managed by UTS data management system, 'STASH'. Research staff will bring the paper-based data back to UTS and transfer to the computer at UTS. Data will be stored both in CloudStor (AARNET) and an independent hard disk. All databases will be securely encrypted and password protected and is only accessed by principal investigators. The hard disk will be backed up twice a month for data security. Study staff will be informed to preserve the confidentiality of all participants. Information of participants will only be used for the purpose of this study project and it will only be disclosed with the permission of the participant, except as required by law.

The participant files, both hardcopy and digital data, will be maintained in storage for a period of 7 years after completion of the study. At the end of the period, research data and primary materials will be disposed of either by achieving or by destroying the digital and paper-based files. For any type of studies including sub-studies, ancillary studies or any research outside of the D4D, which is using data or samples collected by the D4D, it will require a review and agreement from current principal investigator committee.

**10. OTHER STUDY DOCUMENTS**

- Flyer (as attached separately)
- Website: www.d4dresearch.com
- Questionnaire (as attached separately)
- Case report form (CRF) as following:

  CRF 1. Research Proposal (version IV)

  CRF 2. NHMR Participant Information and Consent Form (PICF)

  CRF 3. Major Questionnaire

  CRF 4. Questionnaire - Dietary – 3 days food recall

  CRF 5. Questionnaire – Dietary – Food Frequency Questionnaire (FFQ)

  CRF 6. Explanation of technical terms used

  CRF 7. Evidence of approval from the Therapeutic Good Administration (TGA)

  CRF 8. External organization support letter – Earlwood Medical Centre

  CRF 9. External organization support letter – Bangor Medical Centre

  CRF 10. Flyer

  CRF 11. Confidentiality Agreement (study therapists)

**11.REFERENCES***


Anders, S. & Schroeter, C. 2015, 'Diabetes, diet-health behavior, and obesity', *Front Endocrinol (Lausanne)*, vol. 6, p. 33.

Australian Bureau of Statistics 2012, *Health Status, viewed 12 September 2015,* <http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/1301.0~2012~Main%20Features~Health%20status~229.> [14/09/2015]

Campbell MJ, Machin D. Medical statistics: A commonsense approach. Wiley 1993

Kastorini, C.M. & Panagiotakos, D.B. 2009, 'Dietary patterns and prevention of type 2 diabetes: from research to clinical practice; a systematic review', *Curr Diabetes Rev*, vol. 5, no. 4, pp. 221-7.

Knekt, P., Laaksonen, M., Mattila, C., Harkanen, T., Marniemi, J., Heliovaara, M., Rissanen, H., Montonen, J. & Reunanen, A. 2008, 'Serum vitamin D and subsequent occurrence of type 2 diabetes', *Epidemiology*, vol. 19, no. 5, pp. 666-71.

Magliano, D.J., Peeters, A., Vos, T., Sicree, R., Shaw, J., Sindall, C., Haby, M., Begg, S.J. & Zimmet, P.Z. 2009, 'Projecting the burden of diabetes in Australia--what is the size of the matter?', *Aust N Z J Public Health*, vol. 33, no. 6, pp. 540-3.

National Health and Medical Research Council 2007, *The National Statement on Ethical Conduct in Human Research,* viewed 20 March 2018, <http://www.nhmrc.gov.au/_files_nhmrc/publications/attachments/e72.pdf.> [20/04/2018]

Nowson, C.A., McGrath, J.J., Ebeling, P.R., Haikerwal, A., Daly, R.M., Sanders, K.M., Seibel, M.J., Mason, R.S., Working Group of, A., New Zealand, B., Mineral Society, E.S.o.A. & Osteoporosis, A. 2012, 'Vitamin D and health in adults in Australia and New Zealand: a position statement', *Med J Aust*, vol. 196, no. 11, pp. 686-7.

Pittas, A.G., Harris, S.S., Stark, P.C. & Dawson-Hughes, B. 2007, 'The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults', *Diabetes Care*, vol. 30, no. 4, pp. 980-6.

Pittas, A.G., Sun, Q., Manson, J.E., Dawson-Hughes, B. & Hu, F.B. 2010, 'Plasma 25-hydroxyvitamin D concentration and risk of incident type 2 diabetes in women', *Diabetes Care*, vol. 33, no. 9, pp. 2021-3.

Rahati, S., Shahraki, M., Arjomand, G. & Shahraki, T. 2014, 'Food pattern, lifestyle and diabetes mellitus', *Int J High Risk Behav Addict*, vol. 3, no. 1, p. e8725.

von Hurst, P.R., Stonehouse, W. & Coad, J. 2010, 'Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient - a randomised, placebo-controlled trial', *Br J Nutr*, vol. 103, no. 4, pp. 549-55.

Wallace, T.M. & Matthews, D.R. 2004, 'Recent advances in the monitoring and management of diabetic ketoacidosis', *QJM*, vol. 97, no. 12, pp. 773-80.

Wild, S., Roglic, G., Green, A., Sicree, R. & King, H. 2004, 'Global prevalence of diabetes: estimates for the year 2000 and projections for 2030', *Diabetes Care*, vol. 27, no. 5, pp. 1047-53.

World Health Organization 2015, *Fact sheet N°312 – Diabetes, viewed 12 April 2015,* <http://www.who.int/mediacentre/factsheets/fs312/en/ >. [13/04/2015]

Yu, X.F., Zaslawaki, C. and Lim, C.E.D., 2018. Vitamin D on glycaemia control in type 2 diabetes patients: A systematic review of randomised clinical trials. *Journal of the Australian Traditional-Medicine Society*, 24(2).