Protocol Title

Diabetes **RE**mission **C**linical **T**rial-**Aus**tralia

DiRECT-Aus Study

Protocol Number: X20/0060

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Ethics Statement:

The study will be conducted in accordance with the *National Statement on Ethical Conduct in Human Research* (2007), the *CPMP/ICH Note for Guidance on Good Clinical Practice* and consistent with the principles that have their origin in the Declaration of Helsinki. Compliance with these standards provides assurance that the rights, safety and well-being of trial participants are respected.

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Summary

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Objectives Primary objective

To determine whether a program, designed to achieve remission of T2DM to normal glucose tolerance by substantial weight loss using a very low energy diet (VLED), can be effectively delivered within the routine primary care setting where most people with T2DM are managed.

Secondary objectives

To evaluate the attitudes of participants to the very low energy diet (VLED) program including acceptability, ease of use and perceived value.

Study design

DiRECT-Aus is a translational study based on the active arm of the DiRECT trial (UK) which demonstrated effectiveness in achieving remission of T2DM using a structured weight management program in primary care.

Planned sample size

250 subjects recruited from 5 Primary Health Networks (PHNs) through 5 general practitioner (GP) practices per PHN (total 50 GP practices recruiting 10 subjects per practice).

Selection criteria

- Men and women aged 20-65 years, all ethnicities
- Type 2 Diabetes Mellitus of duration 0-6 years
- Body mass index (BMI)>27 kg/m^2

Study procedure

GP Practices will deliver an VLED phase followed by structured food reintroduction and long term weight loss maintenance. Training for the practice nurses/dietitians in VLED delivery, maintenance diet program and behaviour therapy will be provided by the Metabolism & Obesity Services, Royal Prince Alfred Hospital and Boden Collaboration, University of Sydney

Statistical considerations

The objective of the study is to determine if a VLED and structured weight management program can be instituted as effectively in primary care in Australia as in the original UK DiRECT trial.

Duration of the Study - Active intervention: 12 months per subject. Follow up: 4 years after completion of active intervention (subject to funding)

ABBREVIATIONS

App	Appendix
Appt	Appointment
BMI	Body Mass Index
CHD	Coronary Heart Disease
eGFR	Estimated Glomerular Filtration Rate
GP	General Practitioner
ITT	Intention to Treat
LED	Low Energy Diet
VLED	Very Low Energy Diet
SLHD	Sydney Local Health District
OHA	Oral Hypoglycaemic Agent
PHN	Primary Health Network
RCT	Randomised Controlled Trial
T2DM	Type 2 Diabetes Mellitus
TDR	Total Diet Replacement
GIG	Governance and implementation Group

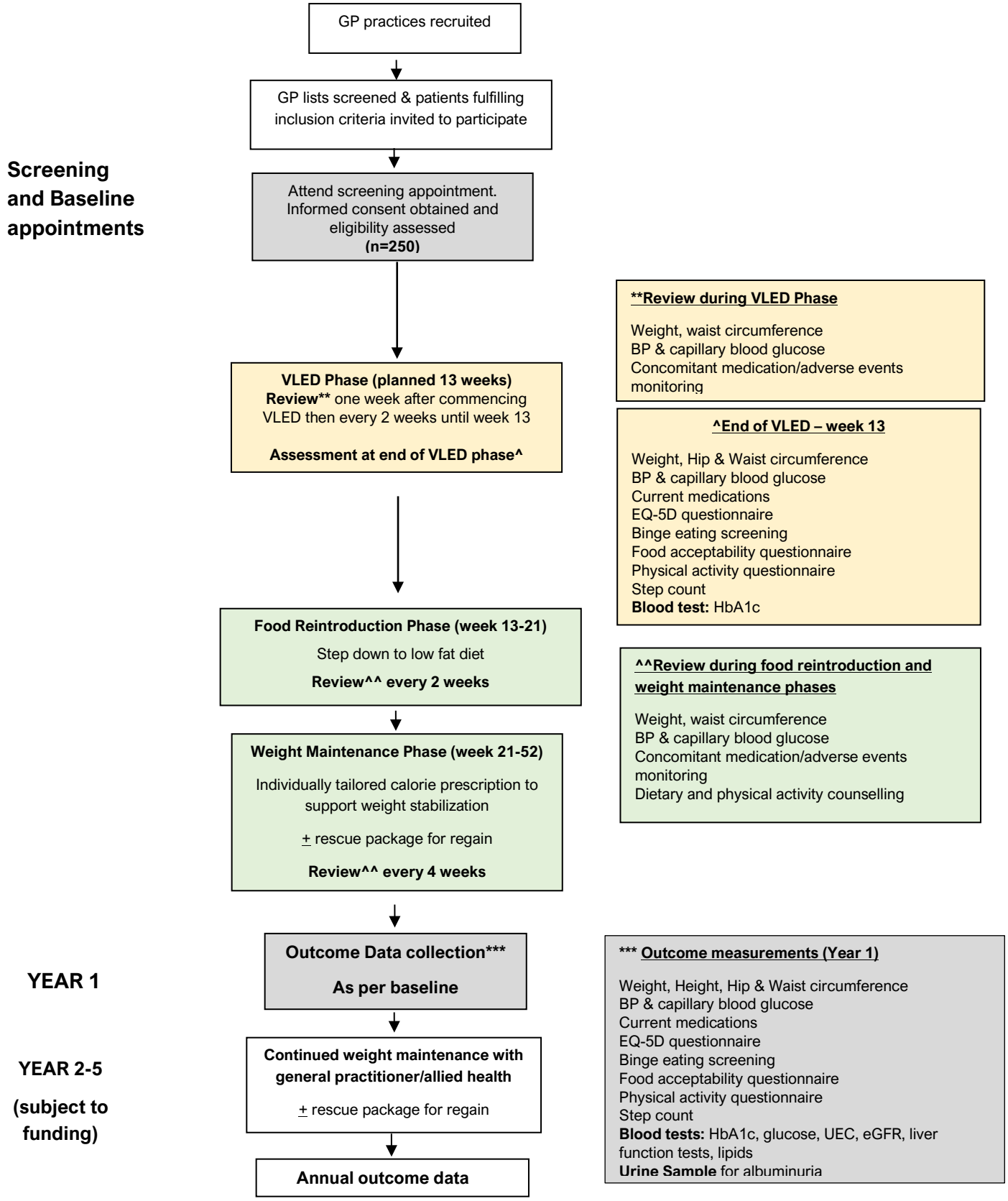
STUDY SYNOPSIS

Title of Study:	**Di**abetes **RE**mission **C**linical **T**rial-**Aus**; **DiRECT-Aus**
Study Centre:	University of Sydney
Duration of Study:	Active intervention: 12 month per subject Follow up: 4 years after completion of active intervention
Primary Objective:	To determine whether a program, designed to achieve remission of T2DM to normal glucose tolerance by substantial weight loss using a very low energy diet (VLED), can be effectively delivered within the routine primary care setting where most people with T2DM are managed in Australia. The Diabetes Remission Clinical Trial (DiRECT) was a study funded by Diabetes UK that tested whether a low calorie-based weight management program, delivered in primary care could result in long term Type 2 diabetes remission. Diabetes UK, the University of Glasgow and Newcastle University have since developed the DiRECT principles, which set out the core elements of health intervention to have the best chance of replicating the outcomes of the DiRECT study. This project intent is to replicate or better the remission results achieved in the UK DiRECT study for people with T2DM in the participating PHN regions and undertaking the intervention in general practice.
Secondary Objective:	To evaluate the attitudes of participants to the VLED program including acceptability, ease of use and perceived value.
Primary Endpoint:	% of participants achieving a non-diabetic HbA1c (<6.5%; <48 mmol/mol) at 12 months having ceased all diabetes medication for at least the preceding 2 months
Rationale:	Bariatric surgery can convert 70-80% of people with T2DM to the non-diabetic state. The DiRECT trial provided evidence that T2DM could also be reversed by a strict energy restricted diet, with 10-15kg weight loss. The present study will determine if the results of the DiRECT trial can be replicated in an Australian primary care setting and establish whether it is possible to produce remission of T2DM at 12 months and sustain it over 5 years. An VLED can be provided relatively cheaply in the primary care setting where obesity and T2DM are managed, using a total diet replacement (TDR), such as Optifast, which is readily available to the Australian general public. The study will also assess quality of life and attitudes of subjects during the intervention.

Methodology:	The study will be 'realistic' to ensure transferability into routine care and will be set within primary care where T2DM is managed. Consenting general practices within 5 Primary Health Networks (PHNs) in NSW will participate in delivering the intervention, which is a weight management program that includes a TDR phase, followed by structured food reintroduction and long-term weight loss maintenance. To increase access in regional areas, the intervention may be delivered via telehealth but all participants will attend their GP practice for safety monitoring and collection of study data. Participants will otherwise continue to be managed as usual, following current guidelines.
Sample Size:	250 subjects recruited from 5 PHNs through 5 GP practices per PHN (total 25 GP practices recruiting 10 subjects per practice).
Screening:	Potential participants will be identified by GPs either as part of routine care or a search of patient records in participating GP practices. GPs may request the assistance of researchers at Diabetes NSW & ACT with recruitment which will entail sending of invitation letters to potential participants and discussing the study with potential participants over the telephone. Potential participants will have access to a toll-free phone number monitored by Diabetes NSW & ACT and a study website for more information about the study. A study poster, brochure and Information Pack will also be available in participating GP practices.
Main Inclusion Criteria:	• Men and women aged 20-65 years, all ethnicities • T2DM of duration 0-6 years • Body mass index (BMI)>27 kg/m^2
Main Exclusion Criteria:	• Current insulin use • HbA1c ≥ 86 mmol/mol (10%) at screening • eGFR ≤ 45 ml/min/1.73^2 at screening • Severe or unstable heart failure (≥ New York Heart Association class 3) • Patients with unstable mental illness Substance abuse • Substance abuse • History of active or untreated malignancy or in remission from a clinically significant malignancy for less than 5 years. Exceptions to this criterion include basal or squamous cell skin cancer, in situ carcinoma of the cervix or in situ prostatic cancer

	• Myocardial infarction within previous 6 months • Learning difficulties which in the opinion of the investigator prevent the subject providing informed consent and complying safely with the diet • Use of weight loss agents or medications taken to primarily reduce weight (eg orlistat, lorcaserin, Qysmia, Contrave, GLP-1 receptor analogues, over the counter or herbal weight loss agents) within the past 3 months • Have ever been diagnosed with and eating disorder or engaged in purging behaviour • Pregnant/ considering pregnancy • people currently participating in another clinical research trial • Allergy to Optifast or any of its ingredients
Product, Dose, Modes of Administration:	The intervention is a 3400kJ (800kcal)/day TDR, followed for 13 weeks, with stepped food reintroduction to long-term weight loss maintenance using a tested energy-restricted nutritionally balanced (30% fat, < 10% saturated fat) maintenance diet using food-group exchanges, and support for behaviour change. Physical activity will be encouraged with a recommendation of at least 30 minutes brisk-walking daily and aiming to reach and maintain an individual sustainable maximum with a target of 15,000 steps/day. Participants will continue to receive standard care under current clinical guidelines for T2DM. Intention to treat analysis will be conducted, with follow-up data continuing to be collected even if treatment is stopped. The intervention will be delivered in primary care practices by practice nurses/dietitians (according to local availability and practice) with training, support and mentoring from the Boden Collaboration, University of Sydney.
Duration of Treatment:	12 months. Subject to additional funding, at least annual follow up for 5 years
Statistical Analysis:	Data will be analysed primarily on an intention-to-treat (ITT) basis, using last observation carried forward for weight and diabetes status for subjects who discontinue the formal weight management program or experience an adverse event. A 'completers analysis' of participants who complete the study will also be performed.

STUDY FLOW CHART



10 INTRODUCTION

1.1 Background: the problem

T2DM is closely linked to obesity and is the main contributor to the rising costs of obesity.[1, 2] It seldom develops with BMI <21 kg/m^2 and most affected individuals have BMI >25 kg/m^2 with about 50% having BMI >30 kg/m^2[2,3,4]. At a BMI >35 kg/m^2, 20% of all men and 11% of women have known diabetes[5]. There is increasing concern about the most rapidly rising categories of severe obesity that demand greater weight loss to control secondary medical consequences. There is overwhelming evidence that modest sustained weight loss, e.g. current target of 5-10%, prevents the onset of most new T2DM in people with pre-diabetes[6] and it improves *all* aspects of diabetes control (glycaemia, blood pressure, lipids and microvascular damage [7] with reductions in drug doses[8, 9]). Advice to lose and maintain 5-10% weight loss, by diet and exercise, is included in most guidelines. However, most patients with T2DM are now managed in primary care, many do not see a dietitian and few achieve even 5% weight loss. Following guidelines, most obese/overweight patients who develop T2DM will be prescribed 4-6 drugs (hypoglycaemic, statin, anti-hypertensives) plus drugs/treatments for other conditions attributable largely to their obesity, e.g. angina, arthritis, gastro-oesophageal reflux, obstructive sleep apnoea and depression. The reduction in coronary heart disease (CHD) risk by this polypharmacy, following current guidelines, has been estimated to be only 5-10%.[10,11] Compliance with drug treatments is poor[12] in part because some commonly used anti-diabetic and antihypertensive drugs cause further weight gain[13] and costs are substantial. The prognosis of obesity with T2DM thus remains poor. For a person with diabetes aged between 50 and 60 years, life expectancy is reduced by 6 years.[14] The diagnosis is also stigmatising and brings personal costs through insurance penalties and employment problems.

T2DM is characterised by defects in both insulin sensitivity and beta-cell function. It is commonly perceived as steadily progressive, with an inevitable decline in beta cell function and requirement for insulin therapy after an average of 10 years.[15,16] However, bariatric surgery has been shown to reverse the metabolic abnormalities of T2DM rapidly at least in patients up to 6 years after diagnosis.[17] The Counterpoint study in Newcastle demonstrated that this benefit can be reproduced by negative energy balance alone, and that the normalisation of fasting plasma glucose persists for up to 3 months after return to normal diet.[18] It is clear that for at least some patients, the beta cells are not permanently damaged but merely metabolically inhibited in T2DM, as previously hypothesised.[15] This proof of principle study reported a dramatically sudden return of fasting blood glucose to normal,

associated with a rapid fall in hepatic fat content to non-diabetic control levels during an 8 week 2510 kJ (600 kcal)/day diet. Observation of beta cell function using a gold-standard method demonstrated the slower, gradual return of normal first phase insulin response over 8 weeks in association with a steady fall in pancreas fat to non-diabetic control levels. The time-course of these observations suggest that the two characteristic defects of T2DM - decreased acute insulin secretion and insulin resistance – are brought about by adverse effects of fatty acids in pancreas and liver respectively. In the DiRECT trial[19] subjects with type 2 diabetes were either treated with a LED (3500 kJ (836 kcal)/day) followed by a structured program to maintain weight loss (intervention arm) or received best practice care (control arm). As expected, there was substantially greater weight loss in the intervention group (10.0 (SD 8.0) vs 1.0 (3.7) kg) and, at 12 months, diabetes remission occurred in 46% of those in the intervention group compared to just 4% in the control arm. Remissions were sustained at 2 years in 36% of those in the intervention group 3% of controls.[20] The durability of the remission was related to the extent of sustained weight loss. Similar weight loss with cardiometabolic improvements have been achieved with an LED (3400 kJ), using formula food, in subjects with obesity, again in a primary care setting, in the DROPLET study[21].

1.2 Rationale

The major clinical question is whether a VLED and structured weight management program can be instituted as effectively in primary care in Australia.

While previous guidelines have retained a 5-10% weight-loss target, the 2010 SIGN Obesity guideline, recognising changes in obesity prevalence and also recent evidence for more aggressive interventions, has set a new weight loss/maintenance target of >15-20% for those with BMI >35 kg/m^2 or >30 kg/m^2 with serious medical complications such as T2DM.[20] However, in routine diabetes care, few people achieve a weight loss of >15kg (or >15%). Although bariatric surgery is recommended for patients with T2DM and obesity by both the Australian Diabetes Management guidelines[22] and the Australian Obesity Management Algorithm[23], there is little realistic prospect of its being offered to most such patients because of surgical and follow-up resource limitations. Furthermore, many patients will not agree to surgery. However, there is clear evidence that a combined medical program of diet, exercise and anti-obesity drugs can generate and maintain >15kg weight loss for many patients.[24]

The DiRECT trial[19] clearly demonstrated that a structured weight management program conducted in the primary care setting enabled people to lose weight and maintain weight loss for up to 2 years such that a substantial proportion of participants achieved remission of T2DM. Whether this model of care for weight loss and remission of T2DM is feasible, acceptable and translatable to an Australian primary care setting needs to be determined.

1.3 Study hypothesis

Losing weight using a structured weight management program, which includes an initial period of total diet replacement, followed by carefully managed food reintroduction and then weight loss maintenance, is a viable treatment for inducing remission of T2DM and can be implemented in a primary care setting where large numbers of overweight and obese people with T2DM are managed in the Australia.

2. STUDY OBJECTIVES

This research will establish whether it is possible to produce remission of T2DM and how sustainable this is over 5 years. Optimised weight management will be achieved using an LED, with the meal replacement Optifast, in routine Primary Care, where most T2DM is managed. The study will also assess quality of life and attitudes during the intervention.

- **The study endpoint is**
    - Remission of diabetes at 1 year (HbA1c <6.5%, 48 mmol/mol and off diabetes treatment for at least the preceding 2 months)

- **Secondary endpoints**
    - Weight change
    - Quality of Life
    - Physical Activity
    - Serum Lipids
    - Attitudes to the VLED
    - Effect of VLED on eating behaviour
    - Durability of diabetes remission

3. STUDY DESIGN

DiRECT-Aus is a translational study based on the active arm of the UK DiRECT trial, which demonstrated effectiveness in achieving remission of T2DM using a structured weight management program in primary care.

3.1 Study Population

250 patients will be recruited to the study from general practices within the following Primary Health Networks:

1. SNPHN Limited trading as Sydney North Health Network
2. WentWest Limited trading as Went West
3. SWSPHN Limited trading as South Western Sydney Primary Health Network
4. Healthy North Coast Limited trading as North Coast Primary Health Network
5. Western Health Alliance Limited trading as Western NSW Primary Health Network (WNSW PHN)

Participating GP patient lists will be screened to identify patients, aged 20-65 years diagnosed with T2DM within the previous 6 years, who would be potentially eligible to participate. GPs will review these lists and remove any patients they consider would be ineligible or unsuitable to approach.

3.2 Inclusion criteria

- Written informed consent
- Men and women aged 20-65 years, all ethnicities
- T2DM of duration 0-6 years (diagnosis based on Australian diagnostic criteria)
- HbA1c criteria at study entry:
    - 48 mmol/mol ($\geq$ 6.5%) **or**
    - HbA1c > 42 mmol/mol (6%), but < 48 mmol/mol (6.5%) if subject is taking blood glucose lowering medication(s)
- Body Mass Index (BMI)>27 kg/m^2
- Women of childbearing potential must be ready and able to use highly effective methods of birth control that result in a low failure rate of less than 1% per year when used consistently and correctly, unless truly abstinent (as a lifestyle choice), in a committed relationship with a male who is medically sterile or exclusively same sex attracted.

3.3 Exclusion criteria

- Current insulin use
- HbA1c ≥10% (86mmol/mol) at screening
- Weight loss of >5kg within the last 6 months
- eGFR ≤ 45 ml/min/1.73^2 at screening
- Substance abuse
- History of active or untreated malignancy or in remission from a clinically significant malignancy for less than 5 years. Exceptions to this criterion include basal or squamous cell skin cancer, in situ carcinoma of the cervix or in situ prostatic cancer
- Myocardial infarction within previous 6 months
- Severe or unstable Heart Failure defined as equivalent to the New York Heart Association (NYHA):
  - Grade 3 - marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or breathlessness, and
  - Grade 4 - unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.
- Learning difficulties which in the opinion of the investigator prevent the subject providing informed consent and complying safely with the diet
- Use of weight loss agents or medications taken to primarily reduce weight (eg orlistat, lorcaserin, Qysmia, Contrave, GLP-1 receptor analogues, over the counter or herbal weight loss agents) within the past 3 months
- Have ever been diagnosed with and eating disorder or engaged in purging behaviour
- Pregnant/ considering pregnancy
- Patients with unstable mental illness
- People currently participating in another clinical research trial
- Allergy to Optifast or any of its ingredients

3.4 Identification of participants and consent

Potential participants will be identified by the GP either during routine care or from a search of practice records, performed either by the GP or practice staff and reviewed by the GP to identify patients who in the GP's opinion are appropriate for the study. The study will also be advertised via a study poster, brochure, and Information Pack available in participating GP practices. A study website

[www.diabetesnsw.com.au/directaus] accessible using a Quick Response (QR) code will be used to communicate information about the study to potential participants. The website will provide details including the purpose of the study, eligibility criteria, what is involved in participation, who is conducting the research, and access to a downloadable version of the Information Pack. The website will clearly state that participation in the study is optional and voluntary and will not affect their relationship with their GP or routine care. The website will also be used to communicate information to GPs in a restricted access section.

The QR code will be displayed on the poster and participant brochure. The poster, brochure, Information Pack and website will also display a toll free number monitored by researchers at Diabetes NSW & ACT which participants may use to obtain additional study information and undergo pre-screening for the study. Verbal consent will be obtained by researchers at Diabetes NSW & ACT to record personal contact information and outcome of pre-screening of potential participants who contact the study team using the toll free number in a recruitment database which will be password protected.

Patients identified during routine care

Patients identified during routine care as potentially eligible will have the opportunity to discuss the study with the GP. They will be provided with the Patient Information Statement (PIS) and encouraged to schedule a screening appointment by calling the practice if interested in participating. Verbal consent will be obtained to share the patient's contact details with researchers at Diabetes NSW & ACT for the purpose of recording recruitment activities and being contacted by Diabetes NSW & ACT regarding participation in the study. Reception staff at GP practices will be instructed to notify Diabetes NSW & ACT when any new screening appointments for the study are booked. Diabetes NSW & ACT will update the recruitment database accordingly. Diabetes NSW & ACT will periodically check if patients who expressed interest through their GP have made a screening appointment. GPs will be notified if a patient has not made an appointment and the GP or Diabetes NSW & ACT will contact the patient. Patients will be followed up until they express that they do not wish to participate or do not wish to be contacted further.

Patients identified from GP records

Patients identified as potentially eligible from a review of GP records will be contacted directly by the GP practice (via telephone) or, if the GP wishes to take a less active role, sent an invitation letter by the research team at Diabetes NSW & ACT.

Patients telephoned by the GP Practice

For patients contacted by the GP, a similar process to the above will be followed except the discussion between patient and GP will take place over the telephone and patients will be directed to the study website for access to written information about the study including the PIS. If interested in participating they will be encouraged to schedule a screening appointment by calling the practice and consent will be obtained as above for information to be shared with Diabetes NSW & ACT. As above, Diabetes NSW & ACT will periodically check if patients who expressed interest through their GP have made a screening appointment and if not, they will be followed up by the GP or Diabetes NSW & ACT.

Patients receiving invitation letter

For patients receiving the invitation letter, the letter will explain the purpose of the study and what is involved in participation, who is conducting the research and how they have been identified. The letter will clearly state that participation is optional and voluntary and will not affect their relationship with their GP or routine care. The PIS will be enclosed.

Interested participants will be asked to contact the research team at Diabetes NSW & ACT using a toll free number to discuss the study further. Patients who call the toll free number will be asked for verbal consent to undergo telephone pre-screening, which will involve answering questions regarding medical history and recent HbA1c results. Patients who appear eligible will be encouraged to contact their GP to make a screening appointment. Patients will be asked if they agree to having their personal contact details and outcome of pre-screening if conducted entered into a recruitment database which will be password protected and securely stored on the Diabetes NSW & ACT server. Patients who do not wish to undergo telephone pre-screening or who wish to discuss the study with their GP will be asked to make an appointment with their GP.

Reception staff at GP practices will be instructed to notify Diabetes NSW & ACT when any new screening appointments for the study are booked. Diabetes NSW & ACT will update the recruitment database accordingly. Diabetes NSW & ACT will periodically follow up patients who have expressed interest but have not yet made a screening appointment. Patients will be followed up until they express that they do not wish to participate or do not wish to be contacted further.

To maximise recruitment a non-response letter will be sent to patients who have not responded to the initial invitation, one month after the original invitation. This non-response letter will explain the purpose of the study and what is involved in participation, who is conducting the research and how

they have been identified. The letter will clearly state that participation is optional and voluntary and will not affect their relationship with their GP or routine care.

3.4.1 Non respondents

The age, sex, BMI and duration of diabetes of all patients from the GP lists who are identified as satisfying the recruitment criteria for DiRECT-Aus and who are invited to participate will be recorded using an anonymised list from each GP practice. Data will be compared for patients who agree to be in the study and those who decline to participate or do not respond to the invitation letter to determine differences, if any, between those who participate and those who do not. Such analyses are important to identify any recruitment bias and determine the representativeness of the study participants.

3.5 Withdrawal of subjects

Patients who withdraw from the study after commencement of participation in the study will continue to have data collected from their routine GP visits, unless they specifically withdraw consent for this. Data on weight and HbA1c recorded in GP notes within 3 months either side of the patients planned 12 months follow-up date will be used. Data analysis will use best available follow-up weights (from routine attendances) and end of study diabetes status for subjects who discontinue the formal weight management program.

Diet intolerance or poor-compliance will be recorded: these patients will be included in ITT analysis, but excluded in 'completers analyses'. The same procedures will be used to obtain the five year follow-up data.

4. Trial procedures

Practices will deliver an VLED phase followed by structured food reintroduction and long term weight loss maintenance. Training for the practice nurses/dietitians in VLED delivery, maintenance diet program and behaviour therapy will be provided by the Boden Collaboration, University of Sydney. Training for the practice nurses/dietitians in the maintenance diet program and behaviour therapy will be provided by Diabetes NSW & ACT. To increase access in regional areas, practices may deliver the intervention via telehealth but all participants will attend their GP practice for safety monitoring and collection of study data.

4.1 Diet intervention

4.1.1 VLED phase (0-13 wks): A commercial micronutrient-replete VLED (3400 kJ (800 kcal)/day) will be provided (Optifast, Nestle Health Science) to replace normal meals along with ample fluids and low starch vegetables for 13 weeks. Participants will be required to add 1 teaspoon of olive oil daily (to assist with gall bladder contraction and thereby reduce the chance of biliary complications) and may add a psyllium husk based fibre supplement if constipation develops. Participants with a BMI >40 kg/m^2 will have an additional meal replacement product with the goal of preserving lean body mass during weight loss.

Participants will return for review one week after commencement of the VLED and at two weekly intervals thereafter until week 13 (total of 7 appointments) and the commencement of the food reintroduction stage.

To allow some flexibility for patients whose commitments vary, the VLED phase may be permitted to continue up to 21 weeks. Any patient whose BMI falls below 23 kg/m^2 before week 13 will be moved forward to the 'food reintroduction and weight maintenance' phase**.** Reasons for moving to food reintroduction before week 13 will be recorded.

Food Reintroduction phase (weeks 13-18):

A stepped transition to food-based Weight Maintenance in which the VLED will be gradually replaced with meals that contain 30% of energy from fat. During this phase participants will attend for review appointments every 2 weeks.

Week 13: step down to 2 Optifast meal replacement products per day + 1 low-fat meal/day + 2 servings of fruit, 1 serve low fat dairy and free (low starch) vegetables. Total intake 4200kJ (1000kcal)/day.

Week 15: step down to 1 Optifast meal replacement product per day + 2 low-fat meals/day + 2 servings of fruit, 2 serves low fat dairy and free vegetables. Total intake will 5000kJ (1200kcal)/day.

Week 17: 3 low-fat meals per day + 2 servings of fruit, 2-3 serves low fat dairy and free vegetables. Total intake 6000kJ (1400kcal)/day.

To allow flexibility for patients whose confidence varies, the food introduction phase will be permitted to be varied between the protocol-defined limits of 2-8 weeks before switching to full food-based weight maintenance. Reasons for moving to weight loss maintenance without completing food reintroduction will be recorded.

4.1.2 Weight Maintenance Phase (weeks 21-52):

Individuals will be provided with an individually tailored calorie prescription using a food units system to support weight stabilisation and prevent weight regain with monthly review appointments.

Maintenance Diet - low-fat healthy eating weight loss maintenance intervention [target below 30% energy from fat to a maximum of 35% energy from fat, flexibility is to optimise compliance].

Physical Activity - All subjects who are physically capable will be advised about increasing daily physical activity. As an aid, patients will be provided with a step-counter and recommended to aim to reach and maintain their individual sustainable maximum, with target of 15,000 steps/day.

4.1.3 Rescue Package for weight regain or re-emergence of diabetes

Many patients find weight maintenance difficult. Some patients relapse temporarily and gain weight rapidly and others may let things slip more gradually. Pilot studies showed the value of a sympathetic, but firm approach to relapse/regain management.

If weight regain occurs or if diabetes is found to have returned (HbA1c > 48 mmol/mol [6.5%]) at any time during the weight loss maintenance stage, 'rescue plans' for weight gain prevention will be offered:

1) **Weight regain of >2 and up to 4kg**: offer the use of Optifast to replace one main-meal per day for 4 weeks.
2) **Weight gain of >4kg or re-emergence of diabetes at any time**: offer 4 weeks VLED with fortnightly practice nurse/dietitian review and then a 2-4 weeks food re-introduction (adding 1 meal/week as before). Low-fat dietary advice and physical activity will be reinforced for weight maintenance.

4.2 Medications

4.2.1 Recording of medications

All medications will be recorded at screening on a CRF with information on start and stop date, dose, route, frequency and indication. The indication must match a medical history term or adverse event term. Participants will be prompted regarding changes to medications at each visit (including start date, stop date & dose changes). Changes will be recorded on the medications CRF**.**

4.2.2 Management of blood glucose lowering and blood pressure lowering medications

Hypoglycaemic agents will be withdrawn on commencement of the VLED. Patients will be educated on detecting deteriorating glycaemia and glycaemia will be measured at each visit using capillary blood glucose measurement. HbA1c will also be measured 3-monthly. If capillary blood glucose is >15mmol/L or HbA1c >9% or >1% change in HbA1c from previous measurement, the GP will consider re-introducing oral hypoglycaemic medication. Recommencement of medication due to elevated blood glucose will be captured in the medication log and the reason noted. Hyperglycaemia will also be recorded as an adverse event (see section 5).

Blood pressure will be measured at each visit during the first 12 months of the study. Subjects will be asked about symptoms of postural hypotension. If blood pressure is <110/60 mmHg, blood pressure medication will be reviewed and the medication will either be withdrawn or the dose reduced. If blood pressure is >140/90, prescription of blood pressure lowering medication will be considered by the GP.

All changes to blood glucose lowering and blood pressure lowering medications will be recorded on the medications CRF.

Other medications will be maintained, and their continued need and dosage reviewed as part of routine care.

4.3 Study assessments

Anthropometric and laboratory measurements will be collected throughout the study to assess eligibility, safety and efficacy. The procedure for these measurements is described below and the timing of these measurements is detailed in the study schedule (Section 4.6).

4.3.1 Height

Height will be measured to the nearest mm, using a stadiometer. Height will be measured at screening and Appt 20 (Week 52). Measurements will be taken in socks, stockings or bare feet. The patient is to stand with their back to the wall, feet together and heels touching the wall and feet flat on the ground with the head held horizontal.

4.3.2 Body weight

Body weight will be measured to the nearest 100g in light clothing without shoes using approved calibrated scales. The scale will be placed on a hard, flat surface. Weight will be measured at all appointments.

4.3.3 Waist circumference

Waist circumference will be measured at the mid-point between the iliac crest and last rib and recorded to the nearest 0.5 cm. If the rib and hip are indiscernible, girth is to be taken at the narrowest point. Measurements will be taken at the end of a normal expiration with the arms relaxed by the side and feet shoulder width apart. Two measurements will be taken and if measurements vary by >0.5cm, a third measurement is to be taken and the mean of the two nearest values recorded. Waist circumference will be measured at all appointments.

4.3.4 Hip circumference

Hip circumference will be measured at the widest point across the hips/buttocks area with patients standing tall, feet flat on the floor, arms comfortably to the side and bulky clothing removed, if possible. The tape will be placed horizontal to the floor but. Two measurements will be taken and if measurements vary by > 0.5cm a third measurement will be taken and the mean of the two nearest values recorded to the nearest 0.5cm. Hip circumference will be measured at screening and Appt 20 (Week 52)

4.3.5 Blood pressure –

Blood pressure will be measured while seated after 5 minute rest using either a stethoscope and sphygmomanometer or digital sphygmomanometer. The same type of equipment should be used for each participant for the duration of the study. The arm should be relaxed and resting on a table

or desk so that the participant is not to supporting their own arm. The appropriate cuff size must be used to ensure accurate measurements. The upper arm should be encircled by at least 80% of the total length of the cuff. The cuff is to be applied around the upper arm so that the midpoint of the length of the cuff lies over the brachial artery and mid-height of the cuff is at heart level.The bottom of the cuff should be approximately 2 cm above the elbow crease. If measuring blood pressure manually, stethoscope will be placed over brachial artery and the cuff inflated to 160mmHg (in those with no history of hypertension) or 200mmHg (for those with a history of hypertension) and slowly deflated at 2-3mmHg. The first Karotkoff sound will be recorded for systolic blood pressure and the last Karotkoff sound will be recorded for diastolic blood pressure. Three recordings will be collected 2-3 minutes apart. The same arm will be used to measure blood pressure throughout the study. Patients will be asked about symptoms of postural hypotension and blood pressure will be measured at all appointments.

4.3.6 Capillary blood glucose measurement

Capillary blood glucose measurement will be performed by the researcher or by the patient witnessed by the researcher. The glucose test strip will be prepared by inserting into a meter without touching the sensor tip and the lancing device will be primed to no more than 2.0mmprick. Prior to measurement, the hands will be washed with warm water and soap and dried thoroughly and the arm dropped to the side to encourage blood flow. The edge of the finger will be pricked and after five seconds the blood droplet will be wiped away with the second droplet used for analysis. Downward pressure may need to be applied to assist with blood flow. Capillary blood glucose will be measured at all appointments.

4.3.7 Physical activity

Physical activity will be measured by step count using a mobile phone app of the patient's preference and the Baecke Physical activity questionnaire. If the patient does not have a phone with pedometer function physical activity will measured by questionnaire alone. Average step count during two weeks will be recorded at Appt 2 (Baseline), Appt 9 (End of VLED) and Appt 20 (Week 52). The Baecke Physical Activity questionnaire will be administered electronically at the same appointments.

4.3.8 Questionnaires

Quality of Life (EQ-5D), Binge Eating and Food Acceptability Questionnaires will be administered electronically at Appt 2 (Baseline), Appt 9 (End of the VLED) and Appt 20 (Week 52). Questionnaires will be self-completed at the end of the specific appointment.

4.4 Laboratory Tests

Blood and urine laboratory tests will be performed as per Table 1 below. Laboratory services will be supplied by Douglas Hanly Moir (DHM) commercial laboratories. At each appointment where a pathology test is to be performed, the participant will be provided with a DHM request form to be completed within two days of the appointment. The dietitian/nurse will check pathology results online and ensure that all participants have completed requisite pathology tests after the appointment. The GP will review all pathology results within a week of reporting and a signed copy of the pathology results will be retained in the participant file. Screening pathology test results will be reviewed and signed by the GP prior to appointment 2/Baseline and commencement of VLED.

Table 1: laboratory tests

Time	Tests	Fasting (yes/No)
Appt 1 (Screening)	HbA1c Glucose urea & electrolytes creatinine eGFR Ca, PO4 magnesium liver function tests lipids full blood count Microalbuminuria	Yes
Appt 9 (End of VLED) Appt 13 (Week 25) Appt 16 (Week 37)	HbA1c	No
Appt 20 (Week 52	HbA1c Glucose	Yes

	urea & electrolytes creatinine eGFR lipids, Liver function tests Microalbuminuria	

4.5 Outcome measurements

• 4.5.1 Primary Outcome Measure

The study primary outcome measurements are:

- reversal of diabetes (HbA1c <6.5% (48mmol/mol), off treatment for at least 2 months at 1 year (52wks)

• 4.5.2 Secondary Outcome Measure

Change in:

- Weight
- Quality of Life measured by EQ-5D
- Impact of VLED on eating behaviours measured by Binge Eating Score,
- VLED acceptability measured by Food Acceptability Questionnaire
- Physical Activity measured by the Baecke physical activity questionnaire and where available step count

Serum Lipids

Change in medications

HbA1c

lipids

LFTs

Renal function

and questionnaire scores.

The remaining outcome measurements will be collected at baseline and repeated at Appt 9 (End of VLED) and Appt 20 (Week 52). Subject to funding, these measurements will be repeated at 2 years and then every 12 months up to 5 years.

4.6 Study schedule

Eligibility for the study and reintroduction of blood glucose lowering and blood pressure lowering medication, if required, will be determined by the GP. All other aspects of the study appointments may be delegated to the study dietitian or nurse according to local preferences and where the study dietitian and/or nurse are willing and able to perform the procedures in the GP's opinion. The GP will be available for discussion and guidance if required by the study dietitian or nurse.

Appointment (Appt) 1 (Week -2): Screening

- Review and discuss study participation
- Secure informed consent
- Assign study ID,
- Eligibility check performed by GP
- Record medical history and medications
- Measurement of: height, weight, waist & hip circumference & blood pressure
- Provide request form for fasting blood test and urine test to be completed prior to the baseline visit: HbA1c, glucose, urea & electrolytes, creatinine, eGFR, CaPO4, magnesium, liver function tests, lipids, full blood count and urine sample for albuminuria
- Perform Urine pregnancy test in women of childbearing potential
- Advise patient that two week step count monitoring will be collected at next visit

Appt 2 (Week 0) Baseline

- Collect 2 weeks record of daily steps
- Measurement of weight, waist circumference, blood pressure and capillary blood glucose (measured by blood glucose meter)
- Record any changes to medications
- Record any adverse events
- Hypoglycaemic medications discontinued. If capillary blood glucose > 15mmol/L the GP will determine what actions to be taken with hypoglycaemic medications.
- Antihypertensive medications reduced or ceased only if BP <110/60

- Commence VLED phase of intervention
- Questionnaire completion: EQ-5D, Binge Eating Disorder, Beacke Physical Activity and Food Acceptability Questionnaire
- Provide 1 week supply of Optifast and instructions for ordering Optifast

Appt 3-9 (Weeks 1-13): Continue VLED

- Measurement of weight, waist circumference & blood pressure
- Capillary blood glucose measured by blood glucose meter
- Record any changes to medications
- Record any adverse events
- Continue VLED intervention
- Check participant supply of Optifast

Appt 9 (Week 13) - Food reintroduction

- Begin structured food reintroduction (Step 1)
- Provide request form for non-fasting blood test to be completed within 2 days of appointment: HbA1c
- Measurement of weight, waist circumference & blood pressure
- Capillary blood glucose measured by blood glucose meter
- Record any changes to medications
- Record any adverse events
- Collect two week record of daily steps
- Questionnaire completion: EQ-5D, Binge Eating Disorder, Beacke Physical Activity and Food Acceptability Questionnaire

Appt 10 & 11 (Weeks 15-21) - Continue Food reintroduction

- Measurement of weight, waist circumference & blood pressure
- Capillary blood glucose measured by blood glucose meter
- Record any changes to medications
- Record any adverse events
- Continue structured food reintroduction (Step 2 & 3)

Appt 12-19 (Weeks 21-51) - Weight Maintenance

- Measurement of weight, waist circumference & blood pressure
- Capillary blood glucose measured by blood glucose meter
- Record any changes to medications
- Record any adverse events
- Behavioural weight loss maintenance intervention

Appointment 20 (Week 52) – End of Core Period

- Measurement of: height, weight, waist & hip circumference & blood pressure Provide request form for fasting blood test and urine test to be completed within 2 days of appointment: HbA1c, glucose, urea & electrolytes, eGFR, LFTs, lipids, urine for albuminuria
- Record any changes to medications
- Record any adverse events
- Collect 2 week record of daily steps
- Questionnaire completion: EQ-5D, Binge Eating Disorder, Baecke Physical Activity and Food Acceptability Questionnaire

5. ASSESSMENT OF SAFETY

Given the nature of the intervention there is very low likelihood of safety concerns. Patients will be closely monitored throughout the study with review appointments 2 weekly during the VLED and Food Reintroduction phases of the study and then monthly until week 52.

At each appointment blood pressure and postural hypotension will be monitored and antihypertensive therapy reduced, withdrawn or reintroduced if necessary, by the GP as described in section 4.2.2. Similarly, glycaemia will be monitored throughout the study as described in section 4.2.2 and appropriate treatment provided by the GP.

Any observations/results which may pose a risk to health will be discussed with the patient and their GP.

5.1 Adverse Event Monitoring

Adverse events

Adverse events are defined as any new medical event or worsening of an existing condition (including a clinically significant laboratory result) with onset after the signing of consent, whether or not the adverse event is deemed related to the study procedures. Participants will be questioned regarding the onset of any adverse events at each appointment in a non leading way (e.g how are you feeling). Participants will also be encouraged at the start of the study to spontaneously report any changes they notice while on the study. The following information will be recorded:

Adverse event term

Note: This should be 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

- Start date
- Status (resolved/recovered, resolving/recovering, not resolved/recovered, resolved/recovered with sequelae)
- End Date
- Seriousness (serious or not serious)
- Severity (mild, moderate or severe based on impact to daily functioning)
- Relationship to study treatment (definitely related, likely related, possibly related, unlikely related, not related)
- Treatment required (medication, other, none)
- Action taken with study treatment (no change in study treatment, study treatment modified, study treatment stopped

The adverse events information may be collected and recorded by the dietitian/nurse. If the dietitian/nurse is unsure regarding relatedness and action to be taken with study procedures, they must consult the GP. If the adverse event requires treatment, this must be prescribed by the GP or another appropriately qualified health care professional.

Glycaemia and blood pressure adverse events

Hyper- and hypoglycaemia and low and high blood pressure will be recorded as adverse events using the criteria below:

Hyperglycaemia
Capillary blood glucose >15 mmol/L or HbA1c >9% or >1% change in HbA1c from previous measurement

Hypoglycaemia
Capillary blood glucose < 4 mmol/L

Low blood pressure
Systolic < 110 or diastolic <60

High blood pressure
Systolic >140 or diastolic > 90

Serious Adverse Events

Serious adverse events (SAE) are those which meet any of the following criteria:

- Results in death
- Is life threatening.

Note: this refers to an event in which the participant 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.

- Hospital admission or prolonged hospital admission

Note: hospitalisation for elective treatment of a pre-existing condition that did not worsen from signing of consent is not considered an AE

- Congenital abnormality
- Permanent damage or disability

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

- Other important medical event

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 participant, or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or

malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or the abuse of study treatments

The Adverse Events form should be completed with the question regarding seriousness (serious or not serious) answered in the affirmative. Additional information including summary of the event should be recorded in the Serious Adverse Event form. It is the responsibility of the GP/dietitian/nurse to review all documentation (e.g. hospital progress notes, laboratory, and diagnostic reports) related to the event and record all relevant information in the SAE form. The event must be followed up and new information added until the event has resolved or there is no new information

Serious adverse event reporting

The Principal Investigator (PI) must be notified as soon as the GP/dietitian/nurse is aware of the SAE and within 24 hours of becoming aware. The PI must review the information in the SAE form and make a determination regarding relationship of the adverse event to the study treatment and expectedness of the adverse event. The PI must notify the sponsor (DNSW & ACT) of the SAE including assessment of causality. In the case of a Suspected Unexpected Serious Adverse Reaction (SUSAR) the HREC must also be notified as soon as the SUSAR is reported and within 24 hours of becoming aware. If the PI needs more information or wishes to discuss the event further the GP/dietitian/nurse must be available to discuss the event with the PI. Clinical oversight will be provided by the PI and where deemed necessary the participant and GP will be provided follow up correspondence.

Other safety reporting

In addition to any local SUSARs/ Unexpected and Related Serious Adverse Event (URSAEs) arising from the site, The Research Governance Office (RGO) is to receive all significant safety issues (SSIs) as defined below and the annual Safety Report. These will be submitted by the investigator to the local RGO on the relevant Notification forms.

SLHD RPA - Research Ethics and Governance Office - Safety Reporting

Summary of safety notifications to the HREC and RGO (therapeutic goods trials)

Type of event	Who reports	To whom	When	How
Significant Safety Issue (SSI) implemented as an Urgent Safety Measure (USM)	Sponsor	The reviewing HREC (and all investigators participating in the study).	As soon as possible and no later than 72 hours of the sponsor becoming aware of the USM	SSI Notification Form or sponsor's template
Significant Safety Issue (SSI) not implemented as an Urgent Safety Measure (USM)	Sponsor	The reviewing HREC (and all investigators participating in the study).	Within 15 days of the sponsor becoming aware of the SSI	SSI Notification Form or sponsor's template
All Significant Safety Issues (SSIs)	Principal Investigator	The Research Governance Officer (RGO) for the site where the event occurred	As soon as possible and no later than 72 hours of the PI becoming aware of the SSI	SSI Notification Form or sponsor's template
Suspected Unexpected Serious Adverse Reaction (SUSAR) events and Unanticipated Serious Adverse Device Effects (USADEs) occurring at the site	Principal Investigator	The Research Governance Officer (RGO) for the site where the event occurred	Within 72 hours of the PI becoming aware of the event	SUSAR/USADE/URSAE Notification Form
Investigator's Brochure/Addenda	Sponsor	The reviewing HREC (and all investigators participating in the study).	As and when updates are generated	Submitted with a cover sheet or as part of an annual progress/annual safety report
Annual Safety Report	Coordinating Principal Investigator or Sponsor	The reviewing HREC	Within annual progress report sent to the HREC or aligned with the safety reporting cycles of global companies	Annual Progress Report or sponsor's template

Note: For trials where Sydney Local Health District is the sponsor, the sponsor functions should be delegated to the Co-ordinating Principal Investigator.

6. STATISTICS AND DATA ANALYSIS

Statistical analyses and data management will be conducted by specialist staff, in accordance with a pre-specified Statistical Analysis Plan, at the Boden Collaboration, University of Sydney.

The Boden Collaboration will build a database (in RedCap) for the DiRECT study. All data will be entered by the 5 x dietitians from the 5 x PHNs. They will be given unique password protected logins. The Boden Collaboration will oversee the data collection and integrity.

Through specific data identifiers, the data from the DiRECT study can then be linked with the Lumos data linkage project administered by the NSW Government, Department of Health.

The main objective of the study is to determine if a VLED and structured weight management program can be instituted as effectively in primary care in Australia as in the original UK DiRECT trial.

Data will be analysed primarily on an intention-to-treat (ITT) basis with last observation carried forward data on weight and diabetes status for subjects who discontinue the formal weight management program. A 'completers analyses' of participants completing the study will also be performed. Trial documentation and data will be retained for at least 15 years after study completion.

7.0 STUDY CLOSURE / DEFINITION OF END OF TRIAL

The intervention and follow up period for each trial participant will last for 12 months with the possibility of extending to a total of 5 years if additional funding is secured. The initial 12 month study period will continue for a further 6 months to allow final data analysis, write up of final report and preparation of publications.

8. DATA HANDLING

8.1 Case Report Forms

A case report form (CRF) will be used to collect study data. The CRF will be developed by the Boden Collaboration in conjunction with Diabetes NSW/ACT with input from study practices. Remote Data Capture (REDCap) will be used for data entry and storage. Access to the pooled CRF data will be restricted, with only authorised site-specific personnel able to make entries or amendments to their patients' data.

Data will be validated at the point of entry into the CRF and at regular intervals during the study. Data discrepancies will be flagged to the study site and any data changes will be recorded in order to maintain a complete audit trail (reason for change, date change made, who made change).

8.2 Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records), all original signed informed consent forms, serious adverse event forms, source documents, and detailed records of treatment disposition in accordance with Ethic Committee requirements.

All data received via study secure web portal will be stored on a secure database and any original files received from third parties will be stored in their received format in secure file storage. Data will be held for a minimum of 15 years

9. STUDY MONITORING/AUDITING

The Governance and Implementation Group (GIG) will oversee the study. Members of the GIG include:

1. DNSW & ACT – Narelle Sohier (Product Program and Development Manager), Kate Gudorf (Program Lead)
2. Boden Collaboration, University of Sydney / Evaluation partner: Professor Stephen Colagiuri, A/Professor Tania Markovic
3. Primary Health Networks
   Northern Sydney – Cynthia Stanton
   South West Sydney – Vitor Rocha
   Western Sydney – Kieren Morgan
   North Coast – Monika Wheeler
   Western NSW – Michele Pitt
4. NSW Agency for Clinical Innovation – Marina Sarkis
5. Ministry of Health – Patricia Correll
6. Consumer representatives – Suellyn Harrison
7. GP representative Dr Chee Khoo and Dr Chaminda de Silva

The GIG will be responsible for the overall implementation of the study, safety and budget, and will meet at least 3 monthly.

10. PROTOCOL AMENDMENTS

Any change in the study protocol will require an amendment. Variations in the durations of the treatment phases, within the limits described in Section 4 above, will not require an amendment. Any proposed protocol amendments will be initiated by the CI and submitted to the ethics committee and sponsor. The CI will liaise with study sponsor to determine whether an amendment is non-substantial or substantial. All amended versions of the protocol will be signed by the CI and Sponsor representative. Before the amended protocol can be implemented favourable opinion/approval must be sought from the Ethics Committee.

11. ETHICAL CONSIDERATIONS

The study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and its revisions (Tokyo [1975], Venice [1983], Hong Kong [1989], South Africa [1996] and Edinburgh [2000]).

Favourable ethical opinion will be sought from an appropriate Ethics Committee before patients are entered into this study. Patients will only be allowed to enter the study once they have provided written informed consent. The CI will be responsible for updating the Ethics committee of any new information related to the study.

12. INSURANCE AND INDEMNITY

In SNHN Services Agreement with Diabetes NSW/ACT

The Liability Minimum Limit $20,000,000 for any one occurrence in the annual aggregate

Professional Indemnity Minimum Limit $20,000,000 for any one occurrence in the annual aggregate

13. FUNDING

Primary Health Networks to contribute $114,000 per PHN (5) = $570,000

Diabetes NSW/ACT $188,991 plus GST of $18,899

14. ANNUAL REPORTS

Annual reports will be submitted to the ethics committee with the first submitted one year after the date that all trial related approvals are in place.

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APPENDIX A: DiRECT-Aus SCHEDULE OF ASSESSMENTS

			Total Diet Replacement Phase							Food Reintroduction Phase		
Appointment		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Week		**-2**	**0**	**1**	**3**	**5**	**7**	**9**	**11**	**13**	**15**	**17**
Study Procedure	**Responsibility**											
Review & discuss study participation	GP/nurse/dietitian	√										
Obtain Informed Consent	GP/nurse/dietitian	√										
Review Inclusion/Exclusion Criteria	GP	√										
Collect medical history	GP/nurse/dietitian	√										
Record medications	GP/nurse/dietitian	√	√	√	√	√	√	√	√	√	√	√
Height	Nurse/dietitian	√										
Weight	Nurse/dietitian	√	√	√	√	√	√	√	√	√	√	√
Waist Circumference	Nurse/dietitian	√	√	√	√	√	√	√	√	√	√	√
Hip Circumference	Nurse/dietitian	√										
Blood Pressure	Nurse/dietitian	√	√	√[a]	√[a]	√[a]	√[a]	√[a]	√[a]	√[a]	√[a]	√[a]
Blood & urine samples	Pathology	√										
Hypoglycemic agents discontinued	Nurse/dietitian[b]		√									
Capillary blood glucose	Nurse/dietitian		√	√[c]	√[c]	√[c]	√[c]	√[c]	√[c]	√[c]	√[c]	√[c]
Repeat HbA1c	Pathology									√		
EQ-5D questionnaire	Participant		√							√		
Binge Eating Questionnaire	Participant		√							√		
Food Acceptability Questionnaire	Participant		√							√		
Baecke Physical Activity	Participant		√							√		
Record steps previous two weeks	Nurse/dietitian		√[c]							√		
Urine pregnancy test	Nurse/dietitian	√										
Adverse events monitoring	Nurse/dietitian		√	√	√	√	√	√	√	√	√	√

Schedule of Assessments (continued)

	Weight Maintenance Phase (Year 1)								
Visit	**12**	**13**	**1**	**15**	**16**	**17**	**18**	**19**	**20**
Week	**21**	**25**	**29**	**33**	**37**	**41**	**45**	**49**	**0+52**
Study Procedure									
Record medications	√	√	√	√	√	√	√	√	√
Height									√
Weight	√	√	√	√	√	√	√	√	√
Waist Circumference	√	√	√	√	√	√	√	√	√
Hip Circumference									√
Blood Pressure	√[a]	√[a]	√[a]	√[a]	√[a]	√[a]	√[a]	√[a]	√[a]
Blood & urine samples									√
Capillary blood glucose	√[c]	√[c]	√[c]	√[c]	√[c]	√[c]	√[c]	√[c]	√[c]
HbA1c		√			√				√
EQ-5D questionnaire									√
Binge eating scale									√
Food Acceptability Quest.									√
Baecke Physical Activity									√
Record steps previous two weeks									√
Urine pregnancy test									
Adverse event monitoring	√	√	√	√	√	√	√	√	√

[a] Blood pressure medication reduced if BP <110/60 mmHg or reintroduced if BP subsequently >140/90 mmHg

[b] GP to make medication adjustment if capillary blood glucose > 15mmol/L

[c] hypoglycaemic agents reintroduced if capillary blood glucose >15 mmnol/L or HbA1c >9% or >1% change from last measurement