

**Trial Title:** A short-term ketogenic diet combined with short-term fasting before chemotherapy in treating patients with acute leukaemia: a randomised controlled trial.

**Internal Reference Number / Short title:** An sFKD diet and chemoprotection

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There are no conflicts of interest to declare

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# KEY TRIAL CONTACTS

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| **Funder(s)** | This research has been funded by an NHMRC Investigator Grant Scheme awarded to Professor Luigi Fontana and a grant from the Philip Bushell Foundation |
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| **Committee** | Data Safety Monitoring Board: Professor Ralph Nanan, Associate Professor Emily Hibbert, Associate Professor Stuart Lane |

# LAY SUMMARY

About 50% of Australians will develop cancer during their lifetime and most will be treated with chemotherapy. Cancer treatment with chemotherapy is necessary but associated with major DNA, cellular and organ damage. Despite a marked improvement in 5-yr cancer-free survival, the cellular and organ damage that results from aggressive chemotherapy has resulted in 10% of survivors developing a second cancer in the following 30 years. Currently, there are no strategies for maintaining normal function and genomic integrity of cells and tissues during chemotherapy treatment. Studies in animals show that short-term fasting can protect normal cells from chemotherapy toxicity. In addition, a ketogenic diet in human subjects mimics the hormonal changes of short-term fasting. However, human studies of the effects of these hormonal changes on protecting normal cells from chemotherapy are lacking. The man aim of this study is to compare the effect of short-term fasting combined with a ketogenic (KD) diet, given immediately before and during chemotherapy, on protecting normal cells in patients treated for acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL). Damage to normal cells in the gut and the blood increases the risk of severe infection and death. The main aim of the study is to compare the number of these complications in patients who receive the study diet to those who receive a normal diet. We have chosen to study AML and ALL because bone marrow biopsies are taken before starting chemotherapy treatment and following each cycle of treatment. Most of the cells in the bone marrow after each of the 2-5 treatments will be normal blood cells and we will compare the amount of damage in these cells in patients who receive the study diet to those who do not receive the diet.

# SYNOPSIS

|  |  |
| --- | --- |
| Trial Title | A short-term ketogenic diet combined with short-term fasting before chemotherapy in treating patients with acute leukaemia: a randomised controlled trial. |
| Trial registration | The Universal Trial Number (UTN): U1111-1251-0734 |
| Sponsor  | Nepean Blue Mountains Local Health District and Western Local Health District |
| Funder  | Professor Luigi Fontana, NHMRC Investigator Grant Scheme |
| Clinical Phase  | Phase 2 |
| Trial Design | Multi-centre randomised controlled trial |
| Trial Participants | Patients aged 18 years and older with newly diagnosed acute myeloid or lymphoblastic leukaemia |
| Sample Size | 134 patients (67 in each arm) |
| Planned Trial Period  | May 2022 – May 2027 |
| Planned Recruitment period  | May 2022 – May 2025 |
| **Aims** | **Objectives** | **Outcome Measures** | **Timepoint(s)**  |
| **Primary** | Compare the incidence of major infection in the short-term ketogenic with 24-hour fasting before and during chemotherapy (sFKD) group to the standard diet group. | The incidence of major infection [pneumonia, bacteraemia or fungaemia causing a blood stream infection (primary BSI), or pneumonia accompanied by bacteraemia or fungaemia (secondary BSI)] will be compared between the 2 groups. A diagnosis of pneumonia requires a compatible chest x-ray or computed tomography scan. A diagnosis of bacteraemia or fungaemia will be made on a positive blood culture. A diagnosis of bacteraemia as a result of frequent contaminants such as coagulase-negative Staphylococcus requires two positive blood cultures.  | This outcome will be evaluated every 28 days from baseline (Day -5) until completion of chemotherapy and every 3 months thereafter until final follow-up at 24 months. |
| **Secondary** | 1. Neutrophil recovery following induction and consolidation therapy for AML and ALL | Time from commencement of chemotherapy (day 1) to absolute neutrophil count ≥ 0.5 x 109/L for 3 consecutive days for each cycle of chemotherapy. | Daily full blood count with absolute neutrophil count greater than or equal to 0.5 x 109/L for 3 consecutive days for each chemotherapy cycle. |
| 2. Evaluate the effect on the toxicity profile of chemotherapy | Assess oral mucositis using the National Cancer Institute's Common Terminology Criteria for Adverse Events. | Daily for each cycle of chemotherapy and at 3 monthly periods thereafter until final follow-up at 24 months. |
|  | Assess diarrhoea using the National Cancer Institute's Common Terminology Criteria for Adverse Events. | This outcome will be evaluated from commencing the diet until final follow-up at 24 months after completing final cycle of chemotherapy. |
| 3. Assess the effect on circulating signalling molecules. | Investigate changes in plasma glucose. | Daily from commencement of ketogenic diet (5 days before chemotherapy) to day 28 or discharge from hospital, whichever is later. |
|  | Investigate changes in plasma insulin. | Daily from commencement of ketogenic diet (5 days before chemotherapy) to day 28 or discharge from hospital, whichever is later. |
|  | Investigate changes in plasma insulin-like growth factor 1 (IGF-1). | Daily from commencement of ketogenic diet (5 days before chemotherapy) to day 28 or discharge from hospital, whichever is later. |
|  | Investigate changes in plasma IGF-1 binding proteins. | Daily from commencement of ketogenic diet (5 days before chemotherapy) to day 28 or discharge from hospital, whichever is later. |
| 4. Assess the effect on molecular markers of cellular damage. | Quantification of genotoxic stress measured at single cell level. | Daily blood tests from commencing chemotherapy until discharge. Bone marrow biopsies as per standard of care, before and after the first cycle of chemotherapy and after each cycle of-chemotherapy thereafter. |
|  | Analysis of chromosome instability | Daily blood tests from commencing chemotherapy until discharge. Bone marrow biopsies as per standard of care, before and after the first cycle of chemotherapy and after each cycle of-chemotherapy thereafter. |
|  | Somatic mutation rate. | Daily blood tests from commencing chemotherapy until discharge. Bone marrow biopsies as per standard of care, before and after the first cycle of chemotherapy and after each cycle of-chemotherapy thereafter. |
|  | Quantification of DNA damage response signalling proteins. | Daily blood tests from commencing chemotherapy until discharge. Bone marrow biopsies as per standard of care, before and after the first cycle of chemotherapy and after each cycle of-chemotherapy thereafter. Representative timepoints for collection of buccal mucosa swabs and hair follicles if available. |
| Assess the effect on molecular markers of cell senescence. | Mass spectrometry assessment of senescence-associated secretory phenotype. qPCR assessment of senescence-associated markers. | Daily blood tests from commencing chemotherapy until discharge. Bone marrow biopsies as per standard of care, before and after the first cycle of chemotherapy and after each cycle of-chemotherapy thereafter. Standard punch biopsy to collect skin and subcutaneous fat, at baseline and at the time of haematological recovery. |
| 5. Assess the effect on cardiac toxicity. | Cardiac troponin I measurements. | Daily blood tests from commencing each cycle of chemotherapy until discharge. |
| . | Changes in cardiac function as measured by echocardiography.  | Baseline before chemotherapy and 24 months after completion of chemotherapy. |
| 6. Assess changes in the mononuclear cell transcriptome, metabolomics, proteomics, and gut microbiome | Assess changes in single-cell transcriptome (in mononuclear cells).  | Daily blood sample from commencing diet to day 28 or discharge, whichever is later for each cycle of chemotherapy. |
|  |  | Assess changes in the mononuclear cell proteome. | Daily blood sample from commencing diet to day 28 or discharge, whichever is later for each cycle of chemotherapy. |
|  |  | Assess changes in the metabolomic “fingerprint” using plasma metabolomics analysis | Daily plasma from commencing diet to day 28 or discharge, whichever is later for each cycle of chemotherapy. |
|  | . | Assess changes in the gut microbiome. | Daily stool sample from commencing diet to day 28 or discharge, whichever is later for each cycle of chemotherapy. |
|  |  | Assess changes in gut permeability. | Representative days at baseline, during chemotherapy and post chemotherapy. |
|  |  | Analysis of mitochondrial function: | T cells will be harvested from peripheral blood. Seahorse XF Analyzers will be used to measure oxygen consumption rate and extracellular acidification rate of live cells that report key cellular functions such as mitochondrial respiration and glycolysis. These measurements will provide a systems-level analysis of cellular metabolic function in cultured T cells and ex-vivo samples. |
|  | 7. Food acceptability |  | Measured daily using validated questionnaires whilst on both the intervention and standard hospital diet. |
|  | 8. Food craving |  | Measured using validated questionnaires whilst on the diet intervention and standard hospital diet |
|  | 9. Death |  | This outcome will be evaluated from baseline (D-5) until final follow-up at 24 months. |
| **Intervention** | Classic ketogenic diet (90% energy from fat, 5-7% from protein, and 3-5% from carbohydrate) started between 3-6 days before commencing chemotherapy and during administration of chemotherapy combined with a 16-hour fast before administration of the first dose of chemotherapy. The diet is administered during induction and consolidation phases of chemotherapy (Appendix A). |
| **Comparator**  | Control participants will receive meals according to The Nutrition standards for adult inpatients in NSW hospitals (2011) https://www.aci.health.nsw.gov.au/resources/nutrition/nutrition-food-in-hospitals/nutrition-standards-diets . Control participants will not fast. |

# ABBREVIATIONS

|  |  |
| --- | --- |
| AE | Adverse event |
| AML | Acute myeloid leukaemia |
| ALL | Acute lymphoblastic leukaemia |
| AR  | Adverse reaction |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CT | Clinical Trials |
| CTRG | Clinical Trials and Research Governance |
| DMSC | Data Monitoring and Safety Board |
| DSR | Differential stress response |
| DSUR | Development Safety Update Report |
| GCP | Good Clinical Practice |
| GP | General Practitioner |
| HDC | High dose chemotherapy |
| IB | Investigators Brochure |
| ICF | Informed Consent Form |
| IRB | Independent Review Board |
| RES |  Research Ethics Service  |
| PI | Principal Investigator |
| PIL | Participant/ Patient Information Leaflet |
| REC | Research Ethics Committee |
| SAE | Serious Adverse Event |
| SAR | Serious Adverse Reaction |
| SDV | Source Data Verification |
| sFKD | short-term ketogenic diet combined with short-term fasting  |
| SOP | Standard Operating Procedure |
| SASP | Senescence-associated secretory phenotype |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| TMF | Trial Master File |

# BACKGROUND AND RATIONALE

**HYPOTHESIS OF THE PROPOSAL**

Recent work from our group and others in model systems has shown that short-term fasting is highly effective in differentially protecting normal, but not cancer, mammalian cells, against **chemotherapy-induced toxicity** [1, 2]. This protective **differential stress resistance** (DSR) response is mediated mainly by inhibition of **Akt/mTOR** and stimulation of **FOXO signalling as a result of decreased insulin and IGF-1 binding to the IGF-1 receptor** [1, 3, 4]. Short-term fasting and ketogenic (KD) diets, reduce plasma insulin and IGF-1 in healthy humans, and are safe in cancer patients as an adjuvant to chemotherapy. We hypothesise that this diet-induced reduction in insulin/IGF-1 signalling will protect the normal bone marrow and other tissues from acute and chronic cellular damage induced by high-dose chemotherapy (HDC) in AML and ALL patients.

**BACKGROUND AND SIGNIFICANCE**

**The burden of acute myeloid and lymphoblastic leukaemia**. Each year, approximately 1,000 Australians are diagnosed with AML and 400 with ALL, and the lifetime risk of diagnosis is ~ 1 in 200 (Australian Institute of Health & Welfare). Currently, the most effective initial therapeutic option is an anthracycline drug (idarubicin or daunorubicin) combined with cytarabine (7+3 regimen) [5]. The median age of patients with AML is ~ 70 years, and treatment outcome declines progressively with increasing age [6]. Many patients experience variable treatment failures, side effects and relapse; and standard practice has changed very little over the past 30 years [5]. In general, older patients treated with intensive high dose chemotherapy (HDC) have better outcomes compared to those receiving palliative treatment [6]. However, the use of HDC is often compromised by increased toxic side effects caused by the therapy. Most treatment regimens for ALL are centred on vincristine, corticosteroids, and anthracycline (daunorubicin, doxorubicin, idarubicin), with or without cyclophosphamide or cytarabine. There are several protocols that combine multiple cycles of induction cycles, with post-remission consolidation and maintenance therapy for 2 – 3 years. If patients have Philadelphia chromosome positive ALL, in addition they will receive a specific tyrosine kinase inhibitor such as imatinib.

**The challenge of toxicities from chemotherapy.**

The lifetime risk of developing a malignant cancer is ~40% in men and women. Treatment with chemo- and radiotherapy is necessary but is associated with major cellular and organ damage. Reducing acute and chronic toxicity, but at the same time improving disease remission and cure rates is a major challenge. Animal data show that dietary interventions (e.g. KD and fasting) that lower insulin, IGF-1 and other growth factors protect normal cells from chemotherapy toxicity. However, nothing is known in humans. The proposed research has great potential to impact human health by reducing toxicity of chemotherapy. The future development of optimal KD diet programs will generate commercially valuable intellectual property as these interventions become standard of care for chemo- and radio-therapy regimens in acute leukaemia, and other haematological malignancies and solid tumours. Following the successful completion of the study, there is potential for future research opportunities in optimising the composition of chemo-protective diets, fasting-mimicking products, probiotics and research into specific markers of cellular damage. Furthermore, in line with the growing interest in personalised medicine, future studies researching the genetic composition may be able to identify and prognosticate those in which the diet regimen will be able to provide the greatest protective benefit.

Several studies suggest more intensive anthracycline and/or cytarabine dosing is therapeutically beneficial during AML treatment. However, despite improved long-term outcomes, toxicities have forced reductions in both anthracycline and cytarabine doses [7, 8]. This is also the case for ALL patients [9]. For improved disease remission and cure rates, dose-limiting toxicity is a major challenge for both dose-intensification in younger patients, and delivery of standard doses to older patients with acute leukaemia. Furthermore, the prevalence of chronic toxicities is increasing as the number of long-term cancer survivors increases, which in the United States is expected to be > 20.3 million by 2026 [10].

***Haematologic toxicity*:** Acutely, cytarabine and idarubicin cause bone marrow failure, leucopenia, neutropenia, thrombocytopenia, and anaemia. Cancer survivors are at high risk of developing second malignancies [11], and patients who receive chemotherapy are at ~ 5-fold higher risk for developing treatment-related AML compared to the general population [12]. Patients who receive topoisomerase II inhibitors, such as anthracyclines, can develop leukaemia within 5 years [13]. The incidence of leukaemia also correlates with the dose of chemotherapy [14]. In addition to treatment-related AML and myelodysplasia, there is a 17% increase in solid cancers in patients with AML compared to the general population [15]. There is also a significant increase in oral cavity and pharyngeal, lung and breast cancer in young adults, and gastrointestinal cancer in older adults [15, 16].

***Cardiotoxicity*:** Anthracycline drugs can cause cardiotoxicity, particularly in patients with pre-existing cardiac conditions. These patients are 5 times more likely to develop clinical cardiotoxicity and are at 5 times higher risk of sudden death compared to those who do not receive anthracyclines [17, 18]. Older patients are at yet higher risk for developing cardiotoxicity, and for each 10-year increase in age, the risk of developing congestive heart disease is doubled [18].

**BACKGROUND SPECIFIC TO THE PROPOSAL**

***Differential stress response.*** Data from animal studies indicate that induction of a DSR has the potential to maximise chemotherapy toxicity to cancer cells while protecting normal cells. A fasting-dependent DSR in neuroblastoma (NXS2)-bearing mice increased resistance of normal cells, particularly haematopoietic cells, to the topoisomerase II inhibitor etoposide, but not to cancer cells [19].

Self-sufficiency for growth signals is one of the major hallmarks of cancer cells [20], because these cells can generally proliferate in the absence of growth factors due in part to hyperactivation of one or several components of insulin and IGF-1 receptor (IR and IGF1R) signalling through Ras/Akt, and mammalian target of rapamycin (mTOR) pathways [21, 22]. Inhibition of Akt following mTORC2 depletion activates the forkhead box protein O1 (FOXO1) and FOXO3a transcription factors that control the expression of genes involved in DNA repair, oxidative stress resistance, autophagy, cell-cycle arrest and apoptosis. In contrast, inhibiting the transcriptional functions of FOXOs by Akt contributes to cell survival, growth and proliferation (Fig. 1) [23-25]. A sFKD would counteract this signalling cascade by normalizing glucose and insulin levels [26, 27].

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***Diet and IGF-1***. Nutritional status, specifically protein and energy intake, regulates somatomedin (IGF-1, vitronectin and IGF-2) production in humans [28]. IGF-1 levels decrease by 70% within 2-3 days of fasting and recover after 5 days of a normal diet [28]. KDs mimic the metabolic effects of fasting by inducing a physiological rise in the two main circulating ketone bodies, acetoacetate and beta-hydroxybutyrate (BHB). A 7-day KD (2000-2500 kcal/day primarily as lipids, 0.8 g protein/kg body weight/day, < 40 g carbohydrate/day), reduces serum IGF-1 levels by approximately 50% [29]. Cancer cells predominantly utilize glycolysis instead of oxidative phosphorylation to produce ATP, and some cancers lack the ability to metabolize ketone bodies [30, 31]. Thus, the rationale for providing a fat rich, low-carbohydrate diet is to reduce circulating glucose, insulin and IGF-1 levels, and produce ketones that cancer cells cannot use for energy, while normal cells adapt their metabolism to use ketone bodies and survive.

***Cellular senescence.*** Cellular senescence is a complex stress response that entails an essentially irreversible arrest of cell proliferation, resistance to cell death, and development of a multi-component senescence-associated secretory phenotype (SASP) that can drive hyperplastic and neoplastic pathologies [32, 33]. Senescent cells are generated by many types of cancer chemotherapies and SASP factors, particularly the pro-inflammatory arm of the SASP, can potentially fuel many aspects of cancer progression [34].Dampening mTOR activity, which can be achieved by dietary restriction [34], can modify the effects of senescent cells on the tissue and systemic environment [35].

***Mitochondrial damage.***Immune-based therapies are now more commonly used as a supplement to conventional chemotherapy or in the setting of relapsed disease. However, chemotherapy-exposed T cells have persistent dysfunction that affects ex vivo adoptive cell therapy techniques and potentially clinical efficacy. To explore implications for future adoptive cell therapies, we will analyse mitochondrial function in chemotherapy exposed T cells in patients receiving a sfKD compared to standard diet.

# OBJECTIVES AND OUTCOME MEASURES

|  |  |  |
| --- | --- | --- |
| **Primary Objective** | **Primary Outcome Measures** | **Timepoint(s)**  |
| Compare the incidence of major infection and death in the sFKD group compared to the standard diet group. | The incidence of major infection (pneumonia, bacteraemia, or fungaemia causing a blood stream infection (primary BSI), or pneumonia accompanied by bacteraemia or fungaemia (secondary BSI) will be compared between the 2 groups. A diagnosis of pneumonia requires a compatible chest x-ray or computed tomography scan. A diagnosis of bacteraemia as a result of frequent contaminants such as coagulase-negative Staphylococcus requires two positive blood cultures.  | This outcome will be evaluated every 28 days from day -5 until chemotherapy finishes and every 3 months thereafter until final follow-up at 24 months. |
| **Secondary Objectives** | **Secondary Outcome Measures** | **Time point(s)**  |
| 1. Assess the effect of a short-term ketogenic diet combined with short-term fasting (sFKD) on neutrophil recovery following induction and consolidation therapy for AML and ALL | Time from commencement of chemotherapy (day 1) to absolute neutrophil count ≥ 0.5 x 109/L for 3 consecutive days for each cycle of chemotherapy. | Daily full blood count with absolute neutrophil count greater than or equal to 0.5 x 109/L for 3 consecutive days for each chemotherapy cycle. |
| 2. Evaluate the effect on the toxicity profile of chemotherapy | Assess oral mucositis using the National Cancer Institute's Common Terminology Criteria for Adverse Events. | Daily for each cycle of chemotherapy and at 3 monthly periods thereafter until final follow-up at 24 months. |
|  | Assess diarrhoea using the National Cancer Institute's Common Terminology Criteria for Adverse Events. | This outcome will be evaluated from commencing the diet until final follow-up at 24 months after completing final cycle of chemotherapy . |
| 3. Assess the effect on circulating signalling molecules. | Investigate changes in plasma glucose. | Daily from commencement of ketogenic diet (5 days before chemotherapy) to day 28 or discharge from hospital, whichever is later. |
|  | Investigate changes in plasma insulin. | Daily from commencement of ketogenic diet (5 days before chemotherapy) to day 28 or discharge from hospital, whichever is later. |
|  | Investigate changes in plasma insulin-like growth factor 1 (IGF-1). | Daily from commencement of ketogenic diet (5 days before chemotherapy) to day 28 or discharge from hospital, whichever is later. |
|  | Investigate changes in plasma IGF-1 binding proteins. | Daily from commencement of ketogenic diet (5 days before chemotherapy) to day 28 or discharge from hospital, whichever is later. |
| 4. Assess the effect on molecular markers of cellular damage and cell senescence. | Quantification of genotoxic stress measured at a single cell levels. | Daily blood tests from commencing chemotherapy until discharge. Bone marrow biopsies as per standard of care, before and after the first cycle of chemotherapy and after each cycle of-chemotherapy thereafter. |
|  | Analysis of chromosome instability | Daily blood tests from commencing chemotherapy until discharge. Bone marrow biopsies as per standard of care, before and after the first cycle of chemotherapy and after each cycle of-chemotherapy thereafter. |
|  | Somatic mutation rate. | Daily blood tests from commencing chemotherapy until discharge. Bone marrow biopsies as per standard of care, before and after the first cycle of chemotherapy and after each cycle of-chemotherapy thereafter. |
|  | Quantification of DNA damage response signalling proteins. | Daily blood tests from commencing chemotherapy until discharge. Bone marrow biopsies as per standard of care, before and after the first cycle of chemotherapy and after each cycle of-chemotherapy thereafter. Representative timepoints for collection of buccal mucosa swabs and hair follicles if available. |
| Assess the effect on molecular markers of cell senescence. | Mass spectrometry assessment of senescence-associated secretory phenotype. qPCR assessment of senescence-associated markers. | Daily blood tests from commencing chemotherapy until discharge. Bone marrow biopsies as per standard of care, before and after the first cycle of chemotherapy and after each cycle of-chemotherapy thereafter. Standard punch biopsy to collect skin and subcutaneous fat, at baseline and at time of haematological recovery. |
| 5. Assess the effect on cardiac toxicity of anthracycline therapy for AML and ALL | Cardiac troponin I measurements.  | Daily blood tests from commencing each cycle of chemotherapy until discharge. |
|  | Changes in cardiac function as measured by echocardiography.  | Baseline before chemotherapy and 24 months after completion of chemotherapy. |
| 6. Assess changes in transcriptomic, metabolomics, proteomic and gut microbiome profile | Assess changes in single-cell transcriptome (in mononuclear cells).  | Daily blood sample from commencing diet to day 28 or discharge, whichever is later for each cycle of chemotherapy. |
|  | Assess changes in the mononuclear cell proteome. | Daily blood sample from commencing diet to day 28 or discharge, whichever is later for each cycle of chemotherapy. |
|  | Assess changes in the metabolomic “fingerprint” using plasma metabolomics analysis | Daily plasma from commencing diet to day 28 or discharge, whichever is later for each cycle of chemotherapy. |
|  | Assess changes in the gut microbiome. | Daily stool sample from commencing diet to day 28 or discharge, whichever is later for each cycle of chemotherapy. |
|  | Assess changes in gut permeability. | Representative days at baseline, during chemotherapy and post chemotherapy. |
|  | Analysis of mitochondrial function: | T cells will be harvested from peripheral blood. Seahorse XF Analyzers will be used to measure oxygen consumption rate and extracellular acidification rate of live cells that report key cellular functions such as mitochondrial respiration and glycolysis. These measurements will provide a systems-level analysis of cellular metabolic function in cultured T cells and ex-vivo samples. |
| 7. Food acceptability |  | Measured daily using validated questionnaires whilst on both the intervention and standard hospital diet. |
| 8. Food craving |  | Measured using validated questionnaires whilst on the diet intervention and standard hospital diet |
| 9. Death |  | This outcome will be evaluated from day -5 until final follow-up at 24 months. |

# TRIAL DESIGN

A multi-centre randomised controlled open labelled study of the efficacy of a sFKD diet compared to a standard diet in patients treated with chemotherapy for AML and ALL.

The trial settings are Nepean and Westmead Hospital.

The isocaloric KD (Section 10 and Appendix A for detailed description) will consist of 90% energy from fat, 5-7% from protein, and 3-5% from carbohydrate. The ketogenic diet intervention will be administered 3 times per day (breakfast, lunch, and dinner) beginning 2-6 days before scheduled chemotherapy. The number of days prior to chemotherapy is variable because the start of chemotherapy depends on whether the patient has been admitted, has a central line in place, has completed all required pre-chemotherapy testing, and is clear of any infections or secondary conditions that delay chemotherapy. Generally, most patients will consume the ketogenic diet for 4-5 days. A minimum of 48 h is generally necessary to enter ketosis. The subject will fast, that is eat and drink nothing except water for 16 hours before scheduled chemotherapy. The ketogenic diet will then be continued 3 times per day during chemotherapy (7 days for the first cycle and, optionally,5 days for subsequent cycles). The total duration of the dietary intervention is 9-15 days for the first cycle of treatment and up to 10 days for subsequent cycles. For participants 60 years of age and younger, a further 2-4 cycles of therapy will be administered, and for those over 60, a further 1-2 cycles will be administered. Each cycle of treatment is administered at a frequency of approximately 28 days. In patients deemed unfit for intensive chemotherapy, treatment will be venetoclax and azacytidine, consisting of continuous oral venetoclax combined with a 7-day course of daily subcutaneous azacytidine repeated every 28 days until disease progression or unacceptable toxicity. The usual treatment for ALL patients is hyper-CVAD, with part A receiving 4 days chemotherapy and Part B, 3 days, during which the KD will be given. Administration of the KD will be adjusted for other ALL regimens.

Upon randomisation to the intervention group, the study team will notify the dietetics department to start the patient in the ketogenic diet for the induction chemotherapy cycle. The hospital will administer the ketogenic diet that consist of a fixed menu including several different breakfast meals (e.g. scrambled eggs and bacon, avocado, and Hollandaise sauce) and several lunch/dinner meals (e.g. Keto mashed potato, poached fish and hollandaise sauce, avocado pulp). To increase meal variety and compliance, the study team will provide additional keto snacks to the patient (roasted nuts, keto chocolate, etc.), approved by the dietician. A list of approved keto snacks and recipes will be provided to the patient and their relatives in case they wish to bring food from home that is compliant with the intervention diet. The list and recipes will comply with the Food Safety protocols established by the hospital dietetics department. If food intake is insufficient or inadequate, the hospital dietician will offer 200 ml Ketocal drinks as a supplement. Each meal will supply a 4:1 ratio of fat: protein/CHO. The meals and snacks will be eaten *ad-libitum* and will provide approximately 2000 calories per day for female and 2500 calories per day for male participants. Participants dietary preferences will be considered, with the possibility to exclude certain meals and substitute them for the patient’s preference within the keto menu.

The ketogenic diet will be optional for the subsequent consolidation cycles, depending on the patient’s wishes, prior compliance, and safety and suitability as determined by the study team. Compliance issues identified by lack of ketosis or dislike of the diet in the first cycle will suggest that continuing the intervention diet in subsequent cycles may not be recommended. The chemotherapy provided in the first (induction) cycle is high dose, therefore it is hypothesised that the patient will benefit from a single cycle of dietary intervention. If compliance and suitability are adequate, the study team will provide the patient with recipes and snacks designed by the dietician and study team so that they can continue the ketogenic diet at home. Urinary strips to measure ketosis will be provided for the patient to monitor their ketosis and report to the study team. A dietitian and/or study team members will review the participants regularly face to face, generally every 2 days,whilst in hospital and via telephone or telehealth as an outpatient.

Adherence to the intervention will be measured using either a food diary, food questionnaires, or the medical record, depending on the patient’s preferences and their ability to complete the diary and questionnaires (for example, patients in ICU may not be able to complete questionnaires and their nutritional intake will be extracted from the medical record as noted by the medical and nursing staff). In addition, urinary ketone levels will be measured regularly by the study team. Positive ketone levels are a strong indicator of compliance. Food acceptability and food craving will be measured using modified questionnaires. The study team and hospital dietitian will review participants regularly and if required, adjust the diet for acceptability while maintaining 4:1 fat to protein and CHO ratio, and caloric intake. (**Fig. 2**). At Nepean Hospital and Westmead Hospital oncology dietitians will assess participant dietary requirements, supervise preparation and delivery of the sFKD or standard diets. The diet is prepared on site at both Hospitals.. Study timelines for ALL will differ depending on the protocol chosen by the treating haematologist (see paragraph 3 of this section above).

Control participants will receive meals according to The Nutrition standards for adult inpatients in NSW hospitals (2011) <https://www.aci.health.nsw.gov.au/resources/nutrition/nutrition-food-in-hospitals/nutrition-standards-diets> . Control participants will not fast.

**Figure 2 – Study timeline for AML**



Data will be collected using questionnaires, anthropomorphic measurements, and blood, urine, buccal swab, stool, and bone marrow collections. Blood will be collected as per standard of care for AML patients: daily blood draws for full blood count (FBC), electrolytes and liver function tests (EUCs and LFTs). Extra blood (10-30 ml) will be collected for study secondary outcomes. Blood will be collected using either a central venous catheter or peripheral veins. If using peripheral veins, a second venepuncture is not required. Bone marrow biopsies will be performed as per standard of care, before chemotherapy and at recovery, prior to each chemotherapy cycle. Extra bone marrow (20 ml) will be collected for study secondary outcomes.

**Flowchart for the project.**

Participants will be treated with standard induction for 7 days [36], and will be randomised to receive either: 1) the sFKD diet for 2-6 days before chemotherapy, fast for 16 hours before commencing chemotherapy and the sFKD diet for 7 days during chemotherapy; or 2) a standard diet (**Fig. 3a and 3b**). Following recovery, disease response will be assessed by a bone marrow biopsy and patients under the age of 60 in remission will receive 2 - 4 cycles of high dose cytarabine for 3 alternate days, or if not suitable for high dose cytarabine, 1 - 2 cycles of idarubicin for 2 days and standard dose cytarabine for 5 days. In patients deemed unfit for intensive chemotherapy, treatment will be venetoclax and azacytidine, consisting of continuous oral venetoclax combined with a 7-day course of daily subcutaneous azacytidine repeated every 28 days until disease progression or unacceptable toxicity. Depending on the protocol ALL patients receive up to 8 cycles of induction therapy followed by post remission induction and 2-3 years maintenance therapy or allogeneic bone marrow transplant. The KD will not be administered in the maintenance phase.

***Subsequent Visits***

Participants will be in-patients from presentation and discharged from hospital following neutrophil recovery, resolution of any infection, commencing a normal diet and mobilisation. Frail patients who may be treated as out-patients will be excluded.

For in-patients, the following will be checked: eligibility check, assessment of outcome measures, assessments of safety including general (e.g. physical examination), specific safety assessments (e.g. specific laboratory tests according to the applicable product information and/or population) and adverse event collection, dispensing of trial diet or standard diet, assessment of compliance with trial diet, recording of concomitant medications.

Figure 3 Flowchart for AML



Consent for Study, if willing and eligible

AML or ALL confirmed

Participation finishes

Pre-consent for Bone Marrow biopsy

167

Exclude from subsequent cycles

Exclude from subsequent cycles

100

Randomisation 60%-40%

or ALL

# PARTICIPANT IDENTIFICATION

## Trial Participants

Participants with acute myeloid or lymphoblastic leukaemia as defined by WHO criteria (Section 9.2).

### Inclusion and Eligibility Criteria

* Participant is willing and able to give informed consent for participation in the trial. Adult male or female subjects ≥18 years of age who can understand study procedures, comply with them, and provide written informed consent before any study-specific procedure.
* Diagnosed with *de novo* acute myeloid leukaemia or acute lymphoblastic leukaemia. History of cytologically or histologically confirmed diagnosis of AML or ALL (except acute promyelocytic leukemia) according to the 2008 World Health Organization (WHO) classification (bone marrow [BM] or peripheral blood [PB] blast counts ≥20%).
* Participant is scheduled to undergo induction chemotherapy as an in-patient.
* Performance status (Eastern Cooperative Oncology Group; ECOG) of 0-2.
* Body mass index (BMI) ≥ 18.5 kg/m^2 (normal and above) or 16-18.5 kg/m^2 (underweight) if considered safe by the treating physician and dietician.
* Adequate renal function (serum creatinine < 1.5 X UNL [upper normal limit] or creatinine clearance > 50 ml/min). Creatinine clearance or glomerular filtration rate ≥30 mL/min as estimated by the Cockroft-Gault (C-G) or other medically acceptable formulas, such as MDRD (Modification of Diet in Renal Disease) or CKD-EPI (the Chronic Kidney Disease Epidemiology Collaboration).
* Ability to complete patient booklet by themselves or with assistance.

Ability and willingness to undergo short-term ketogenic diet combined with short-term fasting prior to and during chemotherapy.

* Subjects who are currently receiving prophylaxis antibiotics, prophylaxis antifungal medication and/or prophylaxis antiviral medication.

### Exclusion and Ineligibility Criteria

* Pregnant and/or nursing women.
* Patients with type 1 diabetes or patients with type 2 diabetes receiving insulin.
* History of syncope with calorie restriction in the past or other medical comorbidity, which would make fasting potentially dangerous.
* History of severe heart failure.
* Psychiatric conditions that preclude adherence to study protocol. Known significant mental illness or other condition such as active alcohol or other substance abuse or addiction that, in the opinion of the investigator, predisposes the subject to high risk of noncompliance with the protocol.
* Inability to maintain adequate nutrition and/or patients receiving parenteral nutrition at admission.
* Primary carnitine deficiency, carnitine palmitoyl transferase I or II deficiency, carnitine translocase deficiency, beta-oxidation defects, medium-chain acyl dehydrogenase deficiency, long-chain acyl dehydrogenase deficiency, short-chain acyl dehydrogenase deficiency, long-chain 3-hydroxyacyl-CoA deficiency, medium-chain 3-hydroxyacyl-CoA deficiency, pyruvate carboxylase deficiency, and porphyria.
* Patients with dietary restrictions incompatible with the trial dietary regimens.
* Treated with any investigational therapy within 2 weeks of the first dose of study treatment.
* Total serum bilirubin >2.5 × upper limit of normal (ULN; except for subjects with Gilbert's Syndrome for whom direct bilirubin is <2.5 × ULN), or liver cirrhosis, or chronic liver disease Child-Pugh Class B or C.
* Refractory congestive heart failure unresponsive to medical treatment; active infection resistant to all antibiotics; or non-AML-associated pulmonary disease requiring >2 liters per minute (LPM) oxygen, or any other condition that puts the subject at an imminent risk of death.

# TRIAL PROCEDURES

## Participant Recruitment

Adults with a potential diagnosis of AML or ALL will be identified by the treating Haematologists at Nepean and Westmead Hospitals, who will order a bone marrow aspirate as per Standard of Care to confirm the diagnosis. AML and ALL are suspected when the patient’s white blood cell (WBC) count is elevated and symptoms are compatible with acute leukaemia (fatigue, bruising, etc.). Suspected acute leukaemia patients will be offered the pre-screening / pre-consent form by the haematology registrars before performing the bone marrow aspirate (or by their treating haematologist or study team member if available). The purpose of the pre-consent form is to collect additional bone marrow for the trial at the time of the SoC aspirate to avoid a second aspirate, minimising the number of invasive procedures. The pre-consent form does not consent to the trial, it exclusively consents to taking a small amount of additional bone marrow, which is necessary to enrol in the trial should the diagnosis be confirmed as AML or ALL. The registrars are trained by the study team to inform the patient of this voluntary additional collection. Following pre-consent, a bone marrow biopsy, as per standard of care will be performed and an extra sample (taken from the same puncture) will be stored for the purposes of the study. Once the bone marrow is collected, there are two scenarios: A) The patient does not have AML or ALL. In this case, their participation finishes here, as stated in their pre-consent form. Their BM sample may be used as a negative control for cellular assays. B) The patient does have AML or ALL. In this case, their treating haematologist will inform them of the diagnosis and discuss treatment options. Their treating haematologist will mention this trial and, if appropriate, hand in the study flyer. The clinical trial coordinator (CTC) will check the patient’s eligibility and visit them to explain the trial and offer them the possibility of participating. The CTC will provide a copy of the PICF. Potential coercion is managed by the involvement of Haematology Clinical Trials Coordinators, who are not part of the treating team and do not have a therapeutic relationship with participants. The Clinical Trial Coordinator visits and discusses the trial with the potential participant and their relatives if appropriate and applicable. Potential participants are given time to consider involvement and are reassured that their treatment and relationship with treating clinicians will not be affected by a decision not to participate. If the CTC is not available, a qualified member of the study team who is not their treating haematologist, will visit the patient and offer the PICF. Following consent, the patient will be randomised to the control or intervention.

## Informed Consent

The treating physician will inform the patient of the study and if interested, will refer the patient to one of the study co-ordinators who provide the PIS and PCF. Real or perceived coercion will be reduced by removing the treating physician from the consent process.

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed.

Written versions of the Participant Information and Informed Consent will be presented to the participants detailing the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, without affecting their legal rights and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the trial. Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent will be suitably qualified and experienced and have been authorised to do so by the Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained at the trial site.

## Randomisation

Method for generating the randomisation schedule / allocation sequence: simple computer-generated random numbers, via a web-based randomisation system.

The statistician will design the randomisation schedule and the study team will hold the allocation. Randomisation will occur after the patient has been determined to be eligible for the study and has consented to participate.

To account for a potentially higher drop-out rate in the intervention group due to the open-labelled nature of the study, participants will be randomised 40% to the control group and 60% to the intervention group.

## Baseline Assessments

***Medical history***

* Include history of RBC and platelet transfusion documentation within 8 weeks prior to first dose, particularly the type of transfusion, number of units, reason for, and date of transfusion. RBC transfusion data should include the haemoglobin concentration prior to transfusion and platelet transfusion data should include the pre-transfusion platelet value.
* Review of concomitant medications and therapies
* Include all prescription, over the counter and herbal preparations taken for any indication within 4 weeks prior to the first dose.
* Demographic data (including date of birth, sex, race, ethnicity)

***Physical examination***

* Vital signs (including weight, height, blood pressure, heart rate and body temperature)

***Laboratory studies (standard of care)***

* Serum or urine bhCG (in women of child-bearing potential), haematology, biochemistry, liver function, clotting function and peripheral blood sampling for PD markers
* Full Blood Count including differential, reticulocytes, and blasts (if present)
* Biochemistry including electrolytes, urea, creatinine, calcium, magnesium, phosphate, random glucose, LDH
* Liver function including ALT, AST, ALP, GGT, total and indirect bilirubin, total protein and albumin
* Coagulation including APTT, PT, INR, fibrinogen
* Ferritin, and DAT
* ECOG assessment (see Appendix B for criteria)
* HIV, HBV, HCV screening (standard of care results available in the medical file up to 56 days prior to screening, may be used for eligibility purposes)
* Diagnostic bone marrow biopsy

## Subsequent Assessments

**Table 1. Patient assessment schedule including standard of care testing (all procedures that are for research only are bolded in red below**)

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Screening** | **Cycle 1** | **Cycles 2-X** |
|  | D-6 | D-5-27 | D28 | D-5-27 | D28 |
| **Informed Consent** | X |  |  |  |  |
| Medical assessment  | X | X | X | X | X |
| Physical exam | X | X | X | X | X |
| Vital signs | X | X | X | X | X |
| HIV, Hepatitis B and C test | X |  |  |  |  |
| Safety Bloods | X | X | X | X | X |
| Pregnancy test | X |  |  |  |  |
| **Research bloods** | X | **X** | **X** | **X** | **X** |
| **Bone marrow aspirate** | **X** |  | **X** |  | **X** |
| **Skin punch biopsy** | **X** |  | **X** |  | **X** |
| Review medications | X | X | X | X | X |
| Side effect assessment |  | X | X | X | X |
| Intervention acceptability |  | X | X | X | X |
| Adherence |  |  |  |  |  |
| **Stool and urine sample** | **X** | **X** | **X** | **X** | **X** |
| **Buccal mucosa swap and hair follicle sample** | **X** | **X** | **X** | **X** | **X** |

### Primary Aim

The incidence of major infection [pneumonia, bacteraemia, or fungaemia causing a blood stream infection (primary BSI), or pneumonia accompanied by bacteraemia or fungaemia (secondary BSI)] will be compared between the sFKD group and the standard diet group. A diagnosis of pneumonia requires a compatible chest x-ray or computed tomography scan. A diagnosis of bacteraemia as a result of frequent contaminants such as coagulase-negative Staphylococcus requires two positive blood cultures. This outcome will be evaluated every 28 days from day -5 until completion of chemotherapy and every 3 months thereafter for 24 months. BSI can be defined as the presence of viable bacteria in the blood (i.e. bacteraemia) documented by a positive blood culture result. Primary BSI (i.e. a BSI without a documented primary source of infection) can be distinguished from secondary BSI (i.e. a BSI secondary to a localized focus of infection, such as pneumonia, biliary tract infection, skin and soft-tissue infection, and wound infection). The CDC surveillance definitions divide primary BSIs into laboratory-confirmed BSIs and clinical sepsis. A diagnosis of laboratory-confirmed BSI is made if at least 1 of 2 criteria is met. First, the patient must have a recognized pathogen cultured from ≥1 blood specimen, and the cultured organism must not be related to an infection at another site. Second, the patient must have fever, chills, or hypotension and at least 1 of the following: (1) a common skin contaminant (e.g., diphtheroids, Bacillus species, Propionibacterium species, coagulase negative staphylococci, or micrococci) isolated from ≥2 blood cultures drawn on separate occasions; (2) a common skin contaminant, as defined above, isolated from at least 1 blood culture from a patient with an intravascular line and for whom the physician institutes appropriate antimicrobial therapy; or (3) a positive result of antigen testing of blood (e.g., positive for Haemophilus influenzae, Streptococcus pneumoniae, Neisseria meningitidis, or group B streptococcus) and signs and symptoms with positive laboratory results that are not related to an infection at another site [37]. Data will be collected using a re-identifiable data management sheet (Appendix D).

### Secondary Aims

***Assess the effect of a short-term ketogenic diet combined with short-term fasting (sFKD) on neutrophil recovery following induction and consolidation therapy for acute leukaemia***

Daily full blood counts, as per standard care, will be taken to assess the time from commencement of chemotherapy (day 1) to absolute neutrophil count ≥ 0.5 x 109/L for ≥ 3 days.

Engraftment is defined as neutrophil recovery greater than 0.5 × 109/L for 3 consecutive days. The time to neutrophil engraftment is defined as the first day of achieving an absolute neutrophil count greater than 0.5 × 109/L for 3 consecutive days. The time to platelet and reticulocyte recoveries is defined as the first days of achieving a platelet count more than 20 × 109/L, and a reticulocyte count more than 1% for 3 consecutive days without transfusions.

The 2 groups will be compared using the Student’s t-test for continuous variables, and categoric variables will be examined with the chi-square test. A linear regression model will be used to examine confounders on time to engraftment. A 2-sidedpvalue of <0.05 will be considered to be significant.

***Evaluate the effect on the toxicity profile of chemotherapy***

Safety, feasibility, and toxicity profile of chemotherapy will be assessed daily using the National Cancer Institute's Common Terminology Criteria for Adverse Events. To assess for differences in toxicity rates between study groups, Fisher's exact tests will be used; the Fisher's exact test is more efficient than a chi-square test when cell counts are small. These tests give the exact P value, rather than an approximation, of the observed cell frequencies. P values < 0.05 will be significant. Odds ratios using logistic regression will be calculated to estimate the degree to which patient demographics and clinicopathologic characteristics determined hematologic toxicity.

***Assess the effect on circulating signalling molecules***.

Changes in plasma glucose, insulin, Insulin-like growth factor 1 (IGF-1) and IGF-1 binding proteins will be measured regularly to discharge from Hospital

***Assess the effect on molecular markers of cellular damage and cell senescence***.

Quantification of genotoxic stress measured at single cell levels, analysis of chromosome instability, somatic mutation rate, and quantification of DNA damage response signalling proteins will be analysed from daily blood tests until discharge, bone marrow biopsies as per standard of care, skin and fat, buccal mucosa, and hair follicles pre- and post-chemotherapy.

***Assess the effect on mitochondrial function***

T cells will be harvested from peripheral blood. Seahorse XF Analyzers will be used to measure oxygen consumption rate and extracellular acidification rate of live cells that report key cellular functions such as mitochondrial respiration and glycolysis. These measurements will provide a systems-level analysis of cellular metabolic function in cultured T cells and ex-vivo samples.

A***ssess the effect on cardiac toxicity of anthracycline therapy for acute leukaemia.***

Cardiac troponin I measurement, BNP measurement, and echocardiography will be performed at baseline, and at representative points during treatment and follow up to 24 months by Professor Kazuaki Negishi and Dr Faraz Pathan.

**Assess changes in transcriptomic, metabolomics, proteomic and gut microbiome profile**

Blood, urine, and stool samples will be collected at baseline and regularly, generally every 2 days, until discharge.

Tissue samples will be re-identifiable, meaning that identifiers are replaced by a code, with the key to the code stored securely and separate to the samples.

After blood, faeces, urine and bone marrow samples have been taken, these samples will be processed by the local NSW Health laboratory or sent to the Charles Perkins Centre and Nepean Clinical School at the University of Sydney. Samples sent to Charles Perkins Centre, University of Sydney will be transported at no cost by Kristen Skarratt, Research Assistant where they will be processed and tested as part of this research project. The samples may need to be shared temporarily with other investigators doing research in similar fields such cancer and molecular biology. These tissue samples might also be used for other research projects in the future. These future studies may provide additional information that will be helpful in understanding the role of diet in modulating cancer risk, and to develop tests, treatments or cures. Some of these research data might also be shared with large data repositories for broad sharing with the research community. Only qualified researchers, who have received prior approval from ethics, will be able to look at this information.

***Laboratory studies (standard of care, performed by NSW Health Pathology)***

* Serum or urine bhCG (in women of child-bearing potential), haematology, biochemistry, liver function, clotting function and peripheral blood sampling for PD markers
* Full Blood Count including differential, reticulocytes, and blasts (if present)
* Biochemistry including electrolytes, urea, creatinine, calcium, magnesium, phosphate, random glucose, LDH
* Liver function including ALT, AST, ALP, GGT, total and indirect bilirubin, total protein and albumin
* Coagulation including APTT, PT, INR, fibrinogen
* Ferritin, and DAT
* ECOG assessment (see Appendix B for criteria)
* HIV, HBV, HCV screening (standard of care results available in the medical file up to 56 days prior to screening, may be used for eligibility purposes)
* Diagnostic bone marrow biopsy (standard of care sample obtained up to 6 weeks prior to C1D1, may be used for eligibility purposes)

***Trial Laboratory studies (Blood)***

Regularly to discharge from hospital:

* Plasma glucose, insulin, insulin-like growth factor 1 (IGF-1) and IGF-1 binding proteins
* Quantification of genotoxic stress measured at single cell levels, analysis of chromosome instability, somatic mutation rate, and quantification of DNA damage response signaling proteins
* Single-cell transcriptome (in white blood cells), metabolomics, proteomics and gut microbiome sequencing
* T cells will be harvested from peripheral blood. Seahorse XF Analyzers will be used to measure oxygen consumption rate and extracellular acidification rate of live cells that report key cellular functions such as mitochondrial respiration and glycolysis. These measurements will provide a systems-level analysis of cellular metabolic function in cultured T cells and ex-vivo samples.

Baseline and 24 months

* Cardiac troponin I

***Trial Laboratory studies (Bone Marrow)***

* Quantification of genotoxic stress measured at single cell levels, analysis of chromosome instability, somatic mutation rate, and quantification of DNA damage response signaling proteins

***Trial Laboratory studies (Stool samples)***

* Gut microbiome sequencing

***Trial Laboratory studies (Urine samples)***

* Urine metabolomics and ketones
* Gut permeability quantification

***Trial Laboratory studies (Buccal mucosa and hair follicles samples)***

* DNA sequencing for fast proliferating cells

One of the outcomes of this study will be the acceptability of a sFKD diet compared to a standard diet in patients treated with chemotherapy for acute leukaemia. The accrual target is enrolment of 167 subjects within 60 months. The retention target is to retain 80% of control participants and 53% of intervention participants at completion. The adherence target is for participants to meet the sFKD goal on 90% of days.

The acceptability of the intervention will be compared to the control group using the modified Food Acceptability Questionnaire and dietary recall data . The questionnaires have been modified to minimise repetition whilst still obtaining the relevant information.

The Food Acceptability Questionnaire asks participants to answer the following questions related to the foods they have been eating, such as:

1. How well do you like these foods?
2. How well do you like the taste of these foods?
3. How appealing or unappealing do you find the appearance of these foods?
4. How boring are these foods?
5. How easy or difficult has it been for you to prepare these foods?
6. How easy or difficult has it been for you to purchase these foods?
7. How easy or difficult has it been for you to maintain your current diet at restaurants?
8. How much effort does it take for you to stay on this diet?
9. How satisfied or dissatisfied do you feel after eating a meal on this diet?
10. Overall, how satisfied or dissatisfied are you with this diet?

The FAQ has been modified by removing questions 5-7 for inpatients and outpatients who will be supplied with the diet. Test–retest reliability of a previous version of the questionnaire was assessed in a sample of 18 respondents completing the questionnaire on two occasions approximately 1 week apart. The test–retest correlations (either Pearson r, or gamma, an index of concordance) ranged from 0.70 to 1.00 [39]. For the Food Acceptability Questionnaire items, the related samples Wilcoxon rank sum test assessed within group changes over time and the independent samples Mann-Whitney U test to compare the diet groups, both at baseline and after each cycle of chemotherapy.

The Food-Craving Inventory is a questionnaire that presents a reliable and valid measure of general and specific food cravings [40]. For Craving Questionnaire scores, paired comparison t tests will be calculated within each diet group to assess whether the mean changes from baseline to after each cycle of treatment are significantly different from zero. Between-subjects t tests will be calculated to determine differences between the diets after each cycle of chemotherapy.

## Early Discontinuation/Withdrawal of Participants

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

* Unacceptable side effects
* The diet being shown not to be effective
* The diet being shown to work and not need further testing
* Decisions made by local regulatory/health authorities.

## Definition of End of Trial

The trial will end 24 months after the enrolment of the last participant.

# TRIAL INTERVENTIONS

Participants will be treated with standard induction chemotherapy consisting of idarubicin 12 mg/m2 daily for 3 days and cytarabine 100 mg/m2 for 7 days [36]. In patients deemed unfit for intensive chemotherapy, treatment will be venetoclax and azacytidine, consisting of continuous oral venetoclax combined with a 7-day course of daily subcutaneous azacytidine repeated every 28 days until disease progression or unacceptable toxicity. Patients will be randomised to receive either: 1. the sFKD diet for 2-6 days before chemotherapy, fast for up to 24 hours before commencing chemotherapy and the sFKD diet for 7 days during chemotherapy; or 2. A standard diet. Following recovery, disease response will be assessed by a bone marrow biopsy and patients in remission will receive 3 cycles of cytarabine 3,000 mg/m2 twice daily for 3 alternate days, or if not suitable for cytarabine, 2 cycles of idarubicin 12 mg/m2 daily for 2 days and cytarabine 100 mg/m2 for 5 days.

## Investigational Intervention Description

### 10.1.1. Ketogenic Classic Diet

**Aim:** To provide a very high fat, very low carbohydrate diet that is adequate in protein.

(The following section is equivalent to section 7. TRIAL DESIGN).

The isocaloric KD (Section 10 and Appendix A for detailed description) will consist of 90% energy from fat, 5-7% from protein, and 3-5% from carbohydrate. The ketogenic diet intervention will be administered 3 times per day (breakfast, lunch, and dinner) beginning 3-6 days before scheduled chemotherapy. The number of days prior to chemotherapy is variable because the start of chemotherapy depends on whether the patient has been admitted, has a central line in place, has completed all required pre-chemotherapy testing, and is clear of any infections or secondary conditions that delay chemotherapy. Generally, most patients will consume the ketogenic diet for 4-5 days. A minimum of 48 h is generally necessary to enter ketosis. The subject will fast, that is eat and drink nothing except water for 16 hours before scheduled chemotherapy. The ketogenic diet will then be continued 3 times per day during chemotherapy (7 days for the first cycle and, optionally,5 days for subsequent cycles). The total duration of the dietary intervention is 10-15 days for the first cycle of treatment and up to 10 days for subsequent cycles. For participants 60 years of age and younger, a further 2-4 cycles of therapy will be administered, and for those over 60, a further 1-2 cycles will be administered. Each cycle of treatment is administered at a frequency of approximately 28 days. In patients deemed unfit for intensive chemotherapy, treatment will be venetoclax and azacytidine, consisting of continuous oral venetoclax combined with a 7-day course of daily subcutaneous azacytidine repeated every 28 days until disease progression or unacceptable toxicity. The usual treatment for ALL patients is hyper-CVAD, with part A receiving 4 days chemotherapy and Part B, 3 days, during which the KD will be given. Administration of the KD will be adjusted for other ALL regimens.

Upon randomisation to the intervention group, the study team will notify the dietetics department to start the patient in the ketogenic diet for the induction chemotherapy cycle. The hospital will administer the ketogenic diet that consist of a fixed menu including 5 different breakfast meals (e.g. scrambled eggs and bacon, avocado, and Hollandaise sauce) and 7 lunch/dinner meals (e.g. Keto mashed potato, poached fish and hollandaise sauce, avocado pulp). To increase meal variety and compliance, the study team will provide additional keto snacks regularly (roasted nuts, keto chocolate, etc.) approved by the dietician. If food intake is insufficient or inadequate, the hospital dietician will offer 200 ml Ketocal drinks as a supplement. Each meal will supply a 4:1 ratio of fat: protein/CHO. The meals and snacks will be eaten ad-libitum and will provide approximately 2000 calories per day for female and 2500 calories per day for male participants. Participants dietary preferences will be considered, with the possibility to exclude certain meals and substitute them for the patient’s preference within the keto menu.

The ketogenic diet will be optional for the subsequent consolidation cycles, depending on the patient’s wishes, prior compliance, and safety and suitability as determined by the study team. Compliance issues identified by lack of ketosis or dislike of the diet in the first cycle will suggest that continuing the intervention diet in subsequent cycles may not be recommended. The chemotherapy provided in the first (induction) cycle is high dose, therefore it is hypothesised that the patient will benefit from a single cycle of dietary intervention. If compliance and suitability are adequate, the study team will provide the patient with recipes and snacks designed by the dietician and study team so that they can continue the ketogenic diet at home. Urinary strips to measure ketosis will be provided for the patient to monitor their ketosis and report to the study team. A dietitian will review the participants regularly face to face whilst in hospital and via telephone or telehealth as an outpatient.

Control participants will receive meals according to The Nutrition standards for adult inpatients in NSW hospitals (2011) <https://www.aci.health.nsw.gov.au/resources/nutrition/nutrition-food-in-hospitals/nutrition-standards-diets> . Control participants will not fast.

### 10.1.2. Nutritional adequacy

A study dietitian will ensure that the diet is nutritional adequate with the inclusion of a ketogenic nutrition supplement.

### 10.1.3. Compliance with Trial Treatment

Important aspects to preparing the ketogenic diet at home:

Prepare only the ingredients/foods specified in each menu.All ingredients/foods supplied, and no substitutions allowed unless discussed with the study team.

If possible, weigh and check all foods precisely.

Use a spatula to clean all fat ingredients from the cooking dish onto the plate.

Adherence to the intervention will be measured using either a food diary, food questionnaires, or the medical record, depending on the patient’s preferences and their ability to complete the diary and questionnaires (for example, patients in ICU may not be able to complete questionnaires and their nutritional intake will be extracted from the medical record as noted by the medical and nursing staff). In addition, urinary ketone levels will be measured regularly by the study team. Positive ketone levels are a strong indicator of compliance. Food acceptability and food craving will be measured using modified questionnaires. The study team and hospital dietitian will review participants regularly and if required, adjust the diet for acceptability while maintaining 4:1 fat to protein and CHO ratio, and caloric intake. (**Fig. 2**). At Nepean Hospital and Westmead Hospital oncology dietitians will assess participant dietary requirements, supervise preparation and delivery of the sFKD or standard diets. The diet is prepared on site at both Hospitals.. Study timelines for ALL will differ depending on the protocol chosen by the treating haematologist (see paragraph 3 of this section above).

### 10.1.5. Common side-effects

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**Constipation**

* One of the main side effects of the ketogenic diet
* Bowel regimens are almost universally required
* Miralax (polyethylene glycol) does not provide any CHO and is therefore a good first-line option. Other fibre supplements that may prevent or ease constipation, and/or protect intestinal barrier integrity may be used if deemed appropriate by the study team, treating haematologist, and oncology dietician.

**Excess uric acid and calcium excreted in urine**

**Acidosis**

* Low serum bicarbonate levels due to acidotic state
* Typically want to keep HCO3- levels >20 mEq/L
* Begin supplementation with sodium bicarbonate 1mEq/kg when HCO3- <20 mEq/L

**Hypoglycaemia**

* Goal BG 3.9-6.1 mmol/L
* Treat when BG<40 or symptomatic; 15 mL juice or 0.25 g/kg dextrose (if NPO)

### 10.1.6. Post-trial Treatment

There will not be provision of the sFKD beyond the trial period.

### Concomitant medications

There are no contraindicated concomitant medications.

## Other Treatments

Participants will be treated with standard induction chemotherapy consisting of idarubicin 12 mg/m2 daily for 3 days and cytarabine 100 mg/m2 for 7 days [36].Following recovery, disease response will be assessed by a bone marrow biopsy and patients in remission will receive 3 cycles of cytarabine 3,000 mg/m2 twice daily for 3 alternate days, or if not suitable for cytarabine, 2 cycles of idarubicin 12 mg/m2 daily for 2 days and cytarabine 100 mg/m2 for 5 days.

## Other Interventions

There are no additional interventions in the trial design.

# SAFETY REPORTING

Safety reporting commences from the time of consent until 30 days after completion of the last cycle of chemotherapy. Refer to Appendix G: NBMLHD Safety Reporting for Clinical Trials Therapeutic Goods

## Adverse Event Definitions

|  |  |
| --- | --- |
| Adverse Event (AE) | Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. |
| Adverse Reaction (AR) | An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant.The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out.All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions. |
| Serious Adverse Event (SAE) | A serious adverse event is any untoward medical occurrence that:* results in death
* is life-threatening
* requires inpatient hospitalisation or prolongation of existing hospitalisation
* results in persistent or significant disability/incapacity
* consists of a congenital anomaly or birth defect\*.

Other ‘important medical events’ may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.NOTE: The term "life-threatening" in the definition of "serious" 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. |
| Serious Adverse Reaction (SAR) | An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided. |
| Suspected Unexpected Serious Adverse Reaction (SUSAR) | A serious adverse reaction, the nature and severity of which is not consistent with the Reference Safety Information for the medicinal product in question set out:* in the case of a product with a marketing authorisation, in the approved summary of product characteristics (SmPC) for that product
* in the case of any other investigational medicinal product, in the approved investigator’s brochure (IB) relating to the trial in question.
 |

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

## Assessment of Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Example:

**Related**: The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.

**Not Related**: The adverse event is probably produced by the participant’s clinical state or by other modes of therapy administered to the participant.

## Procedures for Reporting Adverse Events

AEs occurring during the safety window for the trial as defined above that are observed by the Investigator or reported by the participant, will be reported on the trial CRF. The trial CRF is inbuilt in RedCap.

The following information will be reported on the CRF: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The severity of events will be assessed on the following scale: 1 = mild, 2 = moderate, 3 = severe.

Non-serious AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed up until resolution.

It will be left to the Investigator’s clinical judgment to decide whether or not an AE is of sufficient severity to require the participant’s removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

## Reporting Procedures for Serious Adverse Events

All SAEs must be reported on the SAE Reporting Form to the Sponsor or delegate immediately or within 24 hours of Site Study Team becoming aware of the event being defined as serious.

### 11.5.1. Events exempt from immediate reporting as SAEs

Types of hospitalisation are not classed as SAEs: e.g., Hospitalisation for a pre-existing condition, including elective procedures planned prior to study entry, which has not worsened, does not constitute a serious adverse event; e.g., Hospitalisation for procedures and treatments specified within the protocol, and standard supportive care for the disease under study are not SAEs, and do not require SAE reporting.

Deaths due to the disease under study are exempt from reporting as SAEs.

Disease progression/ relapse/ recurrence are exempt from reporting as SAEs.

### 11.5.2. Procedure for immediate reporting of Serious Adverse Events

* Site study team will complete an SAE report form for all reportable SAEs.
* Where the SAE requires immediate reporting, the SAE report form will be scanned and emailed to Associate Professor Fuller ( stephen.fuller@sydney.edu.au ) immediately i.e., within 24 hours of site study team becoming aware of the event.
* Site study team will provide additional, missing or follow up information in a timely fashion.

All SAEs must be reported on the SAE reporting form within 24 hours of the Central Study Team becoming aware of the event. SAEs that are reported late must be accompanied by an explanation for this. A/Professor Fuller will perform an initial check of the report and request any additional information from the Central Study Team. A/Professor Fuller will ensure the SAE is reviewed by the DSMB on a weekly basis, (note events reported as related are subject to expedited review procedures). The SAE will also be reviewed at the next quarterly DSMB meeting.

**SUSAR Reporting**

All SUSARs will be reported by the sponsor delegate to the relevant Competent Authority and to the HREC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether the event occurred in the current trial.

# STATISTICS

## Statistical Analysis Plan (SAP)

The plan for the statistical analysis of the trial are outlined below. There is not a separate SAP document in use for the trial.

## Description of Statistical Methods

The two-proportion z-test will be used to determine whether the difference between the proportions of serious infection and/or death is significant. The χ2 or Kruskal-Wallis test will be used to compare various pre-treatment characteristics; number of days on study and number of days with neutrophil counts less than 0.5 x 109/L; and rates of diarrhoea, mucositis, and infection in the sFKD and standard diet groups. Time to major infection and time to death will be compared using the log-rank test.

For the Food Acceptability Questionnaire items, the related samples Wilcoxon rank sum test assessed within group changes over time and the independent samples Mann-Whitney U test to compare the diet groups, both at baseline and after each cycle of chemotherapy. For Craving Questionnaire scores, paired comparison t tests will be calculated within each diet group to assess whether the mean changes from baseline to after each cycle of treatment are significantly different from zero. Between-subjects t tests will be calculated to determine differences between the diets after each cycle of chemotherapy.

Exploratory analyses using appropriate regression methods will also be used to further investigate the secondary endpoints above. This will help offset the loss of power associated with subgroup analyses. For time to neutrophil engraftment the 2 groups will be compared using the Student’s t-test for continuous variables, and categoric variables will be examined with the chi-square test. A linear regression model will be used to examine confounders on time to engraftment. A 2-sidedpvalue of <0.05 will be considered to be significant.

To assess for differences in toxicity rates between study groups, Fisher's exact tests will be used; the Fisher's exact test is more efficient than a chi-square test when cell counts are small. These tests give the exact P value, rather than an approximation, of the observed cell frequencies. P values < 0.05 will be significant. Odds ratios using logistic regression will be calculated to estimate the degree to which patient demographics and clinicopathologic characteristics determined hematologic toxicity.

## Sample Size Determination

This is a phase-II comparative study powered at 80% to detect a 50% reduction in infection rate. The total sample size required is 167 patients (67 in each arm, with 67 enrolled in the control arm, and 100 enrolled in the intervention arm to account for the expected higher dropout rate). The baseline infection rate is assumed to be 40%. This translates into a 20% infection rate in the in the group of patients who received short-term ketogenic diet combined with short-term fasting before chemotherapy. The test statistic used is the two-sided Z-test with pooled variance. The significance level of the test was targeted at 0.10. The overall sample is adjusted with 10% lost-follow-up rate.

## Analysis Populations

All randomised participants will be analysed on an intention to treat basis. The intent-to-treat population will include all enrolled participants who received at least one sFKD meal or control.

## The Level of Statistical Significance

A statistically significant result is one where the observed p-value is less than or equal to 0.05.

## Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation from the original statistical plan will be described and justified in the final report.

# DATA MANAGEMENT

## Records and reports

The Principal Investigator or designee is responsible for preparing and maintaining adequate and accurate case histories designed to record all observations and other data pertinent to the investigation on each individual treated with the investigational product. Data reported on the CRF (RedCap) that are derived from source documents must be consistent with the source documents or the discrepancies must be explained.

## Source Data

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the study. Source documents include, but are not limited to, participant medical records, laboratory reports, ECG tracings, X-rays, radiologist reports, biopsy reports, ultrasound photographs, participant progress notes, pharmacy records and any other similar reports or records of procedures performed in accordance with the protocol. It is not acceptable for the CRF to be the only record of the participant’s study participation and progress as these must also be recorded in the participant medical record. This is to ensure that anyone accessing the participant’s medical record has adequate knowledge of their participation in a clinical study.

Any document that acts as a source document (the point of the initial recording of a piece of data) should be signed and dated by the person recording or reviewing the data for issues of medical significance (for example the review of laboratory reports). Persons signing the source documents must be listed, on the appropriate study documentation (site delegation log), as a site staff member.

## Access to Data

## Data Recording and Record Keeping

The Investigator must retain investigational product disposition records, copies of CRFs (or electronic files) and source documents for the maximum period required by applicable regulations and guidelines, or Institution procedures, or for 15 years, whichever is longer. The Investigator must contact the Sponsor (NBMLHD) prior to destroying any records associated with the study.

If a Principal Investigator withdraws from the study (e.g. relocation, retirement), the records will be transferred to a mutually agreed-upon designee or site (i.e. another Investigator or IRB). Notice of such transfer will be given in writing to the Sponsor (NBMLHD).

Electronic data will be de-identified and stored as linked data.

All paper records containing identifiable participant information will be securely stored in locked cabinets within the Nepean Hospital and Westmead Hospital Clinical Trials centres when not in use. Only authorised study personnel will be able to access these locked cabinets.

All electronic records containing identifiable participant information will be password protected and/or encrypted in the secure University of Sydney Research Data Store. This includes any identifiable data exported from the system in another format such as spreadsheet or hardcopy. Any data exported from the system that contain identifiable participant information will be destroyed when no longer needed. To avoid access by unauthorised staff, computers will be logged-off or locked when not in use. All passwords used to protect the electronic record will conform to the minimum institutional password guidelines.

Electronic records will be regularly backed up according to a back-up and recovery plan. The Research Data Store and RedCap are secure and backed up by University of Sydney IT. The plan will ensure archival sets are stored in a separate, physical location from the primary source. All identifiable electronic data will be fully contained within and protected by the Nepean Hospital and Westmead Hospital and University of Sydney networks and firewalls. Any computer systems containing copies of, or hosting, the electronic record will be protected by up to date anti-virus and firewall software.

# QUALITY ASSURANCE PROCEDURES

## Monitoring

The Principal Investigator is responsible for retaining all essential documents listed in ICH Good Clinical Practice (GCP) guidelines. These must be organised in a comprehensive filing system that is accessible to study monitors and other relevant personnel.

## Trial committees

### 14.3.1 Safety Monitoring Committee

Responsibilities of the Data and Safety Monitoring Board

The DSMB will evaluate participant safety data throughout the duration of the trial; evaluate the efficacy of the study intervention at intervals specified in the DSMB charter (described below); and independently provide recommendations to the study sponsor to either continue, amend or terminate the trial based on this information.

The Principal Investigator will appoint the DSMB, which will act as an independent advisory group. DMSB will have three voting members. The DSMB will meet every quarter.

***Open session***

The DSMB will focus on the status of the study, problems with accrual and follow-up, baseline demographic data, compliance issues, frequency of adverse events, documentation of endpoints, data quality issues, flow of forms, and data-based protocol modification issues. The principal investigator, co-investigators, and statisticians may attend the open session and present information during the meeting.

***Closed Session***

During the closed session, the discussions will focus on treatment safety, efficacy data, whether the primary study question has been answered, the interim results and results of Board actions and recommendations made in the previous meeting.

The DSMB will keep a record or minutes of all meetings.

# PROTOCOL DEVIATIONS

Any protocol deviations will be submitted to the sponsor for review when appropriate. Serious Breaches (SB) and Significant Safety Issues (SSI) will be reported to the HREC for review.

# SERIOUS BREACHES

The NBMLHD HREC will be made aware of deviations that have a significant impact on the continued safety or rights of participants or the reliability and robustness of the data generated in the trial.

# ETHICAL AND REGULATORY CONSIDERATIONS

## Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki. NB. The 2008 Declaration of Helsinki provides detail on what must be included in a protocol: funding, sponsorship, affiliations and potential conflicts of interest, incentives to participate, compensation for harm and post-trial access to drugs and care.

## Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

## Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Human Research Ethics Committee (HREC), and host institution(s) for written approval.

The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

## Participant Confidentiality

The study will comply with The Australian Privacy Principles, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s), with the exception of the CRF, where participant initials may be added. The study code will used be as follows: AL\_PX\_YZ\_Hospital, where AL stands for Acute Leukaemia, P stands for patient, X stands for patient number (1, 2, 3, etc), Y stands for patient age, Z stands for patient sex, and Hospital stands for Nepean or Westmead. All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants’ personal data.

# FINANCE AND INSURANCE

## Funding

This research has been funded by an NHMRC Investigator Grant Scheme awarded to Professor Luigi Fontana. In kind funding has been provided by NBMLHD for 2 x 0.1FTE dietitians and the University of Sydney has provided in-kind support for 0.2 FTE Level D Academic (A/Prof. Fuller).

## Complaints and compensation

If a participant suffers any injuries or complications as a result of this research project, they will contact the study team as soon as possible and assisted with arranging appropriate medical treatment. If eligible for Medicare, they can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

# PUBLICATION POLICY

The overall results of this research project will be disseminated (e.g. journal publications and book chapters, conference presentations, student theses, creative works). It is anticipated that one or more study publications will be authored on completion of the study. All proposed manuscripts should be submitted to the PSC at least 60 days before they are to be submitted to a journal for peer review. Authors of the published study will include the Chief Investigator and additional authors as determined by the Protocol Steering Committee.

# ARCHIVING

Data will be retained for a minimum of 15 years.

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