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Oral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting: a study protocol for a pilot and definitive randomised double-blind placebo-controlled trial (CannabisCINV)

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ABSTRACT

Introduction Chemotherapy-induced nausea and vomiting (CINV) remains an important issue for patients receiving chemotherapy despite guideline consistent antiemetic therapy. Trials using delta-9-Tetrahydrocannabinol-rich (THC) products demonstrate limited antiemetic effect, significant adverse events, and flawed study design. Trials using cannabinoid-rich (CBD) products demonstrate improved efficacy and psychological adverse event profile. No definitive trials have been conducted to support the use of cannabinoids for this indication, nor has the potential economic impact of incorporating such regimens into the Australian healthcare system been established. CannabisCINV aims to assess the efficacy, safety and cost-effectiveness of adding *TN-TC11M*, an oral cannabidiol-rich THC/CBD extract to guideline-consistent anti-emetics in the secondary prevention of CINV.

Methods and analysis The current multi-centre, 1:1 randomised cross-over, placebo-controlled pilot study will recruit 80 adult patients with any malignancy, experiencing CINV during moderate to highly emetogenic chemotherapy despite guideline consistent antiemetics. Patients receive oral *TN-TC11M* (2.5/2.5mg) capsules or placebo capsules TDS on day -1 to day 5 of cycle A of chemotherapy, followed by the alternative drug regimen during Cycle B of chemotherapy, and the preferred drug regimen during cycle C. The primary end-point is the proportion of subjects attaining a complete response to CINV. Secondary and tertiary endpoints include regimen tolerability, impact on quality of life and health system resource use. The primary assessment tool is patient diaries, which are filled from day -1 to day 5. A subsequent randomised placebo-controlled parallel phase III trial will recruit a further 250 patients.

Ethics and dissemination The protocol was approved by ethics review committees for all participating sites. Results will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration number Pre-results, ACTRN number 12616001036404)

Strengths and limitations of the study

- Largest and most definitive trial of cannabis for secondary prevention of CINV
- First study to assess the impact on heath resource use and cost-effectiveness of cannabis within the Australian health system
- Participants and staff blinded to intervention
- Utility of patient-reported outcomes
- Self-titrating dose of THC/CBD

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) remains a significant cause of morbidity in oncology patients despite the best current antiemetic prophylaxis[1].

The Multinational Association of Supportive Care in Cancer (MASCC) has published guidelines which recommend a standardised regimen of a 5-HT_3 receptor antagonist, with dexamethasone, and for most regimens an NK-1 antagonist for optimal antiemetic prophylaxis of moderate or high emetic risk[2]. Even amongst patients receiving guideline-consistent antiemetic prophylaxis, contemporary observational studies of moderate or highly emetogenic chemotherapy found that 46-57% experienced significant nausea, and 9-37% experienced vomiting[3-6].

Cannabinoids for chemotherapy-induced nausea and vomiting

The mechanism of delayed nausea and vomiting is incompletely understood, but may involve non-serotonergic receptors including the cannabinoid CB_1 receptor, with a potential role for cannabis products in its amelioration[7]. There is limited evidence of the efficacy of cannabis products for the prevention and treatment of CINV[8]. Whilst several studies have been carried out using smoked marijuana or synthetic oral tetra-hydrocannabinol medicines (THC: *Dronabinol*, *Nabilone*) for treating CINV, most showed limited efficacy, were inadequately powered and utilized outdated control antiemetic arms[9].

The major limitations of current oral THC-rich cannabinoids for this indication are unpredictable gastrointestinal absorption, poor bioavailability, delayed onset of action, and inability to rapidly self-titrate the dose for nausea control depending on tolerance[9]. Furthermore, THC-only medications

can be limited in their therapeutic potential by their intoxicating and disorientating central nervous system effects at the higher doses often needed to control nausea and vomiting[9]. CBD is known to counteract the psychiatric adverse effects of THC, and has inherent anxiolytic properties[10]. The addition of CBD to THC should ameliorate the intoxicating effects of THC, and allow delivery of higher therapeutic doses, without increasing the overall intoxication, paranoia and euphoria associated with THC, with diminished potential for abuse[11].

Nabiximols (*Sativex*; GW Pharmaceuticals, UK) is a THC/CBD cannabis extract derived from the *Cannabis sativa* plant containing THC and CBD in defined and near-equal amounts, and presented as a buccal spray[11]. A published small pilot double-blind randomised trial of nabiximols for secondary prevention of CINV found substantial efficacy, high patient acceptability, and manageable side effects[12]. In this study, 16 patients who experienced CINV after moderately emetogenic chemotherapy, despite prophylaxis with a guideline-consistent anti-emetic regimen[12], were randomised to nabiximols or placebo. Participants received up to 8.1mg THC/7.5mg CBD over 2 hours, then up to 21.6mg THC/20mg CBD every 24 hours for 5 x 24 hour periods. In the nabiximols group, the mean dose per 24 hours was 13mg THC (range 5.4-13.5)/12mg CBD (range 5-12.5) and the median duration was 3 days (range 1-5). The short dose titration was tolerated in 86% receiving nabiximols, with one patient discontinuing because of transient psychiatric effects. Adverse effects were experienced in 86% receiving nabiximols and 67% receiving placebo. Substantial efficacy was observed, with complete response in 71% vs 22%, (difference 49% (95% CI 1%, 75%)), absence of delayed emesis in 71% vs 22%, and nausea in 57% vs 22%, however no difference in acute nausea nor vomiting[12]. Nabiximols is licenced for the indication of neurospacticity in Multiple Sclerosis, but is not commercially available in Australia, and is not available for use in our proposed trial. There is a paucity of data on the cost-effectiveness of nabiximols outside of Multiple Sclerosis[13].

This study will use a novel oral THC/CBD capsule liposomal formulation ('*TN-TC11M*', Tilray). The product is intended to provide equivalent systemic exposures to THC and CBD as nabiximols and will be dosed similarly to the Duran study, commencing 24 hours prior to chemotherapy to confirm tolerability.

HYPOTHESIS

Primary hypothesis

We hypothesise that the addition of *TN-TC11M* to standard guideline-based antiemetics will improve the control of CINV, leading to improved quality of life. The potential resource implications are of higher CINV regimen drug costs, but reduced costs of the management of refractory CINV through the reduced need for rescue medications and reduced hospitalisation.

METHODS AND ANALYSIS

The Cannabis for Chemotherapy Induced Nausea and Vomiting (CannabisCINV) trial is an Australian-based, double-blind, placebo-controlled, two-stage randomised controlled trial. The primary aim is to determine the efficacy of adding an oral cannabidiol-rich THC extract (*TN-TC11M)* for secondary prevention of CINV after failure of a guideline consistent prophylactic anti-emetic regimen.

Study objectives

The primary objective of this study is to compare, amongst patients randomised to *TN-TC11M* or placebo, the ability to control emesis and nausea, as determined by:

- The proportion of patients achieving a 'complete response' during the overall phase of treatment (0 – 120 hours), defined as no nausea, no emesis and no use of rescue medications

The pilot study (cross-over) and definitive trial (parallel) will use different methods of analysis as outlined in the statistical analysis section.

The secondary objectives are to compare, amongst patients randomised to *TN-TC11M* or placebo:

- Efficacy

- Proportions of patients during acute (0 – 24 hours), delayed (24 – 120 hours) and overall (0 – 120 hours) phases of cycles A, B and C with (i) complete response, (ii) no emesis (vomiting or dry retching), (iii) no significant nausea, and (iv) no use of rescue medications
- Number of emetic episodes during 0 – 120 hours of cycles A, B and C

- Cannabinoid-related and other adverse events
  - Endpoint: Proportions with specified cannabinoid-related and other adverse events (structured checklist, CTCAE)
- Health-related quality of life
  - Endpoint: Summary scales (nausea, vomiting) of Functional Living Index-Emesis, and all items of AQOL-8D
- Regimen's acceptability
  - Endpoint: Adherence (patient diaries, pill counts), preference

The tertiary and correlative objectives are:

- To compare health system resource use and costs between randomised groups
  - Endpoint: Health system resource use and costs
- To model the cost-effectiveness of cannabinoid therapy compared to placebo or other anti-emesis alternatives, for prevention of CINV, from the perspective of the healthcare system
  - Endpoint: Health outcomes relative to costs

Trial oversight and monitoring

The CannabisCINV trial is a collaboration between the Chris O'Brien Lifehouse; the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney; and the Lambert Initiative for Cannabinoid Therapeutics, University of Sydney.

Safety and feasibility endpoints will be reviewed at 3-monthly intervals by the Independent Data and Safety Monitoring Committee (IDSMC) during both the pilot and phase III trial. The IDSMC will assess the rate of serious adverse events (SAEs) (graded ≥3 by CTCAE criteria) and accrual, with no pause in recruitment planned. Consideration will be given to altering aspects of the study if:

- The accrual rate is insufficient to complete the study in a reasonable timeframe
- The rate of SAEs in the oral *TN-TC11M* arm is unacceptably high compared with the placebo arm
- Medical or ethical reasons emerge affecting continued performance of the study

Trial design

The protocol consists of a pilot phase II, double-blinded, randomised, placebo-controlled cross-over study followed by a planned definitive phase III, blinded, randomised, parallel, placebo-controlled trial (see figure 1). The pilot trial will be conducted at 10 sites across the state of NSW, Australia, in both tertiary referral centres and regional centres in outpatient comprehensive cancer care units. A list of the study sites can be accessed from the Australia and New Zealand Clinical Trials Registry (ANZCTR).

Figure 1

Inclusion criteria

Adult patients with any malignancy receiving moderate to highly emetogenic intravenous chemotherapy (Day 1) in a 14 or 21-day cycle, who have experienced significant CINV despite guideline consistent anti-emetics. Patients must be planned for at least 2 further cycles of the same chemotherapy regimen, with an ECOG performance status of 2 or less.

Exclusion criteria

Patients with the following characteristics will be excluded from study enrolment:

- Symptomatic central nervous system/leptomeningeal disease, gastro-intestinal tract obstruction or disease-related nausea or vomiting requiring daily antiemetic therapy
- Oral chemotherapy during study treatment (eg. oral Capecitabine)
- Radiotherapy to the brain, abdomen or pelvis within the week prior to commencing study treatment, or planned during study treatment
- Contra-indication to cannabinoid treatment
    - Unstable cardiovascular disease (uncontrolled hypertension, unstable ischaemic heart disease, unstable congestive cardiac failure)
    - History of epilepsy or recurrent seizures
    - History of schizophrenia, other psychotic illness, severe personality disorder, suicidal ideation, or other significant psychiatric disorder, other than depression associated with the underlying condition
    - Substance use disorder (ICD-10 criteria of abuse or dependence) to alcohol, opioids, benzodiazepines, cannabis or illicit stimulants
    - Unwilling/unable to avoid driving or operating heavy machinery during and for up to 72 hours after taking study medication
    - Concerns regarding safe storage of medication
- Cannabis or cannabinoid-based medications within 30 days of study or unwilling to abstain for the duration of the study
- Prior hypersensitivity or intolerable adverse reaction to cannabis or cannabinoid-based medications, $5HT_3$ antagonist, dexamethasone or NK_1 antagonist
- Pregnancy, lactation, or inadequate contraception. Women must be post-menopausal, infertile, or use a reliable means of contraception. Women of childbearing potential must have a negative pregnancy test done within 7 days prior to registration. Men must have been surgically sterilised or use a (double if required) barrier method of contraception.

Investigational medical product

TN-TC11M

This study will use a novel oral THC/CBD capsule liposomal formulation ('*TN-TC11M*', Tilray) derived from *Cannabis Sativa L*. extract. It contains Delta-9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) in a 1:1 ratio, with each oral capsule containing 2.5mg THC and 2.5mg CBD. This is intended to provide equivalent systemic exposures to THC and CBD as those obtained from nabiximols (a single dose of nabiximols which comprises 2.7mg THC and 2.5mg CBD) and will be dosed similarly to the Duran study[12]. Investigational product administration will commence 24 hours prior to chemotherapy to confirm tolerability.

Placebo

The placebo will be in white capsules, identical in appearance to that of the active treatment.

Double-blind conditions

Pharmaceutical Packaging Professionals (PPP) will store and distribute the drug on behalf of the study sponsor to all participating sites upon receipt of all drug order forms.

Background treatment

All patients will receive antiemetics including 5HT3 antagonist, corticosteroid, and (where indicated) NK1 antagonist; according to a pre-specified choice of regimen consistent with guidelines from eviQ Cancer Treatments Online[14] and/or MASCC guidelines for optimal anti-emetic prophylaxis of chemotherapy[2].

The following rescue therapies are permitted:

- Lorazepam, eg 1mg PO bd prn

- Metoclopramide, eg 10mg PO tds prn
- Haloperidol, eg 0.5 – 1mg PO tds prn
- Prochlorperazine, eg 5 – 10mg PO tds prn, 25mg sup PR q8h prn
- Olanzapine, eg 5mg PO bd or 10mg PO mane for 3 days

Note:

- 5HT3 antagonists should only be used when other rescue therapies have failed

Recruitment and consent

Patient screening and enrolment undertaken at participating sites will be overseen by the site principal investigator and performed by trained study personnel. A screening log will document all eligible patients screened and approached along with reasons for any exclusions. Patients will provide written informed consent prior to study enrolment.

Pilot study

The phase II pilot trial (N=80) will be a multi-site, 1:1 randomised, double-blind, placebo-controlled trial (Figure 1). The dosing regimen will be similar to that used in the nabiximiols study by *Duran* et al described above, which was shown to be well tolerated and effective, however patients will also receive study drug for 24 hours prior to chemotherapy to confirm tolerability. It will utilise a crossover design and a significance level of 10% to increase efficiency, and allow patients to nominate a preferred drug in the final cycle.

In the pilot study, during chemotherapy cycle A, subjects will be randomised to receive oral *TN-TC11M* capsules *(*2.5/2.5mg) TDS from day -1 to 5, or identical placebo capsules, in addition to guideline consistent anti-emetics. For cycle B, subjects will cross-over to receive the alternative formulation in the same schedule.

On treatment, patients will be able to self-titrate their *TN-TC11M* /placebo exposure based on tolerance, with a maximum does of 30mg/30mg per day (12 tablets) (Table 1). Following cycle B, subjects are asked to nominate their preferred regimen after cycle B, and where relevant will receive that agent with cycle C.

Table 1: On treatment schedule with dose modifications

Day	Time	Dose	Dose titration	Maximum dose per 24-hour period
-1	Mane	1 capsule	N/A	5 capsules 12.5mg TCH/CBD or placebo
	Midi (at least 4 hours after previous dose)	2 capsules	Miss dose if intoxicated	
	Nocte (at least 4 hours after previous dose)	1–2 capsules	Miss dose if intoxicated Reduce dose by 1 capsule if previous dose not tolerated Maintain dose if previous dose tolerated	
1	60 min prior to chemotherapy	1–2 capsules	Miss dose if intoxicated Reduce dose by 1 capsule if previous dose not tolerated Maintain dose if previous dose tolerated, with nausea control Increase dose by 1 capsule if previous dose tolerated, but	8 capsules 20mg TCH/CBD or placebo
	Immediately after completion of Day 1 chemotherapy infusion	1–3 capsules		
	4 hours after completion of Day 1	1–3 capsules		

	chemotherapy infusion		inadequate nausea control	
2 3 4	Continue tds Mane Midi Nocte	1–4 capsules	Miss dose if intoxicated Reduce dose by 1 capsule if previous dose not tolerated Maintain dose if previous dose tolerated, with nausea control	12 capsules 30mg TCH/CBD or placebo
5	Mane Take final dose Midi Day 5	1–4 capsules	Increase dose by 1 capsule if previous dose tolerated, but inadequate nausea control	8 capsules 20mg TCH/CBD or placebo

Table 1 shows the starting dose will be 1 capsule PO on the morning of Day -1, with the next scheduled dose of 2 capsules (if tolerated, at midday), followed by 2 capsules that evening (if tolerated). On Day 1 subjects receive 1–2 capsules 60 minutes prior to chemotherapy infusion, followed by 1–3 capsules immediately after completion of Day 1 infusional chemotherapy, then 1–3 capsules 4 hours after completion of Day 1 infusional chemotherapy. On Days 2-5 subjects take 1-4 tablets TDS, with instruction to dose-titrate according to intoxication, tolerance of prior dose, and nausea control. The final dose is at midday on Day 5, with no further treatment until Day -1 of the next chemotherapy cycle.

Definitive study

The definitive randomised phase 3 study (N=250) will have a parallel group design, to reduce bias given the possibility of carry-over effect from cross-over in subsequent cycles, and to investigate longer-term efficacy over multiple chemotherapy cycles.

In the definitive study, during cycle A, subjects will receive oral *TN-TC11M* capsules *(*2.5/2.5mg) TDS from day -1 to 5, or identical placebo capsules, in the same treatment schedule (see table 1). For cycle B (and C if relevant), subjects will re-commence treatment with the investigational product on their maximum tolerated dose from the previous cycle, with further scope to self-titrate according to symptoms.

Data acquisition

The participant will be instructed on the use of the patient diary, which has been designed for this study, to record;

- Nausea (past 24-hour period)
- Date, time and type of rescue medication used
- Vomiting and dry retching episodes

The patient diary will be completed by the patient. There will be daily assessment of patients on days 1 to 6 of each cycle to ensure:

- Study treatments are taken appropriately
- Accurate records in the patient diary
- Completion of structured checklist of cannabinoid-specific adverse events
- Advice is provided regarding management of any adverse events

STATISTICAL CONSIDERATIONS

Sample size estimation

The estimated sample size for the pilot trial is 80 patients (40 per arm), using a primary endpoint of complete response to the study drug and placebo during cycle A and B of treatment. Utilizing a cross-over design, randomising patients to either study drug followed by placebo or placebo followed by study drug, will have 80% power at a 2-sided significance level of 10% to detect a 20% difference in discordant responses (response on one intervention, but not the other). Accrual is expected to take 12 months. The 20% difference is based on the assumption that 42% of patients on

the study drug will respond compared with 22% on placebo, and that the responders in the placebo group will respond/not respond equally on the study drug (11% respond on each).
The estimated sample size for the definitive trial is 250 patients (125 per arm), using a primary endpoint of complete response during cycle A of study treatment. A sample size of 250 patients provides 80% power at 2-sided 5% level of significance to detect improvement in complete response from 22% to 42.5%. Accrual is expected to take 2.5 years.
The sample size for each trial will allow for a drop-out/ineligibility rate of 20%.
The current evidence suggests that this level of improvement is both worthwhile and feasible.

Statistical analysis

Pilot study

Analyses will be conducted using intention to treat (ITT) principles. The primary analyses will include all patients who were randomised. Missing values will not be imputed. The results will be examined for differential effect in the two periods and if necessary, the data from cycle A will be analysed separately.
The primary outcome is complete response. The primary analysis will be a comparison of the proportion of patients with a complete response between the two treatments over cycle A and cycle B, using McNemar's test. In the event that there is differential drop-out between period, or a period by treatment interaction, the results from the first period will be analysed using a chi-square test. Analyses to assess period by treatment interaction will use Generalised Estimating Equations (GEEs) to account for the correlation within a patient. Secondary analyses to adjust for any baseline variables will also use GEEs. All tests will use a two-sided significance level of 10%.

Definitive study

The primary analyses will include all randomised patients using ITT principles, and compare the proportion of patients with complete response in the two treatment arms during the overall phase (0-120 hours) of cycle A, using a Chi-square test. Secondary analyses adjusting for baseline variables will use GEEs. Binary secondary outcomes will be analysed as for the primary outcome. Count data will be analysed using a Generalised Linear Model with a Poisson distribution. Cannabinoid-related adverse events and measures of adherence will be analysed with a chi-square test or two-sample t-test or just listed depending on numbers. All tests will use a two-sided significance level of 5%.

Health economic analysis

A within-trial and modelled economic evaluation will be undertaken to determine the incremental cost-effectiveness of oral cannabinoid therapy compared to placebo and other anti-emetic therapies, from a health system perspective.

For the within-trial analysis, resource use will be identified and measured from trial case report forms (for hospitalisations), and through linkage to Medicare claims data for outpatient visits (MBS) and prescribed medicines (PBS). Australian unit costs will be applied to the resource usage data (e.g. Australian Refined Diagnostic Related Groups (AR-DRG), and Medicare scheduled fees using the most recent reference year). For the modelled evaluation, resource use will be taken from the trial data for cannabinoid and placebo therapies, and supplemented with published estimates of resource use and costs for alternative 'usual care' anti-emetic therapies.

Health outcomes will include the proportion of complete responders (i.e. participants with no emesis and no use of rescue medications); quality of life as measured by the FLIE with 5-day recall and AQOL-8D instruments[15], and quality-adjusted survival. Quality-adjusted survival time will be used to quantify the incremental effectiveness of cannabinoid treatment. Quality-adjusted survival will be calculated by applying utility weights for quality of life derived from the AQOL-8D utility instrument to survival data using established methods.

Two cost-effectiveness outcomes will be reported: 1) the incremental cost per additional complete responder (trial primary endpoint) at 30 days after last dose of study drug, and 2) the incremental cost per quality-adjusted life year (QALY) gained at 12 months, using extrapolated data. These will be expressed as incremental cost-effectiveness ratios and plotted on a cost-effectiveness plane. Bootstrapping will be used to estimate a distribution around costs and health outcomes, and to calculate confidence intervals around incremental cost-effectiveness ratios[16]. A cost-effectiveness acceptability curve (CEAC) will be plotted, providing information about the probability that the intervention is cost-effective given the Australian Government's willingness to pay for a QALY gained[17]. One-way, two-way and probabilistic sensitivity analyses will be undertaken for relevant variables, including cost of the study drug.

ETHICS AND DISSEMINATION

Approval and patient-informed consent

In Australia, the study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans 2007 – updated May 2015, the NHMRC Australian Code for the Responsible Conduct of Research 2007, and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008.

To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the patient has provided written informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a participant. In this circumstance the NHMRC CTC, principal investigator and HREC must be advised immediately.

TRIAL STATUS

Patient enrolment for the pilot study commenced in November 2016 at the Chris O'Brien Lifehouse in NSW, Australia, with the 10th NSW site opened in June 2017. To date 31 patients have been enrolled, with anticipated pilot study enrolment completion by April 2018.

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Contributors PG, PSH, MS, NL, JS, IM, IO, DJA, CG, AK, were responsible for study concept (grant authors) and protocol development, RLM was responsible for protocol development. PG, AT, AM, NW, AW, CH, AK, MS, CG, PF, SC, KB and MA were responsible for study conduct.

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Drug supply Tilray

Competing Interests No authors disclosed a relevant conflict of interest

Ethics approval Sydney Local Health District ethics review committee (Royal Prince Alfred Hospital zone). The results will be disseminated in peer-reviewed journals and at scientific conferences

Provenance and peer review Not commissioned; externally peer reviewed

Data sharing statement This is a protocol paper, and no analysed results are available at this time

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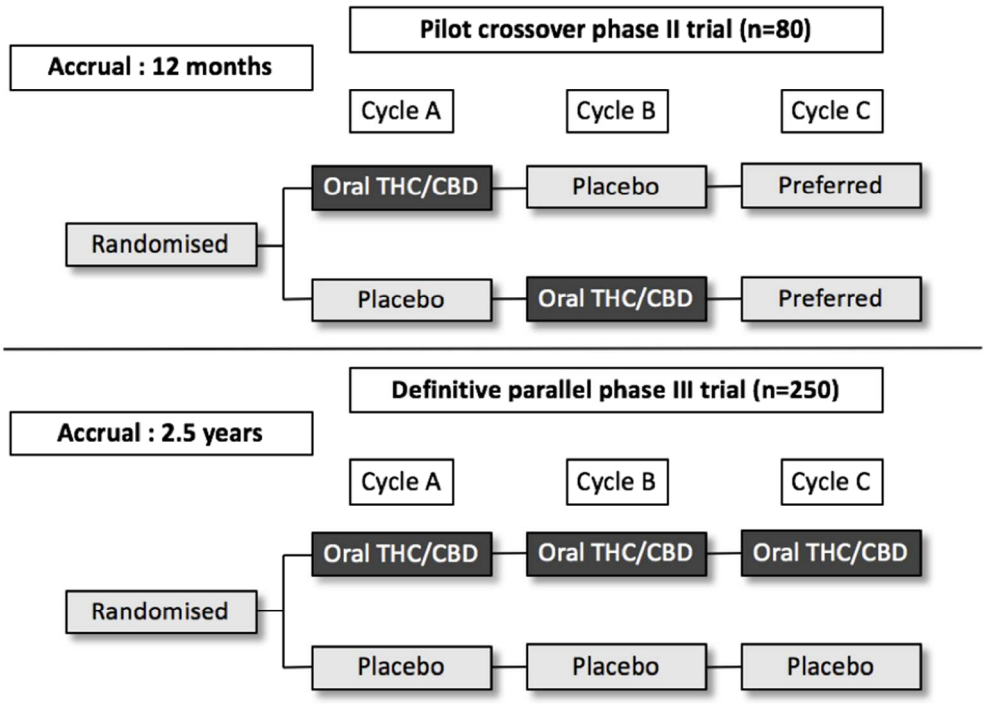

Figure 1 - Study schema

157x115mm (150 x 150 DPI)

BMJ Open

Oral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting: a study protocol for a pilot and definitive randomised double-blind placebo-controlled trial (CannabisCINV)

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Primary Subject Heading:	Oncology

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Oral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting: a study protocol for a pilot and definitive randomised double-blind placebo-controlled trial (CannabisCINV)

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ABSTRACT

Introduction Chemotherapy-induced nausea and vomiting (CINV) remains an important issue for patients receiving chemotherapy despite guideline consistent antiemetic therapy. Trials using delta-9-Tetrahydrocannabinol-rich (THC) products demonstrate limited antiemetic effect, significant adverse events, and flawed study design. Trials using cannabinoid-rich (CBD) products demonstrate improved efficacy and psychological adverse event profile. No definitive trials have been conducted to support the use of cannabinoids for this indication, nor has the potential economic impact of incorporating such regimens into the Australian healthcare system been established. CannabisCINV aims to assess the efficacy, safety and cost-effectiveness of adding *TN-TC11M*, an oral cannabidiol-rich THC/CBD extract to guideline-consistent anti-emetics in the secondary prevention of CINV.

Methods and analysis The current multi-centre, 1:1 randomised cross-over, placebo-controlled pilot study will recruit 80 adult patients with any malignancy, experiencing CINV during moderate to highly emetogenic chemotherapy despite guideline consistent antiemetics. Patients receive oral *TN-TC11M* (2.5/2.5mg) capsules or placebo capsules TDS on day -1 to day 5 of cycle A of chemotherapy, followed by the alternative drug regimen during Cycle B of chemotherapy, and the preferred drug regimen during cycle C. The primary end-point is the proportion of subjects attaining a complete response to CINV. Secondary and tertiary endpoints include regimen tolerability, impact on quality of life and health system resource use. The primary assessment tool is patient diaries, which are filled from day -1 to day 5. A subsequent randomised placebo-controlled parallel phase III trial will recruit a further 250 patients.

Ethics and dissemination The protocol was approved by ethics review committees for all participating sites. Results will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration number Pre-results, ACTRN number 12616001036404

Strengths and limitations of the study

Strengths

- Largest and most definitive randomised double-blind placebo-controlled trial of cannabis for secondary prevention of CINV
- First study to assess the impact on heath resource use and cost-effectiveness of cannabis within the Australian health system
- Utility of patient-reported outcomes
- Self-titrating dose of THC/CBD

Limitations

- Primary outcome measure (complete response) does not include nausea assessment, to ensure comparability with other CINV trials

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) remains a significant cause of morbidity in oncology patients despite the best current antiemetic prophylaxis[1].

The Multinational Association of Supportive Care in Cancer (MASCC) has published guidelines which recommend a standardised regimen of a 5-HT_3 receptor antagonist, with dexamethasone, and for most regimens an NK-1 antagonist for optimal antiemetic prophylaxis of moderate or high emetic risk[2]. Even amongst patients receiving guideline-consistent antiemetic prophylaxis, contemporary observational studies of moderate or highly emetogenic chemotherapy found that 46-57% experienced significant nausea, and 9-37% experienced vomiting[3-6].

Cannabinoids for chemotherapy-induced nausea and vomiting

The mechanism of delayed nausea and vomiting is incompletely understood, but may involve non-serotonergic receptors including the cannabinoid CB_1 receptor, with a potential role for cannabis products in its amelioration[7]. There is limited evidence of the efficacy of cannabis products for the prevention and treatment of CINV[8]. Whilst several studies have been carried out using smoked marijuana or synthetic oral tetra-hydrocannabinol medicines (THC: *Dronabinol*, *Nabilone*) for treating CINV, most showed limited efficacy, were inadequately powered and utilized outdated control antiemetic arms[9].

The major limitations of current oral THC-rich cannabinoids for this indication are unpredictable gastrointestinal absorption, poor bioavailability, delayed onset of action, and inability to rapidly self-titrate the dose for nausea control depending on tolerance[9]. Furthermore, THC-only medications can be limited in their therapeutic potential by their intoxicating and disorientating central nervous system effects at the higher doses often needed to control nausea and vomiting[9]. CBD is known to counteract the psychiatric adverse effects of THC, and has inherent anxiolytic properties[10]. The addition of CBD to THC should ameliorate the intoxicating effects of THC, and allow delivery of higher therapeutic doses, without increasing the overall intoxication, paranoia and euphoria associated with THC, with diminished potential for abuse[11].

Nabiximols (*Sativex*; GW Pharmaceuticals, UK) is a THC/CBD cannabis extract derived from the *Cannabis sativa* plant containing THC and CBD in defined and near-equal amounts, and presented as a buccal spray[11]. A published small pilot double-blind randomised trial of nabiximols for secondary prevention of CINV found substantial efficacy, high patient acceptability, and manageable side effects[12]. In this study, 16 patients who experienced CINV after moderately emetogenic chemotherapy, despite prophylaxis with a guideline-consistent anti-emetic regimen[12], were randomised to nabiximols or placebo. Participants received up to 8.1mg THC/7.5mg CBD over 2 hours, then up to 21.6mg THC/20mg CBD every 24 hours for 5 x 24 hour periods. In the nabiximols group, the mean dose per 24 hours was 13mg THC (range 5.4-13.5)/12mg CBD (range 5-12.5) and the median duration was 3 days (range 1-5). The short dose titration was tolerated in 86% receiving nabiximols, with one patient discontinuing because of transient psychiatric effects. Adverse effects were experienced in 86% receiving nabiximols and 67% receiving placebo. Substantial efficacy was observed, with complete response in 71% vs 22%, (difference 49% (95% CI 1%, 75%)), absence of delayed emesis in 71% vs 22%, and nausea in 57% vs 22%, however no difference in acute nausea nor vomiting[12]. Nabiximols is licenced for the indication of neurospacticity in Multiple Sclerosis, but is not commercially available in Australia, and is not available for use in our proposed trial. There is a paucity of data on the cost-effectiveness of nabiximols outside of Multiple Sclerosis[13].

This study will use a novel oral THC/CBD capsule formulation ('*TN-TC11M*', Tilray). The product is intended to provide equivalent systemic exposures to THC and CBD as nabiximols and was formulated for a consistent and reproducible pharmacokinetic profile, allowing patients to self-titrate as needed without a concern for a delayed onset. The product will be dosed similarly to the Duran study, commencing 24 hours prior to chemotherapy to confirm tolerability.

HYPOTHESIS

Primary hypothesis

We hypothesise that the addition of *TN-TC11M* to standard guideline-based antiemetics will improve the control of CINV, leading to improved quality of life. The potential resource implications are of higher CINV regimen drug costs, but reduced costs of the management of refractory CINV through the reduced need for rescue medications and reduced hospitalisation.

METHODS AND ANALYSIS

The Cannabis for Chemotherapy Induced Nausea and Vomiting (CannabisCINV) trial is an Australian-based, double-blind, placebo-controlled, two-stage randomised controlled trial. The primary aim is to determine the efficacy of adding an oral cannabidiol-rich THC extract (*TN-TC11M)* for secondary prevention of CINV after failure of a guideline consistent prophylactic anti-emetic regimen.

Study objectives

The primary objective of this study is to compare, amongst patients randomised to *TN-TC11M* or placebo, the ability to control emesis and nausea, as determined by:

- The proportion of patients achieving a 'complete response' during the overall phase of treatment (0 – 120 hours), defined as no emesis and no use of rescue medications

The pilot study (cross-over) and definitive trial (parallel) will use different methods of analysis as outlined in the statistical analysis section.

The secondary objectives are to compare, amongst patients randomised to *TN-TC11M* or placebo:

- Efficacy
  - Proportions of patients during acute (0 – 24 hours), delayed (24 – 120 hours) and overall (0 – 120 hours) phases of cycles A, B and C with (i) complete response, (ii) no emesis (vomiting or dry retching), (iii) no significant nausea, defined as degree of nausea <2 out of 10 using an 11-point rating scale, and (iv) no use of rescue medications
  - Number of emetic episodes during 0 – 120 hours of cycles A, B and C
- Cannabinoid-related and other adverse events
  - Endpoint: Proportions with specified cannabinoid-related and other adverse events (structured checklist, CTCAE)
- Health-related quality of life
  - Endpoint: Summary scales (nausea, vomiting) of Functional Living Index-Emesis, and all items of AQOL-8D
- Regimen's acceptability
  - Endpoint: Adherence (patient diaries, pill counts), preference

The tertiary and correlative objectives are:

- To compare health system resource use and costs between randomised groups
  - Endpoint: Health system resource use and costs
- To model the cost-effectiveness of cannabinoid therapy compared to placebo or other anti-emesis alternatives, for prevention of CINV, from the perspective of the healthcare system
  - Endpoint: Health outcomes relative to costs

Trial oversight and monitoring

The CannabisCINV trial is a collaboration between the Chris O'Brien Lifehouse; the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney; and the Lambert Initiative for Cannabinoid Therapeutics, University of Sydney.

The University of Sydney is the study sponsor. The NHMRC Clinical Trials Centre will be responsible for trial coordination, monitoring, site audits, management, data acquisition and statistical analysis. Safety and feasibility endpoints will be reviewed at 3-monthly intervals by the Independent Data and Safety Monitoring Committee (IDSMC) during both the pilot and phase III trial. The IDSMC will assess the rate of serious adverse events (SAEs) (graded ≥3 by CTCAE criteria) and accrual, with no pause in recruitment planned. Consideration will be given to altering aspects of the study if:

- The accrual rate is insufficient to complete the study in a reasonable timeframe
- The rate of SAEs in the oral *TN-TC11M* arm is unacceptably high compared with the placebo arm
- Medical or ethical reasons emerge affecting continued performance of the study

Protocol amendments can only be made by the Trial Management Committee and must be approved by the institutional Human Research Ethics Committee (HREC) prior to implementation.

Patient and public involvement

Consumer representatives were involved in the development of this trial. The primary and secondary outcomes of this study, including adverse events, are patient reported outcomes, emphasising the focus of this study on patient priorities, experience and preferences. Results of this study will be disseminated to study participants through peer reviewed journals and at scientific conferences.

Trial design

The protocol consists of a pilot phase II, double-blinded, randomised, placebo-controlled cross-over study followed by a planned definitive phase III, blinded, randomised, parallel, placebo-controlled trial (see figure 1). The pilot trial will be conducted at 10 sites across the state of NSW, Australia, in both tertiary referral centres and regional centres in outpatient comprehensive cancer care units. A list of the study sites can be accessed from the Australia and New Zealand Clinical Trials Registry (ANZCTR).

Figure 1

Inclusion criteria

Patients who fulfil all of the following characteristics will be considered eligible for enrolment;

- Adult patients with any malignancy, and
- Receiving moderate to highly emetogenic intravenous chemotherapy (Day 1) in a 14 or 21-day cycle, and
- Experienced significant CINV, defined as requiring ≥1 dose of rescue medication for vomiting or distress by nausea, and/or ≥ moderate nausea on a 5-point rating scale, at any time during the current chemotherapy regimen despite guideline consistent anti-emetics, and
- Planned for at least 2 further cycles of the same chemotherapy regimen, and
- ECOG performance status of 2 or less.

Exclusion criteria

Patients with the following characteristics will be excluded from study enrolment:

- Symptomatic central nervous system/leptomeningeal disease, gastro-intestinal tract obstruction or disease-related nausea or vomiting requiring daily antiemetic therapy
- Oral chemotherapy during study treatment (eg. oral capecitabine)
- Radiotherapy to the brain, abdomen or pelvis within the week prior to commencing study treatment, or planned during study treatment
- Contra-indication to cannabinoid treatment
    - Unstable cardiovascular disease (uncontrolled hypertension, unstable ischaemic heart disease, unstable congestive cardiac failure)
    - History of epilepsy or recurrent seizures
    - History of schizophrenia, other psychotic illness, severe personality disorder, suicidal ideation, or other significant psychiatric disorder, other than depression associated with the underlying condition
    - Substance use disorder (ICD-10 criteria of abuse or dependence) to alcohol, opioids, benzodiazepines, cannabis or illicit stimulants
    - Unwilling/unable to avoid driving or operating heavy machinery during and for up to 72 hours after taking study medication
    - Concerns regarding safe storage of medication
- Cannabis or cannabinoid-based medications within 30 days of study or unwilling to abstain for the duration of the study
- Prior hypersensitivity or intolerable adverse reaction to cannabis or cannabinoid-based medications, $5HT_3$ antagonist, dexamethasone or NK_1 antagonist
- Pregnancy, lactation, or inadequate contraception. Women must be post-menopausal, infertile, or use a reliable means of contraception. Women of childbearing potential must have a negative pregnancy test done within 7 days prior to registration. Men must have been surgically sterilised or use a (double if required) barrier method of contraception.

Investigational medical product

TN-TC11M

This study will use a novel oral THC/CBD capsule formulation ('*TN-TC11M*', Tilray) derived from *Cannabis Sativa L*. extract. It contains Delta-9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) in a 1:1 ratio, with each oral capsule containing 2.5mg THC and 2.5mg CBD. This is intended to provide equivalent systemic exposures to THC and CBD as those obtained from nabiximols (a single dose of nabiximols which comprises 2.7mg THC and 2.5mg CBD). In contrast to nabiximols, TN-CT11M was formulated for a consistent and reproducible pharmacokinetic profile, allowing patients to self-titrate as needed without a concern for a delayed onset. Investigational product will be dosed similarly to the Duran study[12], and administration will commence 24 hours prior to chemotherapy to confirm tolerability.

Placebo

The placebo will be in white capsules, identical in appearance to that of the active treatment.

Randomisation, allocation concealment and double-blind conditions

Randomisation will be performed centrally using minimization, with stratification by chemotherapy emetogenic risk (moderate vs high by MASCC criteria) and by site.

Pharmaceutical Packaging Professionals (PPP) will store and distribute the drug on behalf of the study sponsor to all participating sites upon receipt of all drug order forms.

Background treatment

All patients will receive antiemetics including 5HT3 antagonist, corticosteroid, and (where indicated) NK1 antagonist; according to a pre-specified choice of regimen consistent with guidelines from eviQ Cancer Treatments Online[14] and/or MASCC guidelines for optimal anti-emetic prophylaxis of chemotherapy[2].

The following rescue therapies are permitted:

- Lorazepam, eg 1mg PO bd (twice a day) prn (when required)
- Metoclopramide, eg 10mg PO tds (three times a day) prn
- Haloperidol, eg 0.5 – 1mg PO tds prn
- Prochlorperazine, eg 5 – 10mg PO tds prn, 25mg sup PR (per rectum) q8h prn
- Olanzapine, eg 5mg PO bd or 10mg PO mane for 3 days

Note:

- 5HT3 antagonists should only be used when other rescue therapies have failed

Recruitment and consent

Patient screening and enrolment undertaken at participating sites will be overseen by the site principal investigator and performed by trained study personnel. A screening log will document all eligible patients screened and approached along with reasons for any exclusions. Patients will provide written informed consent prior to study enrolment.

Pilot study

The phase II pilot trial (N=80) will be a multi-site, 1:1 randomised, double-blind, placebo-controlled trial (Figure 1). The dosing regimen will be similar to that used in the nabiximiols study by *Duran* et al described above, which was shown to be well tolerated and effective, however patients will also receive study drug for 24 hours prior to chemotherapy to confirm tolerability. It will utilise a crossover design and a significance level of 10% to increase efficiency, and allow patients to nominate a preferred drug in the final cycle.

In the pilot study, during chemotherapy cycle A, subjects will be randomised to receive oral *TN-TC11M* capsules *(*2.5/2.5mg) TDS from day -1 to 5, or identical placebo capsules, in addition to guideline consistent anti-emetics. For cycle B, subjects will cross-over to receive the alternative formulation in the same schedule.

On treatment, patients will be able to self-titrate their *TN-TC11M*/placebo exposure based on tolerance, with a maximum does of 30mg/30mg per day (12 tablets) (Table 1). Following cycle B, subjects are asked to nominate their preferred regimen after cycle B, and where relevant will receive that agent with cycle C.

Table 1: On treatment schedule with dose modifications

Day	Time	Dose	Dose titration	Maximum dose per 24-hour period
-1	Mane	1 capsule	N/A	5 capsules 12.5mg TCH/CBD or placebo
	Midi (at least 4 hours after previous dose)	2 capsules	Miss dose if intoxicated	
	Nocte (at least 4 hours after previous dose)	1–2 capsules	Miss dose if intoxicated Reduce dose by 1 capsule if previous dose not tolerated Maintain dose if previous dose tolerated	
1	60 min prior to chemotherapy	1–2 capsules	Miss dose if intoxicated Reduce dose by 1 capsule if previous dose not tolerated Maintain dose if previous dose tolerated, with nausea control Increase dose by 1 capsule if previous dose tolerated, but inadequate nausea control	8 capsules 20mg TCH/CBD or placebo
	Immediately after completion of Day 1 chemotherapy infusion	1–3 capsules		
	4 hours after completion of Day 1 chemotherapy infusion	1–3 capsules		
2 3 4	Continue tds Mane Midi Nocte	1–4 capsules	Miss dose if intoxicated Reduce dose by 1 capsule if previous dose not tolerated Maintain dose if previous dose tolerated, with nausea control Increase dose by 1 capsule if previous dose tolerated, but inadequate nausea control	12 capsules 30mg TCH/CBD or placebo
5	Mane	1–4 capsules		8 capsules 20mg TCH/CBD or placebo
	Take final dose Midi Day 5			

Table 1 shows the starting dose will be 1 capsule PO on the morning of Day -1, with the next scheduled dose of 2 capsules (if tolerated, at midday), followed by 2 capsules that evening (if tolerated). On Day 1 subjects receive 1–2 capsules 60 minutes prior to chemotherapy infusion, followed by 1–3 capsules immediately after completion of Day 1 infusional chemotherapy, then 1–3 capsules 4 hours after completion of Day 1 infusional chemotherapy. On Days 2-5 subjects take 1-4 tablets TDS, with instruction to dose-titrate according to intoxication, tolerance of prior dose, and nausea control. The final dose is at midday on Day 5, with no further treatment until Day -1 of the next chemotherapy cycle.

Definitive study

The definitive randomised phase 3 study (N=250) will assess the efficacy of the addition of TN-TC11M to guideline consistent anti-emetics as secondary prevention of CINV. It will have a parallel group design, to reduce bias given the possibility of carry-over effect from cross-over in subsequent cycles, and to investigate longer-term efficacy over multiple chemotherapy cycles.

In the definitive study, during cycle A, subjects will receive oral *TN-TC11M* capsules *(*2.5/2.5mg) TDS from day -1 to 5, or identical placebo capsules, in the same treatment schedule (see table 1). For cycle B (and C if relevant), subjects will re-commence treatment with the investigational product on their maximum tolerated dose from the previous cycle, with further scope to self-titrate according to symptoms.

Data acquisition

The participant will be instructed on the use of the patient diary, which has been designed for this study, to record;

- Nausea (past 24-hour period), recorded using an 11-point rating scale
- Date, time and type of rescue medication used
- Vomiting and dry retching episodes

The patient diary will be completed by the patient. There will be daily assessment of patients on days 1 to 6 of each cycle to ensure:

- Study treatments are taken appropriately
- Accurate records in the patient diary
- Completion of structured checklist of cannabinoid-specific adverse events
- Advice is provided regarding management of any adverse events

Trial data will be recorded on the (e)CRFs provided and will monitored by clinical trials program staff from the NHMRC Clinical Trials Centre.

Unblinding and post-study care

Following completion of trial treatment, patients who have experienced benefit and require ongoing treatment with the same chemotherapy regimen may be eligible for ongoing access to *TN-TC11M,* free of charge, contingent on unblinding performed by an unblinded statistician.

STATISTICAL CONSIDERATIONS

Sample size estimation

The estimated sample size for the pilot trial is 80 patients (40 per arm), using a primary endpoint of complete response to the study drug and placebo during cycle A and B of treatment. Utilizing a cross-over design, randomising patients to either study drug followed by placebo or placebo followed by study drug, will have 80% power at a 2-sided significance level of 10% to detect a 20% difference in discordant responses (response on one intervention, but not the other). Accrual is expected to take 12 months. The 20% difference is based on the assumption that 42% of patients on the study drug will respond compared with 22% on placebo, and that the responders in the placebo group will respond/not respond equally on the study drug (11% respond on each).

The estimated sample size for the definitive trial is 250 patients (125 per arm), using a primary endpoint of complete response during cycle A of study treatment. A sample size of 250 patients provides 80% power at 2-sided 5% level of significance to detect improvement in complete response from 22% to 42.5%. Accrual is expected to take 2.5 years.

The sample size for each trial will allow for a drop-out/ineligibility rate of 20%.

The current evidence suggests that this level of improvement is both worthwhile and feasible.

Statistical analysis

Pilot study

Analyses will be conducted using intention to treat (ITT) principles. The primary analyses will include all patients who were randomised. Missing values will not be imputed. The results will be examined for differential effect in the two periods and if necessary, the data from cycle A will be analysed separately.

The primary outcome is complete response. The primary analysis will be a comparison of the proportion of patients with a complete response between the two treatments over cycle A and cycle

B, using McNemar's test. In the event that there is differential drop-out between period, or a period by treatment interaction, the results from the first period will be analysed using a chi-square test. Analyses to assess period by treatment interaction will use Generalised Estimating Equations (GEEs) to account for the correlation within a patient. Secondary analyses to adjust for any baseline variables will also use GEEs. All tests will use a two-sided significance level of 10%.

Definitive study

The primary analyses will include all randomised patients using ITT principles, and compare the proportion of patients with complete response in the two treatment arms during the overall phase (0-120 hours) of cycle A, using a Chi-square test. Secondary analyses adjusting for baseline variables will use GEEs. Binary secondary outcomes will be analysed as for the primary outcome. Count data will be analysed using a Generalised Linear Model with a Poisson distribution. Cannabinoid-related adverse events and measures of adherence will be analysed with a chi-square test or two-sample t-test or just listed depending on numbers. All tests will use a two-sided significance level of 5%.

Health economic analysis

A within-trial and modelled economic evaluation will be undertaken to determine the incremental cost-effectiveness of oral cannabinoid therapy compared to placebo and other anti-emetic therapies, from a health system perspective.

For the within-trial analysis, resource use will be identified and measured from trial case report forms (for hospitalisations), and through linkage to Medicare claims data for outpatient visits (MBS) and prescribed medicines (PBS). Australian unit costs will be applied to the resource usage data (e.g. Australian Refined Diagnostic Related Groups (AR-DRG), and Medicare scheduled fees using the most recent reference year). For the modelled evaluation, resource use will be taken from the trial data for cannabinoid and placebo therapies, and supplemented with published estimates of resource use and costs for alternative 'usual care' anti-emetic therapies.

The definitive study will employ a health economic analysis which will use the proportion of patients with 'complete response' (i.e. participants with no emesis and no use of rescue medications, consistent with the primary endpoint); quality of life as measured by the FLIE with 5-day recall and AQOL-8D instruments[15], and quality-adjusted survival. Quality-adjusted survival time will be used to quantify the incremental effectiveness of cannabinoid treatment. Quality-adjusted survival will be calculated by applying utility weights for quality of life derived from the AQOL-8D utility instrument to survival data using established methods. In addition, we will conduct a sensitivity analysis to determine the incremental costs to achieve an outcome of no significant nausea, no emesis and no use of rescue medications.

Two cost-effectiveness outcomes will be reported: 1) the incremental cost per additional complete responder (trial primary endpoint) at 30 days after last dose of study drug, and 2) the incremental cost per quality-adjusted life year (QALY) gained at 12 months, using extrapolated data. These will be expressed as incremental cost-effectiveness ratios and plotted on a cost-effectiveness plane. Bootstrapping will be used to estimate a distribution around costs and health outcomes, and to calculate confidence intervals around incremental cost-effectiveness ratios[16]. A cost-effectiveness acceptability curve (CEAC) will be plotted, providing information about the probability that the intervention is cost-effective given the Australian Government's willingness to pay for a QALY gained[17]. One-way, two-way and probabilistic sensitivity analyses will be undertaken for relevant variables, including cost of the study drug.

ETHICS AND DISSEMINATION

Approval and patient-informed consent

In Australia, the study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July

2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans 2007 – updated May 2015, the NHMRC Australian Code for the Responsible Conduct of Research 2007, and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008.
To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the patient has provided written informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a participant. In this circumstance the NHMRC CTC, principal investigator and HREC must be advised immediately.

TRIAL STATUS

Patient enrolment for the pilot study commenced in November 2016 at the Chris O'Brien Lifehouse in NSW, Australia, with the 10th NSW site opened in June 2017. To date 49 patients have been enrolled, with anticipated pilot study enrolment completion by 3rd quarter 2018.

Acknowledgements Special study personnel, patients and their families

Contributors PG, PSH, MS, NL, JS, IM, IO, DJA, CG, AK, were responsible for study concept (grant authors). PG, PSH, MS, NL, JS, IM, IO, DJA, CG, AK, RML, NW were responsible for protocol development. PG, AT, AM, NW, AW, CH, AK, MS, CG, PF, SC, KB and MA were responsible for study conduct.

Funding NSW Department of Health, drug supply by Tilray

Drug supply Tilray

Protocol version 2.0, 9th June 2017

Data access Data access will be restricted to NHMRC Clinical Trials Centre staff

Competing interests No authors disclosed a relevant conflict of interest

Ethics approval Sydney Local Health District ethics review committee (Royal Prince Alfred Hospital zone).

Dissemination policy Results will be communicated by a writing committee appointment by the trial management committee and disseminated in peer-reviewed journals and at scientific conferences

Provenance and peer review Not commissioned; externally peer reviewed

Data sharing statement This is a protocol paper, and no analysed results are available at this time

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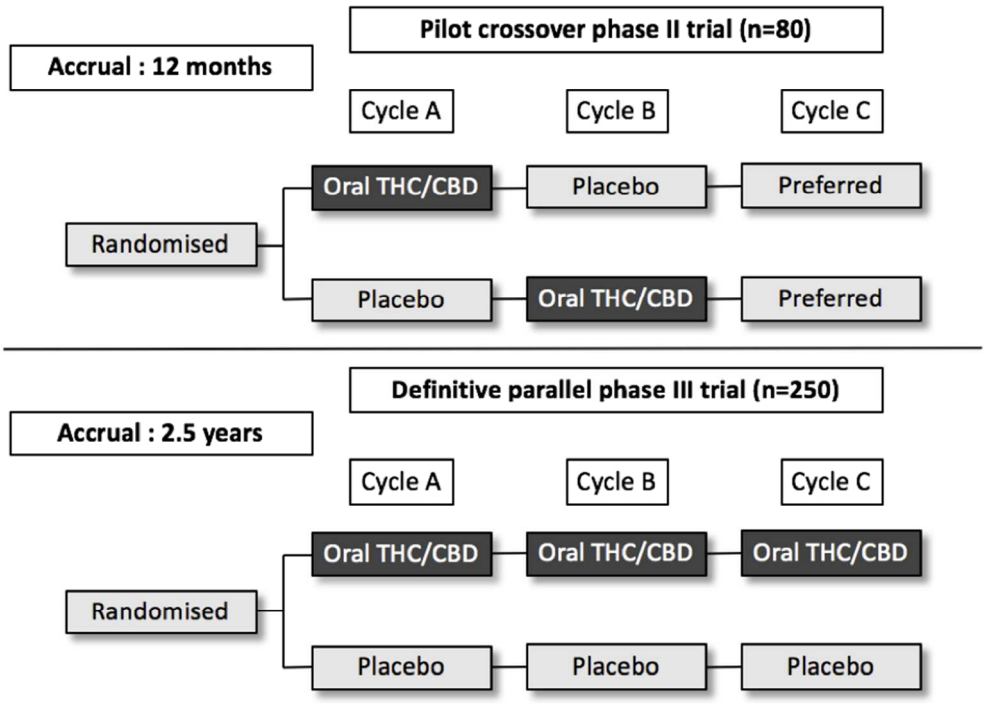

Figure 1 - Study schema

157x115mm (150 x 150 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (page 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (page 2)
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier (Page 10)
Funding	4	Sources and types of financial, material, and other support (page 10)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (pages 1 and 10)
	5b	Name and contact information for the trial sponsor (page 1)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (page 9)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (page 4)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (page 2 and 3)
	6b	Explanation for choice of comparators (page 3)
Objectives	7	Specific objectives or hypotheses (page 3 and 4)

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (pages 4, 7 and 8)
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (page 4)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (pages 4 and 5)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (pages 5, 6 and 7)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (pages 6 and 7)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (pages 7 and 8)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (page 6)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (page 3, 4, 7, 8 and 9)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (page 4, figure 1, pages 6, 7 and 8)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (page 8 and 9)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (page 4)
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (page 6)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned (page 6)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (page 6)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (page 5 and 6)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (page 8)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (page 7 and 8)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols (page 7 and 8)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (page 8)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (pages 8 and 9)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (pages 8 and 9)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (pages 8 and 9)

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (page 4)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (pages 8 and 9)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (page 4)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (page 4)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (page 9)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (page 9)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (page 9)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (pages 8 and 9)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (page 10)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (page 9)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (page 10)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation (page 8)

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (pages 2 and 9)
	31b	Authorship eligibility guidelines and any intended use of professional writers (Page 10)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (page 10)
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (not applicable)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Oral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting: a study protocol for a pilot and definitive randomised double-blind placebo-controlled trial (CannabisCINV)

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Primary Subject Heading:	Oncology

Secondary Subject Heading:	Palliative care
Keywords:	Cannabis, Cannabidiol, Chemotherapy-induced nausea and vomiting, Randomized trial, Antiemetic, Marijuana

Oral cannabinoid-rich THC/CBD cannabis extract for secondary prevention of chemotherapy-induced nausea and vomiting: a study protocol for a pilot and definitive randomised double-blind placebo-controlled trial (CannabisCINV)

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Keywords
Cannabis, cannabidiol, chemotherapy-induced nausea and vomiting, randomized trial, antiemetic

Word count – Abstract - 273, Body - 4139

ABSTRACT

Introduction Chemotherapy-induced nausea and vomiting (CINV) remains an important issue for patients receiving chemotherapy despite guideline consistent antiemetic therapy. Trials using delta-9-Tetrahydrocannabinol-rich (THC) products demonstrate limited antiemetic effect, significant adverse events, and flawed study design. Trials using cannabinoid-rich (CBD) products demonstrate improved efficacy and psychological adverse event profile. No definitive trials have been conducted to support the use of cannabinoids

for this indication, nor has the potential economic impact of incorporating such regimens into the Australian healthcare system been established. CannabisCINV aims to assess the efficacy, safety and cost-effectiveness of adding *TN-TC11M*, an oral cannabidiol-rich THC/CBD extract to guideline-consistent anti-emetics in the secondary prevention of CINV.

Methods and analysis The current multi-centre, 1:1 randomised cross-over, placebo-controlled pilot study will recruit 80 adult patients with any malignancy, experiencing CINV during moderate to highly emetogenic chemotherapy despite guideline consistent antiemetics. Patients receive oral *TN-TC11M* (2.5/2.5mg) capsules or placebo capsules TDS on day -1 to day 5 of cycle A of chemotherapy, followed by the alternative drug regimen during Cycle B of chemotherapy, and the preferred drug regimen during cycle C. The primary end-point is the proportion of subjects attaining a complete response to CINV. Secondary and tertiary endpoints include regimen tolerability, impact on quality of life and health system resource use. The primary assessment tool is patient diaries, which are filled from day -1 to day 5. A subsequent randomised placebo-controlled parallel phase III trial will recruit a further 250 patients.

Ethics and dissemination The protocol was approved by ethics review committees for all participating sites. Results will be disseminated in peer-reviewed journals and at scientific conferences.

Trial registration number Pre-results, ACTRN number 12616001036404

Strengths and limitations of the study

Strengths

- Largest and most definitive randomised double-blind placebo-controlled trial of cannabis for secondary prevention of CINV
- First study to assess the impact on heath resource use and cost-effectiveness of cannabis within the Australian health system
- Utility of patient-reported outcomes
- Self-titrating dose of THC/CBD

Limitations

- Primary outcome measure (complete response) does not include nausea assessment, to ensure comparability with other CINV trials

INTRODUCTION

Chemotherapy-induced nausea and vomiting (CINV) remains a significant cause of morbidity in oncology patients despite the best current antiemetic prophylaxis[1].

The Multinational Association of Supportive Care in Cancer (MASCC) has published guidelines which recommend a standardised regimen of a 5-HT_3 receptor antagonist, with dexamethasone, and for most regimens an NK-1 antagonist for optimal antiemetic prophylaxis of moderate or high emetic risk[2]. Even amongst patients receiving guideline-consistent antiemetic prophylaxis, contemporary observational studies of moderate or highly emetogenic chemotherapy found that 46-57% experienced significant nausea, and 9-37% experienced vomiting[3-6].

Cannabinoids for chemotherapy-induced nausea and vomiting

The mechanism of delayed nausea and vomiting is incompletely understood, but may involve non-serotonergic receptors including the cannabinoid CB_1 receptor, with a potential role for cannabis products in its amelioration[7]. There is limited evidence of the efficacy of cannabis products for the prevention and treatment of CINV[8]. Whilst several studies have been carried out using smoked marijuana or synthetic oral tetra-hydrocannabinol medicines (THC: *Dronabinol*, *Nabilone*) for treating CINV, most showed limited efficacy, were inadequately powered and utilized outdated control antiemetic arms[9].

The major limitations of current oral THC-rich cannabinoids for this indication are unpredictable gastrointestinal absorption, poor bioavailability, delayed onset of action, and inability to rapidly self-titrate the dose for nausea control depending on tolerance[9]. Furthermore, THC-only medications can be limited in their therapeutic potential by their intoxicating and disorientating central nervous system effects at the higher doses often needed to control nausea and vomiting[9]. CBD is known to

counteract the psychiatric adverse effects of THC, and has inherent anxiolytic properties[10]. The addition of CBD to THC should ameliorate the intoxicating effects of THC, and allow delivery of higher therapeutic doses, without increasing the overall intoxication, paranoia and euphoria associated with THC, with diminished potential for abuse[11].

Nabiximols (*Sativex*; GW Pharmaceuticals, UK) is a THC/CBD cannabis extract derived from the *Cannabis sativa* plant containing THC and CBD in defined and near-equal amounts, and presented as a buccal spray[11]. A published small pilot double-blind randomised trial of nabiximols for secondary prevention of CINV found substantial efficacy, high patient acceptability, and manageable side effects[12]. In this study, 16 patients who experienced CINV after moderately emetogenic chemotherapy, despite prophylaxis with a guideline-consistent anti-emetic regimen[12], were randomised to nabiximols or placebo. Participants received up to 8.1mg THC/7.5mg CBD over 2 hours, then up to 21.6mg THC/20mg CBD every 24 hours for 5 x 24 hour periods. In the nabiximols group, the mean dose per 24 hours was 13mg THC (range 5.4-13.5)/12mg CBD (range 5-12.5) and the median duration was 3 days (range 1-5). The short dose titration was tolerated in 86% receiving nabiximols, with one patient discontinuing because of transient psychiatric effects. Adverse effects were experienced in 86% receiving nabiximols and 67% receiving placebo. Substantial efficacy was observed, with complete response in 71% vs 22%, (difference 49% (95% CI 1%, 75%)), absence of delayed emesis in 71% vs 22%, and nausea in 57% vs 22%, however no difference in acute nausea nor vomiting[12]. Nabiximols is licenced for the indication of neurospasticity in Multiple Sclerosis, but is not commercially available in Australia, and is not available for use in our proposed trial. There is a paucity of data on the cost-effectiveness of nabiximols outside of Multiple Sclerosis[13].

This study will use a novel oral THC/CBD capsule formulation ('*TN-TC11M*', Tilray). The product is intended to provide equivalent systemic exposures to THC and CBD as nabiximols and was formulated for a consistent and reproducible pharmacokinetic profile, allowing patients to self-titrate as needed without a concern for a delayed onset. The product will be dosed similarly to the Duran study, commencing 24 hours prior to chemotherapy to confirm tolerability.

HYPOTHESIS

Primary hypothesis

We hypothesise that the addition of *TN-TC11M* to standard guideline-based antiemetics will improve the control of CINV, leading to improved quality of life. The potential resource implications are of higher CINV regimen drug costs, but reduced costs of the management of refractory CINV through the reduced need for rescue medications and reduced hospitalisation.

METHODS AND ANALYSIS

The Cannabis for Chemotherapy Induced Nausea and Vomiting (CannabisCINV) trial is an Australian-based, double-blind, placebo-controlled, two-stage randomised controlled trial. The primary aim is to determine the efficacy of adding an oral cannabidiol-rich THC extract (*TN-TC11M)* for secondary prevention of CINV after failure of a guideline consistent prophylactic anti-emetic regimen.

Study objectives

The primary objective of this study is to compare, amongst patients randomised to *TN-TC11M* or placebo, the ability to control emesis and nausea, as determined by:

- The proportion of patients achieving a 'complete response' during the overall phase of treatment (0 – 120 hours), defined as no emesis and no use of rescue medications

The pilot study (cross-over) and definitive trial (parallel) will use different methods of analysis as outlined in the statistical analysis section.

The secondary objectives are to compare, amongst patients randomised to *TN-TC11M* or placebo:

- Efficacy

- Proportions of patients during acute (0 – 24 hours), delayed (24 – 120 hours) and overall (0 – 120 hours) phases of cycles A, B and C with (i) complete response, (ii) no emesis (vomiting or dry retching), (iii) no significant nausea, defined as degree of nausea <2 out of 10 using an 11-point rating scale, and (iv) no use of rescue medications
- Number of emetic episodes during 0 – 120 hours of cycles A, B and C

♦ Cannabinoid-related and other adverse events
- Endpoint: Proportions with specified cannabinoid-related and other adverse events (structured checklist, CTCAE)

♦ Health-related quality of life
- Endpoint: Summary scales (nausea, vomiting) of Functional Living Index-Emesis, and all items of AQOL-8D

♦ Regimen's acceptability
- Endpoint: Adherence (patient diaries, pill counts), preference

The tertiary and correlative objectives are:

♦ To compare health system resource use and costs between randomised groups
- Endpoint: Health system resource use and costs

♦ To model the cost-effectiveness of cannabinoid therapy compared to placebo or other anti-emesis alternatives, for prevention of CINV, from the perspective of the healthcare system
- Endpoint: Health outcomes relative to costs

Trial oversight and monitoring

The CannabisCINV trial is a collaboration between the Chris O'Brien Lifehouse; the National Health and Medical Research Council (NHMRC) Clinical Trials Centre, University of Sydney; and the Lambert Initiative for Cannabinoid Therapeutics, University of Sydney.

The University of Sydney is the study sponsor. The NHMRC Clinical Trials Centre will be responsible for trial coordination, monitoring, site audits, management, data acquisition and statistical analysis. Safety and feasibility endpoints will be reviewed at 3-monthly intervals by the Independent Data and Safety Monitoring Committee (IDSMC) during both the pilot and phase III trial. The IDSMC will assess the rate of serious adverse events (SAEs) (graded ≥3 by CTCAE criteria) and accrual, with no pause in recruitment planned. Consideration will be given to altering aspects of the study if:

♦ The accrual rate is insufficient to complete the study in a reasonable timeframe

♦ The rate of SAEs in the oral *TN-TC11M* arm is unacceptably high compared with the placebo arm

♦ Medical or ethical reasons emerge affecting continued performance of the study

Protocol amendments can only be made by the Trial Management Committee and must be approved by the institutional Human Research Ethics Committee (HREC) prior to implementation.

Patient and public involvement

Consumer representatives were involved in the development of this trial. The primary and secondary outcomes of this study, including adverse events, are patient reported outcomes, emphasising the focus of this study on patient priorities, experience and preferences. Results of this study will be disseminated to study participants through peer reviewed journals and at scientific conferences.

Trial design

The protocol consists of a pilot phase II, double-blinded, randomised, placebo-controlled cross-over study followed by a planned definitive phase III, blinded, randomised, parallel, placebo-controlled trial (see figure 1). The pilot trial will be conducted at 10 sites across the state of NSW, Australia, in both tertiary referral centres and regional centres in outpatient comprehensive cancer care units. A list of the study sites can be accessed from the Australia and New Zealand Clinical Trials Registry (ANZCTR).

Figure 1

Inclusion criteria

Patients who fulfil all of the following characteristics will be considered eligible for enrolment;

- Adult patients with any malignancy, and
- Receiving moderate to highly emetogenic intravenous chemotherapy (Day 1) in a 14 or 21-day cycle, and
- Experienced significant CINV, defined as requiring ≥1 dose of rescue medication for vomiting or distress by nausea, and/or ≥ moderate nausea on a 5-point rating scale, at any time during the current chemotherapy regimen despite guideline consistent anti-emetics, and
- Planned for at least 2 further cycles of the same chemotherapy regimen, and
- ECOG performance status of 2 or less.

Exclusion criteria

Patients with the following characteristics will be excluded from study enrolment:

- Symptomatic central nervous system/leptomeningeal disease, gastro-intestinal tract obstruction or disease-related nausea or vomiting requiring daily antiemetic therapy
- Oral chemotherapy during study treatment (eg. oral capecitabine)
- Radiotherapy to the brain, abdomen or pelvis within the week prior to commencing study treatment, or planned during study treatment
- Contra-indication to cannabinoid treatment
    - Unstable cardiovascular disease (uncontrolled hypertension, unstable ischaemic heart disease, unstable congestive cardiac failure)
    - History of epilepsy or recurrent seizures
    - History of schizophrenia, other psychotic illness, severe personality disorder, suicidal ideation, or other significant psychiatric disorder, other than depression associated with the underlying condition
    - Substance use disorder (ICD-10 criteria of abuse or dependence) to alcohol, opioids, benzodiazepines, cannabis or illicit stimulants
    - Unwilling/unable to avoid driving or operating heavy machinery during and for up to 72 hours after taking study medication
    - Concerns regarding safe storage of medication
- Cannabis or cannabinoid-based medications within 30 days of study or unwilling to abstain for the duration of the study
- Prior hypersensitivity or intolerable adverse reaction to cannabis or cannabinoid-based medications, $5HT_3$ antagonist, dexamethasone or NK_1 antagonist
- Pregnancy, lactation, or inadequate contraception. Women must be post-menopausal, infertile, or use a reliable means of contraception. Women of childbearing potential must have a negative pregnancy test done within 7 days prior to registration. Men must have been surgically sterilised or use a (double if required) barrier method of contraception.

Investigational medical product

TN-TC11M

This study will use a novel oral THC/CBD capsule formulation ('*TN-TC11M*', Tilray) derived from *Cannabis Sativa L*. extract. It contains Delta-9-Tetrahydrocannabinol (THC) and Cannabidiol (CBD) in a 1:1 ratio, with each oral capsule containing 2.5mg THC and 2.5mg CBD. This is intended to provide equivalent systemic exposures to THC and CBD as those obtained from nabiximols (a single dose of nabiximols which comprises 2.7mg THC and 2.5mg CBD). In contrast to nabiximols, TN-CT11M was formulated for a consistent and reproducible pharmacokinetic profile, allowing patients to self-titrate as needed without a concern for a delayed onset. Investigational product will be dosed

similarly to the Duran study[12], and administration will commence 24 hours prior to chemotherapy to confirm tolerability.

Placebo

The placebo will be in white capsules, identical in appearance to that of the active treatment.

Randomisation, allocation concealment and double-blind conditions

Randomisation will be performed centrally using minimization, with stratification by chemotherapy emetogenic risk (moderate vs high by MASCC criteria) and by site.

Pharmaceutical Packaging Professionals (PPP) will store and distribute the drug on behalf of the study sponsor to all participating sites upon receipt of all drug order forms.

Background treatment

All patients will receive antiemetics including 5HT3 antagonist, corticosteroid, and (where indicated) NK1 antagonist; according to a pre-specified choice of regimen consistent with guidelines from eviQ Cancer Treatments Online[14] and/or MASCC guidelines for optimal anti-emetic prophylaxis of chemotherapy[2].

The following rescue therapies are permitted:

- Lorazepam, eg 1mg PO bd (twice a day) prn (when required)
- Metoclopramide, eg 10mg PO tds (three times a day) prn
- Haloperidol, eg 0.5 – 1mg PO tds prn
- Prochlorperazine, eg 5 – 10mg PO tds prn, 25mg sup PR (per rectum) q8h prn
- Olanzapine, eg 5mg PO bd or 10mg PO mane for 3 days

Note:

- 5HT3 antagonists should only be used when other rescue therapies have failed

Recruitment and consent

Patient screening and enrolment undertaken at participating sites will be overseen by the site principal investigator and performed by trained study personnel. A screening log will document all eligible patients screened and approached along with reasons for any exclusions. Patients will provide written informed consent prior to study enrolment.

Pilot study

The phase II pilot trial (N=80) will be a multi-site, 1:1 randomised, double-blind, placebo-controlled trial (Figure 1). The dosing regimen will be similar to that used in the nabiximiols study by *Duran* et al described above, which was shown to be well tolerated and effective, however patients will also receive study drug for 24 hours prior to chemotherapy to confirm tolerability. It will utilise a crossover design and a significance level of 10% to increase efficiency, and allow patients to nominate a preferred drug in the final cycle.

In the pilot study, during chemotherapy cycle A, subjects will be randomised to receive oral *TN-TC11M* capsules *(*2.5/2.5mg) TDS from day -1 to 5, or identical placebo capsules, in addition to guideline consistent anti-emetics. For cycle B, subjects will cross-over to receive the alternative formulation in the same schedule.

On treatment, patients will be able to self-titrate their *TN-TC11M*/placebo exposure based on tolerance, with a maximum does of 30mg/30mg per day (12 tablets) (Table 1). Following cycle B, subjects are asked to nominate their preferred regimen after cycle B, and where relevant will receive that agent with cycle C.

Table 1: On treatment schedule with dose modifications

Day	Time	Dose	Dose titration	Maximum dose

				per 24-hour period
-1	Mane	1 capsule	N/A	5 capsules 12.5mg TCH/CBD or placebo
	Midi (at least 4 hours after previous dose)	2 capsules	Miss dose if intoxicated	
	Nocte (at least 4 hours after previous dose)	1–2 capsules	Miss dose if intoxicated Reduce dose by 1 capsule if previous dose not tolerated Maintain dose if previous dose tolerated	
1	60 min prior to chemotherapy	1–2 capsules	Miss dose if intoxicated Reduce dose by 1 capsule if previous dose not tolerated Maintain dose if previous dose tolerated, with nausea control Increase dose by 1 capsule if previous dose tolerated, but inadequate nausea control	8 capsules 20mg TCH/CBD or placebo
	Immediately after completion of Day 1 chemotherapy infusion	1–3 capsules		
	4 hours after completion of Day 1 chemotherapy infusion	1–3 capsules		
2 3 4	Continue tds Mane Midi Nocte	1–4 capsules	Miss dose if intoxicated Reduce dose by 1 capsule if previous dose not tolerated Maintain dose if previous dose tolerated, with nausea control	12 capsules 30mg TCH/CBD or placebo
5	Mane	1–4 capsules	Increase dose by 1 capsule if previous dose tolerated, but inadequate nausea control	8 capsules 20mg TCH/CBD or placebo
	Take final dose Midi Day 5			

Table 1 shows the starting dose will be 1 capsule PO on the morning of Day -1, with the next scheduled dose of 2 capsules (if tolerated, at midday), followed by 2 capsules that evening (if tolerated). On Day 1 subjects receive 1–2 capsules 60 minutes prior to chemotherapy infusion, followed by 1–3 capsules immediately after completion of Day 1 infusional chemotherapy, then 1–3 capsules 4 hours after completion of Day 1 infusional chemotherapy. On Days 2-5 subjects take 1-4 tablets TDS, with instruction to dose-titrate according to intoxication, tolerance of prior dose, and nausea control. The final dose is at midday on Day 5, with no further treatment until Day -1 of the next chemotherapy cycle.

Definitive study

The definitive randomised phase 3 study (N=250) will assess the efficacy of the addition of TN-TC11M to guideline consistent anti-emetics as secondary prevention of CINV. It will have a parallel group design, to reduce bias given the possibility of carry-over effect from cross-over in subsequent cycles, and to investigate longer-term efficacy over multiple chemotherapy cycles.

In the definitive study, during cycle A, subjects will receive oral *TN-TC11M* capsules *(*2.5/2.5mg) TDS from day -1 to 5, or identical placebo capsules, in the same treatment schedule (see table 1). For cycle B (and C if relevant), subjects will re-commence treatment with the investigational product on their maximum tolerated dose from the previous cycle, with further scope to self-titrate according to symptoms.

Data acquisition

The participant will be instructed on the use of the patient diary, which has been designed for this study, to record;

- Nausea (past 24-hour period), recorded using an 11-point rating scale
- Date, time and type of rescue medication used
- Vomiting and dry retching episodes

The patient diary will be completed by the patient. There will be daily assessment of patients on days 1 to 6 of each cycle to ensure:

- Study treatments are taken appropriately
- Accurate records in the patient diary
- Completion of structured checklist of cannabinoid-specific adverse events
- Advice is provided regarding management of any adverse events

Trial data will be recorded on the (e)CRFs provided and will monitored by clinical trials program staff from the NHMRC Clinical Trials Centre.

Unblinding and post-study care

Following completion of trial treatment, patients who have experienced benefit and require ongoing treatment with the same chemotherapy regimen may be eligible for ongoing access to *TN-TC11M,* free of charge, contingent on unblinding performed by an unblinded statistician.

STATISTICAL CONSIDERATIONS

Sample size estimation

The estimated sample size for the pilot trial is 80 patients (40 per arm), using a primary endpoint of complete response to the study drug and placebo during cycle A and B of treatment. Utilizing a cross-over design, randomising patients to either study drug followed by placebo or placebo followed by study drug, will have 80% power at a 2-sided significance level of 10% to detect a 20% difference in discordant responses (response on one intervention, but not the other). Accrual is expected to take 12 months. The 20% difference is based on the assumption that 42% of patients on the study drug will respond compared with 22% on placebo, and that the responders in the placebo group will respond/not respond equally on the study drug (11% respond on each).

The estimated sample size for the definitive trial is 250 patients (125 per arm), using a primary endpoint of complete response during cycle A of study treatment. A sample size of 250 patients provides 80% power at 2-sided 5% level of significance to detect improvement in complete response from 22% to 42.5%. Accrual is expected to take 2.5 years.

The sample size for each trial will allow for a drop-out/ineligibility rate of 20%.

The current evidence suggests that this level of improvement is both worthwhile and feasible.

Statistical analysis

Pilot study

Analyses will be conducted using intention to treat (ITT) principles. The primary analyses will include all patients who were randomised. Missing values will not be imputed. The results will be examined for differential effect in the two periods and if necessary, the data from cycle A will be analysed separately.

The primary outcome is complete response. The primary analysis will be a comparison of the proportion of patients with a complete response between the two treatments over cycle A and cycle B, using McNemar's test. In the event that there is differential drop-out between period, or a period by treatment interaction, the results from the first period will be analysed using a chi-square test. Analyses to assess period by treatment interaction will use Generalised Estimating Equations (GEEs) to account for the correlation within a patient. Secondary analyses to adjust for any baseline variables will also use GEEs. All tests will use a two-sided significance level of 10%.

Definitive study

The primary analyses will include all randomised patients using ITT principles, and compare the proportion of patients with complete response in the two treatment arms during the overall phase (0-120 hours) of cycle A, using a Chi-square test. Secondary analyses adjusting for baseline variables will use GEEs. Binary secondary outcomes will be analysed as for the primary outcome. Count data will be analysed using a Generalised Linear Model with a Poisson distribution. Cannabinoid-related adverse events and measures of adherence will be analysed with a chi-square test or two-sample t-test or just listed depending on numbers. All tests will use a two-sided significance level of 5%.

Health economic analysis

A within-trial and modelled economic evaluation will be undertaken to determine the incremental cost-effectiveness of oral cannabinoid therapy compared to placebo and other anti-emetic therapies, from a health system perspective.

For the within-trial analysis, resource use will be identified and measured from trial case report forms (for hospitalisations), and through linkage to Medicare claims data for outpatient visits (MBS) and prescribed medicines (PBS). Australian unit costs will be applied to the resource usage data (e.g. Australian Refined Diagnostic Related Groups (AR-DRG), and Medicare scheduled fees using the most recent reference year). For the modelled evaluation, resource use will be taken from the trial data for cannabinoid and placebo therapies, and supplemented with published estimates of resource use and costs for alternative 'usual care' anti-emetic therapies.

The definitive study will employ a health economic analysis which will use the proportion of patients with 'complete response' (i.e. participants with no emesis and no use of rescue medications, consistent with the primary endpoint); quality of life as measured by the FLIE with 5-day recall and AQOL-8D instruments[15], and quality-adjusted survival. Quality-adjusted survival time will be used to quantify the incremental effectiveness of cannabinoid treatment. Quality-adjusted survival will be calculated by applying utility weights for quality of life derived from the AQOL-8D utility instrument to survival data using established methods. In addition, we will conduct a sensitivity analysis to determine the incremental costs to achieve an outcome of no significant nausea, no emesis and no use of rescue medications.

Two cost-effectiveness outcomes will be reported: 1) the incremental cost per additional complete responder (trial primary endpoint) at 30 days after last dose of study drug, and 2) the incremental cost per quality-adjusted life year (QALY) gained at 12 months, using extrapolated data. These will be expressed as incremental cost-effectiveness ratios and plotted on a cost-effectiveness plane. Bootstrapping will be used to estimate a distribution around costs and health outcomes, and to calculate confidence intervals around incremental cost-effectiveness ratios[16]. A cost-effectiveness acceptability curve (CEAC) will be plotted, providing information about the probability that the intervention is cost-effective given the Australian Government's willingness to pay for a QALY gained[17]. One-way, two-way and probabilistic sensitivity analyses will be undertaken for relevant variables, including cost of the study drug.

ETHICS AND DISSEMINATION

Approval and patient-informed consent

This protocol was approved at the Sydney Local Health District ethics review committee (Royal Prince Alfred Hospital zone) and ethics review committees for all participating sites.

In Australia, the study will be conducted according to the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) and in compliance with applicable laws and regulations. The study will be performed in accordance with the NHMRC Statement on Ethical Conduct in Research Involving Humans 2007 –

updated May 2015, the NHMRC Australian Code for the Responsible Conduct of Research 2007, and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008.
To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the patient has provided written informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a participant. In this circumstance the NHMRC CTC, principal investigator and HREC must be advised immediately.

TRIAL STATUS

Patient enrolment for the pilot study commenced in November 2016 at the Chris O'Brien Lifehouse in NSW, Australia, with the 10th NSW site opened in June 2017. To date 49 patients have been enrolled, with anticipated pilot study enrolment completion by 3rd quarter 2018.

Acknowledgements Special study personnel, patients and their families
Contributors PG, PSH, MS, NL, JS, IM, IO, DJA, CG, AK, were responsible for study concept (grant authors). PG, PSH, MS, NL, JS, IM, IO, DJA, CG, AK, RML, NW were responsible for protocol development. PG, AT, AM, NW, AW, CH, AK, MS, CG, PF, SC, KB and MA were responsible for study conduct.
Funding NSW Department of Health, drug supply by Tilray
Drug supply Tilray
Protocol version 2.0, 9th June 2017
Data access Data access will be restricted to NHMRC Clinical Trials Centre staff
Competing interests No authors disclosed a relevant conflict of interest
Ethics approval Sydney Local Health District ethics review committee (Royal Prince Alfred Hospital zone).
Dissemination policy Results will be communicated by a writing committee appointment by the trial management committee and disseminated in peer-reviewed journals and at scientific conferences
Provenance and peer review Not commissioned; externally peer reviewed
Data sharing statement This is a protocol paper, and no analysed results are available at this time

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Figure 1: Study schema for pilot phase II, double-blinded, randomised, placebo-controlled cross-over study and planned definitive phase III, blinded, randomised, parallel, placebo-controlled trial.

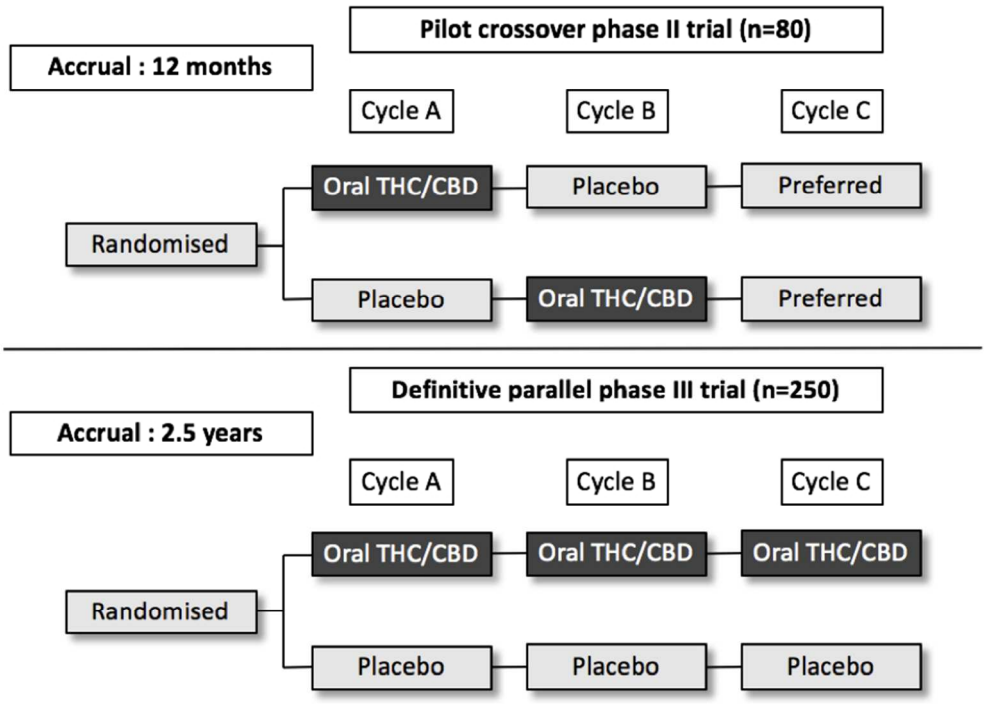

Figure 1 - Study schema

157x115mm (150 x 150 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym (page 1)
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry (page 2)
	2b	All items from the World Health Organization Trial Registration Data Set
Protocol version	3	Date and version identifier (Page 10)
Funding	4	Sources and types of financial, material, and other support (page 10)
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors (pages 1 and 10)
	5b	Name and contact information for the trial sponsor (page 1)
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities (page 9)
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) (page 4)
Introduction		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention (page 2 and 3)
	6b	Explanation for choice of comparators (page 3)
Objectives	7	Specific objectives or hypotheses (page 3 and 4)

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) (pages 4, 7 and 8)
Methods: Participants, interventions, and outcomes		
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained (page 4)
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) (pages 4 and 5)
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered (pages 5, 6 and 7)
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) (pages 6 and 7)
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) (pages 7 and 8)
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial (page 6)
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended (page 3, 4, 7, 8 and 9)
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) (page 4, figure 1, pages 6, 7 and 8)
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations (page 8 and 9)
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size (page 4)
Methods: Assignment of interventions (for controlled trials)		
Allocation:		

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions (page 6)
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned (page 6)
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions (page 6)
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how (page 5 and 6)
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial (page 8)
Methods: Data collection, management, and analysis		
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol (page 7 and 8)
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols (page 7 and 8)
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol (page 8)
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol (pages 8 and 9)
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) (pages 8 and 9)
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) (pages 8 and 9)

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed (page 4)
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial (pages 8 and 9)
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct (page 4)
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor (page 4)

Ethics and dissemination

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval (page 9)
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) (page 9)
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) (page 9)
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable (pages 8 and 9)
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial (page 10)
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site (page 9)
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators (page 10)
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation (page 8)

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions (pages 2 and 9)
	31b	Authorship eligibility guidelines and any intended use of professional writers (Page 10)
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code (page 10)
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable (not applicable)

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.