CLINICAL TRIAL PROTOCOL

AN RCT OF CANNABINOID REPLACEMENT THERAPY (SATIVEX®) FOR THE MANAGEMENT OF TREATMENT-RESISTANT CANNABIS DEPENDENT PATIENTS

Protocol number: 1.4
Date Amended: 2015 1 December 2015

Universal Trial Number: TBA
ANZCTR registration number: TBA

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ABBREVIATIONS

ADIS	Alcohol and Drug Information Service
AIS	Athens Insomnia Scale
ANOVA	Analysis of Variance
AUDIT	Alcohol Use Disorders Identification Test
b.d.	Twice a day
BDI-II	Beck Depression Inventory II
CI	Chief Investigator
CONSORT	Consolidated Standards of Reporting Trials
CPQ	Cannabis Problems Questionnaire
CRF	Case Report Form
CWS	Cannabis Withdrawal Scale
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiogram
FTND	Fagerstrom Test for Nicotine Dependence
GC/MS	Gas Chromatography/Mass Spectrometry
GCP	Good Clinical Practice
GP	General Practitioner
HAD	Hospital Anxiety and Depression Scale
HREC	Human Research Ethics Committee
MANOVA	Multivariate Analysis of Variance
MO	Medical Officer
NCPIC	National Cannabis Prevention and Information Centre
NHMRC	National Health and Medical Research Council
NRT	Nicotine Replacement Therapy
NSW	New South Wales
PAG	Project Advisory Group
PMT	Project Management Team
q.i.d.	Four times a day
RA	Research Assistant
SAE	Serious Adverse Event
SDS	Severity of Dependence Scale
SF-12	Short Form 12
SESLHN	South East Sydney Local Health Network
HNELHN	Hunter New England Local Health Network
SUSAR	Suspected Unexpected Serious Adverse Reaction
TGA	Therapeutic Goods Administration
TLFB	Timeline Followback Method
UDS	Urine Drug Screen
WSLLHD	Western Sydney Local Health District

1 GENERAL INFORMATION

1.1 SYNOPSIS

Study title: An RCT of cannabinoid replacement therapy (sativex®) for the management of treatment-resistant cannabis dependent patients

Protocol number: 1.0

Development phase: Phase III

Indication: Cannabis dependence

Investigational drug: Sativex (1 spray: 2.7 mg THC and 2.5 mg CBD)

Dosage form/strength: Maximum dose of individually titrated doses, up to 8 sprays (21.6 mg THC:20 mg CBD) delivered as buccal spray up to four times a day.

Number of participants: 142

Number of centres: 4

Study duration: 36 months

Duration of subject participation: 24 weeks, comprising of 12 weeks of study intervention with medication at maintenance doses, 1 week of medication taper (week 13), and then follow up at week 24 for research interview. All participants will be followed for research, irrespective of completion of the trial intervention.

Objectives of the study: The study objective is to examine the efficacy, safety and cost-effectiveness of Sativex for treating cannabis dependent patients in the community who have not previously responded to conventional treatment approaches. Specific hypotheses are that:

1. Sativex treatment will result in significantly improved cannabis treatment outcomes (reduced illicit cannabis use and greater treatment retention) compared to placebo.
2. Sativex will have an acceptable adverse event and abuse liability profile in a cannabis-dependent population.
3. Sativex treatment will be cost effective compared to placebo.
4. Sativex treatment will result in significant improvements in a range of physical and mental health, cognitive performance, and psychosocial function measures compared to placebo.

Study design: This project is a phase III multisite (four-sites) outpatient randomised double-blind placebo controlled parallel design comparing a 12-week course of buccal (mouth spray) administered Sativex (Experimental) to placebo (Control) (Figure 1). Both groups will receive structured "best practice" psychosocial counselling, regular case management and clinical reviews over the course of the trial. The medication will be dispensed twice weekly and UDS taken at medication dispense. Medication will be discontinued in week 13, with tapering doses. Participants will be followed up at week 24, 12 weeks after maintenance Sativex/placebo treatment.

Setting. The trial will be coordinated from the University of Sydney. Treatment will be provided at The Langton Centre, South East Sydney Local Health District (SESLHD); The Cannabis Clinic at St George Hospital (SESLHD); Centre for Addiction Medicine, Cumberland Hospital and the Hunter New England Clinical Drug and Alcohol Services Site (Newcastle Cannabis Clinic); services experienced in delivering and evaluating interventions for cannabis users and in pharmacotherapy research. Analytical toxicology services will be provided by the laboratory of CID

Eligibility criteria:

Inclusion criteria*:* (a) *aged 18 to 65 years*, (b) *meet ICD-10 cannabis dependence criteria*; (c) *have previously attempted but not responded to treatment for cannabis use* (operationalized as relapsed to regular cannabis use within 1 month of attempted cessation, with or without outside intervention); and (d) *willing and able to provide informed consent* to study procedures (including not driving or operating machinery whilst engaging in this study).

Exclusion criteria: (a) *Presence of another substance use disorder* (alcohol, other illicit or prescription drug dependence), diagnosed by specialist clinical assessment, including urine drug screen (UDS); (b) *severe medical* (e.g. chronic pain, hepatic or cardiovascular disease) *or psychiatric disorder* (e.g. schizophrenia, recent drug-induced psychosis, severe affective disorder), assessed by the study medical officer; (c) *pregnant or lactating women* (urine β-hCG); (d) *concerns regarding safe storage of medication* (e.g. unsuitable home environment or significant child protection concerns); (e) *not available for follow-up* (e.g. likely travel or imprisonment), (f) Court mandated to attend cannabis treatment. (g) History of epilepsy or recurrent seizures (h) Renal impairment, (i) Current active treatment for cannabis use disorder

These criteria aim to exclude individuals with concurrent conditions that jeopardise safety or confound data interpretation.

Statistical methods: Chi square and ANOVA will identify any baseline covariates that differ between groups for controlling the main analyses. Missing data will be imputed using multiple imputation except for missing urine where cannabis use will be assumed to have taken place. All analyses will use Intention-to-treat. Mixed Models for Repeated Measures (MMRM) will compare groups on changes in outcome variables (cannabis use and secondary outcomes) in the medication phase. Adverse Events will be analysed using chi-square. A Cox proportional hazards model will compare retention in treatment between study arms, controlling for potential confounds. The impact of the intervention on post-medication outcomes will compare changes in cannabis use outcomes at baseline and at follow up between groups using MMRMs. Family-wise error corrections will control for Type 1 errors where multiple comparisons are performed.

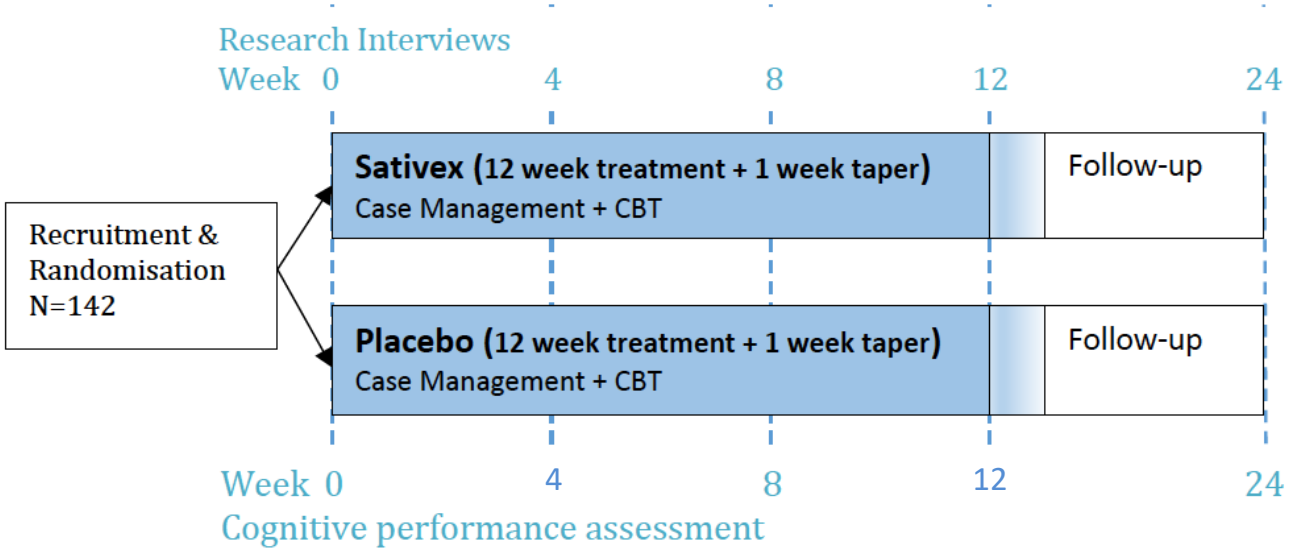

Figure 1. Schematic overview of study design

1.2 Investigators

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1.3 Study physicians

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- Dr Mark Montebello - Study Physician at SESLHD Sites
- Associate Professor Adrian Dunlop - Study Physician overseeing Hunter New England Clinical Drug and Alcohol Services Site
- Dr Craig Sadler - Study Physician at Hunter New England Clinical Drug and Alcohol Services Site

- Dr Nghi Phung – Study Physician overseeing Centre for Addiction Medicine site at Westmead.

1.4 Other personnel

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1.5 Persons authorised to sign protocol and protocol amendments

The University of Sydney is the sponsor of the trial, and Professor Nicholas Lintzeris (CIA) is the scientific delegate of the sponsor and is responsible for the overall conduct of the trial and is authorised to sign the protocol and its amendments. The Principal Investigators (Medical) at each site (Prof. Nick Lintzeris and Ass. Prof. Adrian Dunlop; Dr Nghi Phung) are responsible for the appropriate conduct of the trial at each site, in line with the Clinical Protocol, and so are authorised to sign the protocol and its amendments. A/Prof David Allsop is the Trial Coordinator and responsible for compiling the clinical protocol and obtaining the above senior management teams signed acknowledgement that they are fully aware of and endorse all aspects of the study contained within the protocol.

1.6 Trial site

1.6.1 Clinical

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South East Sydney Local Health District Cannabis Clinic Sites, including:
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The study will be conducted at these specialist outpatient drug treatment units, staffed by medical, nursing and allied health staff, with on-call medical services after-hours.

1.6.2 Laboratory

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1.7 Pharmacy

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As for Langton Centre

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Other sites will perform local in house blood and urine treatment and storage.

2 BACKGROUND INFORMATION

2.1 Treating cannabis dependence

Approximately 180 million people currently use cannabis worldwide, dwarfing the use of all other illicit substances.[1] Up to a third of the adult population in Australia have used cannabis at some stage in their lives,[2] approximately 10% of whom become dependent.[3] Cannabis dependence is associated with a range of health problems (cognitive, psychiatric, cardiovascular and respiratory disorders),[4] and considerable societal burden.[5] A recent estimate (by CIF) of the economic burden of cannabis use in NSW alone identified an annual cost to the criminal justice system of $61 million, to the health care sector of $14 million, and motor vehicle accident related costs of $2.3 million.[6] Cannabis ranks second of all illicit drugs in hospital associated costs,[7] and is the primary drug of concern in 22% of Australian Drug and Alcohol (D&A) treatment episodes,[2] and is identified as a problem in 45% of all of such episodes.[2] As with other drugs of abuse, the majority of costs arise from the small proportion of heavily dependent users who experience most harm.

The effectiveness of existing treatments is far from satisfactory. Reviews of current best practice psychosocial interventions (e.g. cognitive behavioural therapy (CBT)) indicate that around 80% of patients relapse within 1-6 months.[9-11] Treatment of acute cannabis withdrawal is associated with similar relapse rates following withdrawal completion.[8,12] More effective approaches are clearly required for the tens of thousands of Australians seeking help every year for cannabis-related problems. As with the treatment of other chronic addiction and mental health conditions, the importance of adjunctive or substitute medicines to support current best practice psychosocial interventions has been identified.[10] However there are as yet no proven pharmacotherapies for cannabis dependence and a very large unmet treatment demand.[13]

Our own recent work in this area (CIs A to E) involved an NHMRC-funded double blind placebo-controlled RCT recently published in JAMA Psychiatry.8 This demonstrated that Sativex suppressed cannabis withdrawal and cravings in treatment-seekers during inpatient detoxification (Fig. 1A), and retained patients in treatment longer than placebo (Fig. 1B).8 Sativex was administered in doses of up to 32 sprays a day (8 sprays, 6 hourly) on days 1 to 3, and tapered off from days 4 to 6. Although Sativex ameliorated withdrawal symptoms, there were high rates of relapse following discharge (69% at one month) with and relapse rates were similar between the two groups. Thus the benefits of the 6 day Sativex regimen did not persist. This is not entirely surprising: there is little evidence for any medication-assisted withdrawal promoting long-term abstinence without ongoing support.

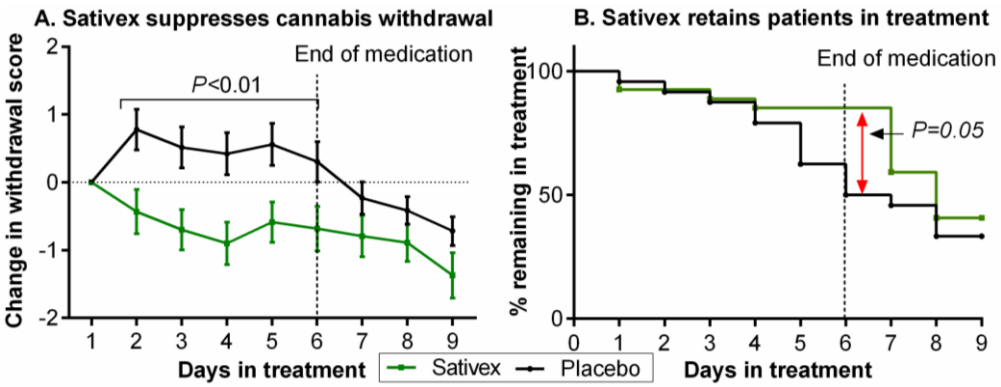


Figure 2. Data from our inpatient trial: (A) Sativex suppresses cannabis withdrawal during inpatient detoxification, and (B) retains patients in treatment longer.

Medication trials for cannabis dependence are an emerging area of research.[14] The majority of trials have either been laboratory based or have focussed only on treating withdrawal symptoms during initial abstinence rather than longer term relapse prevention. Medicines tested for withdrawal

relief include the antidepressants bupropion and nefazodone,[15] the mood stabilizers divalproex[16] and lithium (CIs A-D),[12,17] and the α_2-adrenergic agonist lofexidine.[18] Despite sometimes compelling support from preclinical research, these human trials have only achieved limited outcomes. More promising results have emerged with the use of substitute cannabinoid receptor agonists. Dronabinol, a synthetic analogue of THC that is orally administered, dose-dependently reduced cannabis withdrawal in laboratory[16] and outpatient settings.[26,27] Nabilone, another synthetic THC analogue was efficacious in the laboratory, but is as yet untested in the clinic.[19]

2.2 The case for agonist treatment for cannabis dependence

The high rate of relapse after acute medication-assisted withdrawal has led a number of leading experts to identify the need for longer-term outpatient trials of cannabinoid replacement therapies.[10,13] Agonist replacement therapies have unequivocal safety and efficacy in the treatment of nicotine[20] and opioid dependence.[21] The rationale for agonist medications in cannabis dependence is that they provide a safer route of administration (than smoking), should reduce unsanctioned drug use by preventing withdrawal and reducing cravings,[8] and attenuate the acute effects of smoked cannabis,[11,28] facilitating greater engagement in psychosocial interventions. Together, these anticipated effects should empower patients to make the necessary lifestyle changes, and distance themselves from regular substance use, prior to tapering off the agonist medication.

To date, there has been only one controlled clinical trial of agonist medication for treating cannabis dependence beyond the acute withdrawal period.[22] A 12-week outpatient trial of oral dronabinol (20 mg twice a day) did not significantly reduce cannabis use. However subsequent laboratory research has shown that higher single doses of dronabinol (60 or 120 mg) are required to significantly reduce cannabis withdrawal discomfort, suggesting inadequate dosing in the prior clinical RCT.[23] Furthermore, the pharmacokinetic profile of dronabinol indicates it may not be ideal for this purpose, with poor bioavailability, and a slow onset of action compared to smoked cannabis.[24,25] Nabilone, another oral synthetic THC analogue with better bioavailability than dronabinol, did reduce cannabis use in laboratory studies,[19] but has not been tested clinically.

2.3 The rationale for sativex in treating cannabis dependence

Sativex has been approved in Australia since Nov 2012 for *symptomatic relief of moderate to severe spasticity in multiple sclerosis (MS)* and in 8 other countries for similar indications. It is an oromucosal spray that is absorbed buccally and contains extracts from *Cannabis sativa* plants grown under licence in the UK by the company GW Pharmaceuticals. These extracts, known collectively as *nabiximols*, contain 27 mg/ml THC and 25 mg/ml CBD per spray, with small amounts (4 mg/ml) of other plant-derived cannabinoids. Sativex is delivered in a mechanically actuated pump, with each spray delivering 100µL (2.7 mg THC and 2.5 mg CBD). The buccal route provides a more rapid onset of action and more favourable pharmacokinetics than oral THC.[26]

THC is the primary psychoactive component of cannabis, and its intoxicating and rewarding effects are mediated by its partial agonist properties at cannabinoid type-1 (CB1) receptors.[27] The THC in Sativex provides the agonist substitution component without the spiking in THC than typically seen with smoked illicit cannabis use as a result of its buccal administration route taking more time for the cannabinoids to be absorbed into the blood stream and reach their site of action.[28] Nevertheless Sativex delivers cannabinoids sufficient levels to ameliorate withdrawal and cravings. The high CBD content of Sativex is a major innovation over existing CB1 receptor agonists such as Dronabinol and Nabilone. While structurally similar to THC, CBD has no intoxicating effects and recent research indicates that CBD has powerful anxiolytic, antidepressant and antipsychotic properties, and can attenuate paranoia and other adverse psychological effects of THC.[29]

Whilst the effects of CBD in cannabis on cognitive and memory impairment is less well researched, there is a growing body of interesting findings which suggest plausible research hypotheses in the current study. CBD may minimise the cognitive and memory deficits associated

with THC. High doses of THC are well known to cause memory impairment, mediated through hippocampal and prefrontal CB1 receptors. CBD appears to directly counter these effects. For example, hippocampal volume is inversely correlated with long-term THC levels in the hair of illicit cannabis users but positively correlated with CBD levels.[30] Memory impairment occurs during acute intoxication with illicit cannabis with low CBD content; however, no change from baseline performance was apparent with high-CBD cannabis.[31] Hence, the high CBD levels in Sativex could introduce positive therapeutic effects and counteract the anxiety, low mood and cognitive deficits associated with heavy illicit cannabis use.[8,32] While CBD can occur naturally in cannabis plants, a recent study by CID shows that Australian cannabis generally has high THC levels but very low and often undetectable levels of CBD (Fig. 3A).[33] Our own recent analysis of treatment seeking cannabis users shows high THC levels but virtually no CBD in their plasma,[8,12] (Fig 3B). Thus, the high concentration of CBD in Sativex may therefore counter the anxiety, low mood, agitation, paranoia and cognitive deficits associated with illicit cannabis use, and provide a potentially 'safer' cannabinoid than either synthetic THC or illicit cannabis.[34]

In summary, the pharmacological profile of Sativex suggests it may have advantages over other available THC agonist medications in treating cannabis dependence. Our priority is to build on our expertise in this area and to examine whether the withdrawal benefits we observed in the inpatient environment extend to longer-term relapse prevention in outpatient settings, where the vast majority of treatment for cannabis dependence occurs. Of course treatment with Sativex must carefully address the safety concerns inherent in the use of any agonist medication with psychoactive effects.

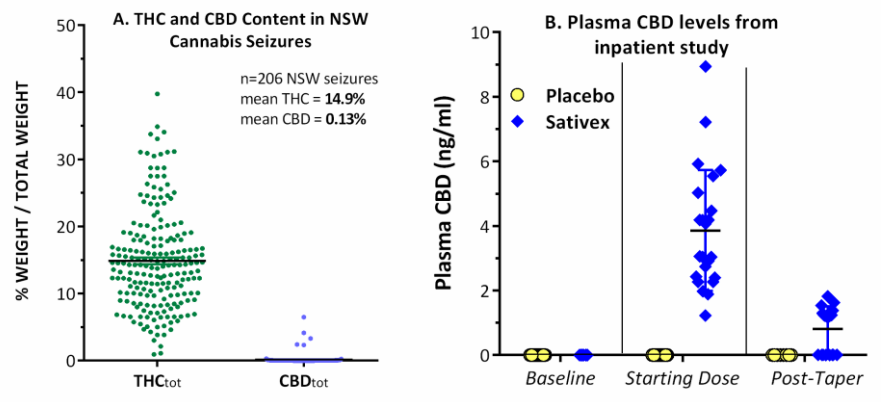


Figure 3. (A) Cannabis seized by NSW police has high THC and very low CBD content. (B) CBD was undetectable in plasma in dependent cannabis users (n=25 per condition) at entry into our inpatient study.

2.4 Safety and abuse liability of sativex

The potential benefits of Sativex must of course to be balanced against safety concerns including: (a) adverse events (AEs): e.g. intoxication, cognitive impairment and psychiatric morbidity, and (b) abuse liability in this patient population. A recent safety assessment conducted by the Therapeutic Goods Administration (TGA) summarised available safety data from all suitable Sativex Phase III trials (n=1821 subjects), and available post-marketing surveillance systems (estimated at 5,500 patient exposure years, often in combination with other medications such as antidepressants, opioids, benzodiazepines). Their conclusion was: *On balance, Sativex is associated with a wide range of undesirable CNS side effects, including dizziness, fatigue and disorientation …. The AE profile is broadly consistent with expectations, given the pharmacological profile of cannabis….. The issues primarily relate to tolerability rather than safety. None of the AEs raise major safety concerns*",[35; p.118] consistent with other reviews of Sativex safety.[36]

Another concern is the possible development of cannabis-related psychiatric morbidity in Sativex-treated patients. However, as highlighted in the TGA review: *The background of illicit (cannabis) use raises some significant concerns about the psychiatric morbidity of cannabis – although it should be acknowledged that recreational use involves higher doses and more rapid*

absorption than seen with Sativex and therefore would be expected to produce more substantial side effects.[35; p.111] Indeed those who discontinue illicit cannabis use with Sativex treatment may experience a reduction of cannabis-related adverse events.

Safety concerns also include the potential for medication abuse or diversion, particularly given the target population. Only one study has examined abuse potential of Sativex in a laboratory setting in which 23 recreational cannabis users were administered single doses of Sativex (4, 8 and 16 sprays), dronabinol (20 and 40 mg) and placebo.[37] Sativex did not produce significant adverse cognitive or psychomotor effects. While Sativex showed similar or lower abuse potential than dronabinol, both medications at higher doses had significant abuse potential compared with placebo, highlighting the need for careful monitoring of abuse and aberrant medication-related behaviours during future research.

2.5 Potential risks and benefits to human subjects

Participation in the trial is associated with potential risks and benefits. Potential benefits include improvement in the clinical condition and circumstances for individuals, commensurate with their treatment goals. Both groups will receive 'best practice' ancillary clinical services, including regular counselling, case management and clinical reviews from multidisciplinary teams experienced in treating clients with cannabis dependence. Sativex may or may not confer benefit over placebo. Sativex however may be associated with a number of potential risks or adverse reactions, including drug-drug interactions.

The key safety concern from Sativex phase III trials to date, and identified by the TGA in their recent review, is the ability to tolerate the cannabis-like effects of Sativex. This summary statement on Sativex was based on research using non cannabis using populations, primarily those suffering from MS. "Cannabis like effects" are obviously less of a concern in our target population (treatment resistant, dependent cannabis users), who will, by definition, have established tolerance to the AE profile of cannabinoids. Indeed, our recent inpatient study demonstrated Sativex was well tolerated with no difference in AEs compared to placebo.[8] Formal cognitive assessment indicated only modest reductions in cognitive performance speed with Sativex and no impairment in accuracy, or practical impairment. Clearly cognitive impairment is not a barrier to further outpatient trials.[38] In addition, subjective and objective ratings of intoxication obtained before and after each dose of Sativex in our inpatient study showed no significant difference between Sativex at high doses and placebo (Fig 4).

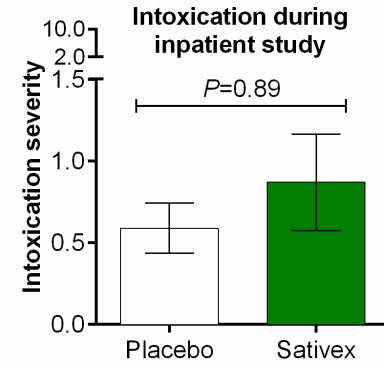


Figure 4. Sativex is not significantly more intoxicating than placebo

Our previous research in an inpatient setting demonstrated tolerable adverse events compared to placebo in a similar clinical population using comparable doses to those proposed here. However, the outpatient nature of this study raises the potential that some participants may also use other substances (alcohol, illicit or pharmaceutical drugs), with the potential for adverse drug-drug interactions, most notably additive intoxication (sedation, impaired cognition and motor performance) with other sedative drugs (e.g. alcohol, benzodiazepines, opioids, tricyclic antidepressants). Participants will be informed and warned of these risks, and regularly monitored clinically throughout the medication phase of the study.

The frequency/incidence of reported adverse reactions to cannabis therapeutics may be influenced by factors such as drug dose, concomitant drug use and disease, the administration setting, the physician's judgement and detection techniques, the patient's subjective opinion, and the ongoing use or overall tolerance to the drug. The most common reported adverse-effects to Sativex are

dizziness, disturbance in attention, dry mouth, tachycardia, and gastro-intestinal symptoms. Short-term memory and attention, motor skills, reaction time and skilled activities may be altered under the influence of this substance. Users may experience feelings of anxiety, dysphoria, paranoia and distortion of time and space. In the elderly, postural-hypotensive effects are of significance. Because of the rate of elimination of cannabinoids adverse effects may persist for more than 24 hours after a single dose; use within a therapeutic dosing regimen can lead to compounding of these adverse effects.

Administration site irritation or oro-mucosal ulceration is very common during both the short-term and long-term use of Sativex®. Regular inspection of the oral mucosa, by the prescribing physician, is advised. Patients should be advised not to continue spraying on to sore or inflamed mucosa. The potential for impaired psychomotor performance makes it inadvisable for anyone under the influence of Sativex or other cannabinoids to operate machinery drive or engage in hazardous activity.

The safety of Sativex may also be impacted by a number of metabolic states and drug-drug interactions. Sativex® is contraindicated in patients with current or previous psychiatric disorders (including manic depressive illness, depression, and schizophrenia), as the symptoms of these disease states may be unmasked or exacerbated by the use of cannabinoids. Sativex® should be used with caution in individuals receiving concomitant therapy with sedatives, hypnotics, or other psychoactive drugs because of the potential for additive or synergistic central nervous system (CNS) effects. Caution should be applied in the dosing of patients with hepatic and renal impairment, and/or concomitant use of drugs that induce/enhance or attenuate hepatic enzymes or alter renal clearance. Corresponding high blood levels of THC can increase the patient's risk of experiencing adverse effects. In elderly patients, the total body water decreases with a corresponding increase in total body fat. Consequently, the distribution and concentration of fat soluble cannabinoids are increased in these subjects.

Cannabidiol (CBD) affects the metabolism of several drugs, including Δ^9-THC, by selectively inhibiting or inactivating isozymes belonging to the cytochrome P_{450} enzyme families CYP2C, CYP3A and CYP2D, resulting in reduced metabolism and clearance of drugs metabolised by these enzymes and increasing plasma levels, including carbamazepine, phenytoin, oral contraceptives, methadone and cyclosporine. Cannabinoids are highly bound to plasma proteins and therefore might displace other protein-bound drugs. These properties have the potential to lead to drug-drug interactions and affect the pharmacokinetics of similar behaving co-administered drugs (e.g. warfarin).

Individuals will be excluded from participating in the trial as considered clinically relevant during screening and assessment by the trial Addiction Medicine Specialists (see exclusion criteria Section 1.1).

Sativex treatment and driving

Whilst our previous work with Sativex suggests that there will be no driving related cognitive impairment produced by the allowable doses delivered in this study, participants will potentially risk legal ramifications if they are road side drug tested by police whilst they are on Sativex. The legal framework governing drug driving in Australia falls under the *Road Traffic Act 1974* which makes provision for two key drug driving offences: Driving with the presence of a prescribed illicit drug in oral fluid or blood; and Driving while impaired by a drug. As such we intend to exclude people who refuse to abstain from driving for the duration of their involvement with the medication arms of this project, and to have people sign a form stating that they voluntarily commit to abstain from driving during their engagement with the trial as it is potentially illegal to drive and they may be road side drug tested at any time under the *Road Traffic Act 1974*.

2.6 Trial conduct

This study will be conducted in compliance with:

- *World Medical Association, Declaration of Helsinki (2000)*
- *National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007)*
- *Australian Code for the Responsible Conduct of Research (2007)*
- The protocol approved by the Human Research Ethics Committee (HREC) of Hunter New England Local Health District (HNELHD), and according to Good Clinical Practice (GCP) standards.

3 TRIAL DESIGN

3.1 OBJECTIVES

3.1.1 Primary objectives

The study objective is to examine the efficacy, safety and cost-effectiveness of Sativex for treating cannabis dependent patients in the community who have not previously responded to conventional treatment approaches. This study is not a detoxification study using primary endpoints of clinical outcomes after the discontinuation of medication, but rather its primary objective is to examine clinical outcomes during the 12-week maintenance phase of the medication. This trial plans to examine the impact of long-term maintenance Sativex treatment.

Specific objectives and hypotheses are:

1. **OBJECTIVE:** To examine the effects of Sativex vs. placebo on a range of cannabis treatment efficacy outcomes, including changes in illicit cannabis use during treatment and effects on retention in treatment.
   HYPOTHESIS: *Sativex treatment will result in significantly improved cannabis treatment outcomes (reduced illicit cannabis use and greater treatment retention) compared to placebo*

2. **OBJECTIVE:** To examine the adverse event profile, and the abuse liability, of Sativex as a take home treatment for cannabis use disorder.
   HYPOTHESIS: Sativex will have an acceptable adverse event and abuse liability profile in a cannabis-dependent population.

3. **OBJECTIVE:** To assess the costs and health related quality of life (HRQoL) associated with the provision of Sativex for treatment of resistant cannabis use disorder and the potential societal savings (decreased health care, improved productivity, and decrease criminal behaviors) from a potential successful treatment due to a decrease in other health care use, decreased criminal behavior, and improved productivity)
   HYPOTHESIS: Sativex treatment will be cost effective compared to placebo in achieving improving ***QALYs*** and cannabis free days

3.1.2 Secondary objectives

4. **OBJECTIVE:** To examine changes in health related outcomes during outpatient treatment with Sativex, including mental and physical health dimensions, cognitive performance, and psychosocial functioning.
   HYPOTHESIS: Sativex treatment will result in significant improvements in a range of physical and mental health, cognitive performance, and psychosocial functioning measures compared to placebo.

3.2 Design

This project is a phase II multisite (four-sites) outpatient randomised double-blind placebo controlled parallel design comparing a 12-week course of buccal (mouth spray) administered Sativex (Experimental) to placebo (Control) (Figure 5). Both groups will receive structured "best practice" psychosocial counselling, regular case management and clinical reviews over the course of the trial. The medication will be discontinued in week 13 using tapering doses of trial medication. Participants will be followed up at week 24, 12 weeks after 'maintenance' Sativex/placebo treatment.

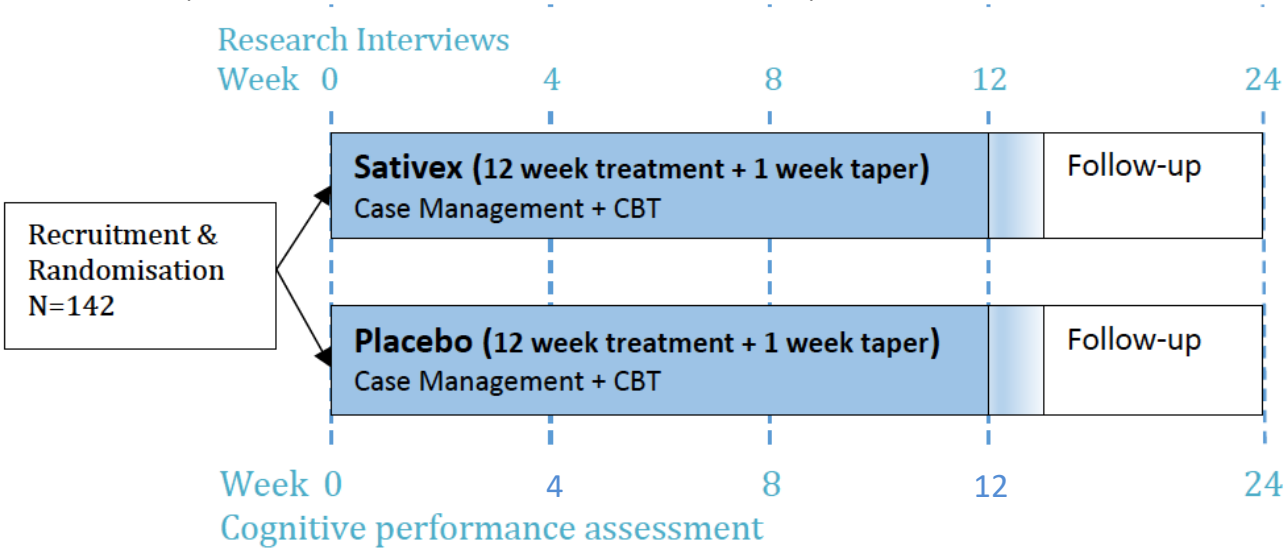


Figure 5. Schematic overview of study design

3.3 Study Outcome Measures

3.3.1 Research Interviews.

Participants will undergo confidential interviews with a research officer at baseline (0), weeks 4, 8, 12 (maintenance phase) and week 24 (follow-up). Information collected at the researcher interviews will remain confidential and not be made available to clinical staff. Subjects will be reimbursed $40 for travel and related expenses to attend each of these research interviews. Participants will be followed-up for research interviews regardless of their continued participation in trial interventions. A range of strategies will be used to enhance research follow-up, described in Section 4.12.

3.3.2 Outcome assessment

Outcome assessment at research interviews will be supported by twice weekly UDS during the medication phase (weeks 1-13) and data from clinical records. *The study is principally interested in*

outcomes during the maintenance medication phase (Weeks 1-12). Data from 24-week follow-up interview will provide valuable information on outcomes after medication cessation, and will include UDS to compare illicit cannabis use between groups 12 weeks after Sativex/Placebo cessation. The outcomes described correspond to each of the primary and secondary objectives identified above.

3.3.3 Primary outcomes

3.3.3.1 Primary outcomes: *Cannabis-related*

(1) **Illicit cannabis use** will be quantified as 4-weekly point prevalence abstinence during the 12 week maintenance phase by combining self-report data from researcher interviews (modified Timeline Followback[39] recording number of days and average daily amount (grams) of cannabis use), with objective measures of illicit cannabis use (weekly UDS with quantitative analysis of urinary THC, THC-COOH and CBD). Illicit cannabis use will also be reported as mean days used. More detail is provided regarding urine drug screen procedures in Section 3.9.

(2) **Treatment retention** (days in protocol treatment) recorded from clinic records.

3.3.3.2 Primary outcomes: *Safety, aberrant medication use and abuse liability*

(3) **Adverse events** will be assessed by self-report using a structured symptom checklist at 4-weekly research interviews, and by clinical assessment with the study medical officer at regular clinical reviews.

(4) **Aberrant medication behaviours** (missed doses, extra doses, misuse or diversion) will be assessed by measuring amounts of medication used at clinical review (by weighing bottles) and by self-report at the researcher interviews using the modified ORBIT,[40] a validated aberrant medication behaviours self-report instrument. In addition, a series of subjective assessments of abuse liability (ratings of subjective liking, comparability to cannabis, strength of effect and subjective physiological effects) will be included in line with recent recommendations by the US FDA.[41]

3.3.3.3 Primary outcomes: *Cost effectiveness*

(5) **Cost effectiveness** analysis will take a societal perspective. The primary outcome will be Quality Adjusted Life Years (QALY) measured by the SF-6D,[42] (4 weekly research interviews) and area under the curve calculated[43] for each individual. Costs will include all clinical resources provided as trial interventions, AE management, other health care (hospital, ED, GP visits, etc.) and crime, and costed using unit costs (CPI adjusted if necessary).[44] Lost productivity and personal costs will be collected by structured self-report (WHO Health and Performance Questionnaire: Clinical Trials Version).[45] The costs will be summed and combined with the outcome measure, and the incremental cost-effectiveness ratio [ICER = $(C_{Sativex}-C_{Control})/(E_{Sativex}-E_{Control})$] calculated. Boot strapping will be conducted to obtain reliable confidence intervals from skewed data, and cost effectiveness acceptability curves calculated. More detail is provided regarding health economics measures in section 3.11.

3.3.4 Secondary outcomes

(6) **Other substance use** (alcohol, opioids, stimulants, benzodiazepines, cigarettes) will be recorded by self-report (number of days used past 4 weeks) by TLFB at 4-week research interviews and validated with UDS and/or breath testing collected to coincide with researcher interviews.

(7) **Health outcomes and psychosocial function.** The SF-36[46] will be administered at 4-week research interviews to assess dimensions of physical and mental health and psychosocial function. Mental health will be also be assessed using the Depression, Anxiety and Stress Scale (DASS-21),[47] Physical health outcomes will be also assessed using the Physical Health Questionnaire-15 (PHQ-15). Self-reported drug related crime (e.g. drug dealing, income generating crime) will be examined using the Crime Section of the Opiate Treatment Index.[48]

(8) **Cognitive function** will be assessed by the researcher at baseline (week 0), during the maintenance phase (week 4 – with ± 1 week flexibility), and at follow-up (week 24) and is timed to coincide with research interviews. A targeted series of tests sensitive to acute THC effects (acute battery: Eriksen Flanker Task, Stop Signal Task, N-Back, Digit-Symbol Substitution, and Rapid Visual Information Processing) as well as a control measure (Wechsler Test of Adult Reading) and a measure of memory and learning (Ray Auditory Verbal Learning Test) will be conducted. At week 8 assessments, cognitive testing (acute battery) will be performed 30 minutes prior to (trough) and 30 minutes after (peak effects) supervised dosing. Blood samples will be taken for plasma cannabinoid levels (THC, CBD) to assist in the interpretation of findings. It will be of particular interest if Sativex use is associated with cognitive improvement relative to Placebo and relative to baseline. Week 24 cognitive performance assessment will examine for within-subject longtitudinal changes over time. More detail is provided regarding cognitive testing in Section 3.10.

(9) **Details regarding participation in trial interventions** will be obtained from electronic and paper clinical records and include details regarding doses of trial medication used (daily 'dosing diary' collected at each dispensing visit), participation in medical, counselling and clinical review sessions, and reasons for trial completion (as per protocol, treatment drop out, administrative or medical discharge). At the completion of the medication phase of the trial (week 12 researcher interview), participants will also be asked to rate their satisfaction with the trial medication, and for them to estimate which medication group they were assigned to (testing the blind) - described further in Section 3.12.

3.4 Study population

3.4.1 Inclusion and Exclusion criteria

Inclusion criteria:

(a) aged 18 to 65 years,

(b) meet ICD-10 cannabis dependence criteria;

(c) Inability to stop cannabis use, , as operationalised as relapse to cannabis use within one month of attempted cessation – either with or without outside intervention; and

(d) willing and able to provide informed consent to study procedures (including not driving or operating machinery if Sativex is affecting their ability to perform these tasks, consistent with the Product Label).

Exclusion criteria:

(a) Presence of another substance use disorder (alcohol, other illicit or prescription drug dependence), diagnosed by specialist clinical assessment, including urine drug screen (UDS);

Patients taking disulfiram for the treatment of alcohol dependence should be excluded due to the possible interaction with the small amounts of alcohol in Sativex. However, patients with a past history of alcohol dependence who are now in remission should not necessarily be discriminated against from participating in the study. Rather, the study medical officer will explain the amount of alcohol in a typical Sativex dose used in this study (usually less than 0.5 gm alcohol per dose or 0.2 standard drink per day), and then discuss with the patient the relative relapse risks. Of course, many individuals with a past history of alcohol dependence and in remission do not strictly adhere to abstinence from alcohol, and many such individuals may consider the risks of participating as acceptable. Others may want to remain completely abstinent from alcohol and avoid even small amounts of alcohol associated with Sativex. Hence in summary, past alcohol dependence in remission is not an automatic exclusion criteria, but will be individualised with each participant.

(b) severe medical (e.g. chronic pain, hepatic or cardiovascular disease, severe renal impairment) or psychiatric disorder (e.g. schizophrenia, recent drug-induced psychosis, severe affective disorder), assessed by the study medical officer;

(c) pregnant or lactating women (urine β-hCG);

(d) concerns regarding safe storage of medication (e.g. unsuitable home environment or significant child protection concerns);

(e) not available for follow-up (e.g. likely travel or imprisonment).

(f) Mandated by court to attend cannabis treatment.

(g) History of epilepsy or recurrent seizures.

(h) Currently in Court mandated treatment (e.g. MERIT, Adult Drug Court)

(i) Current active treatment for cannabis use disorder

Clients in existing treatment (e.g. Specialist Cannabis Clinics (SCC), other D&A services, private psychologist or psychiatrist): Clients already engaged and participating in counselling and/or medication based treatment for their cannabis use disorders are not eligible for the trial at the time of application. This includes a range of medications that are sometimes prescribed for cannabis use disorders (despite minimal evidence base), such as antidepressant or antipsychotic medications. To participate, clients would have to choose to cease their existing treatment (counselling, medication) for a 4 week period prior to being formally assessed for the trial.

Clients entering treatment (through Intake or routine screening for trial): In other circumstances, a cannabis dependent client may contact services (e.g. a specialist cannabis clinic, D&A Intake, routine screening for trial) and be unclear or ambivalent regarding their desired treatment choices. It is appropriate under such circumstances for the SCC clinician to comprehensively assess the client, discuss treatment options and develop a treatment plan, which may include participation in the Sativex RCT (note that structured CBT as routinely provided by SCCs is a component of the Sativex RCT).

Clients engaging in other forms of treatment for related conditions. Clients may already be participating in treatment for conditions that may be related to their cannabis use disorder – but that does not specifically address cannabis use as the target of the intervention. This may include psychosocial interventions or pharmacotherapies for depression, anxiety, sleep or relationship problems, or physical interventions for related respiratory, sleep or pain disorders.

Under such circumstances, the assessing study clinician should get consent from the client to communicate with the treating clinician, and clarify the nature and purpose of the existing treatment. Participation in an alternative treatment that does not primarily target cannabis use disorder is not grounds for exclusion. Where possible, participants should be encouraged to stay in 'stable' treatment (e.g. medication doses, counselling) for other conditions as required for the other condition. Where in doubt, discuss the case with the site investigator.

These criteria aim to exclude individuals with concurrent conditions that jeopardise safety or confound data interpretation.

3.4.2 Subject Numbers and power calculations

Psychotherapy treatment studies for cannabis achieve abstinence rates of 12 to 23% (mean, 20.8%) over follow-up periods from 2-6 months,[14] and medication studies are similar (~23.1% abstinence).[8,22] We thus base our power analysis on the assumption that the Placebo group will achieve abstinence rates at 12-weeks of ~22%. We predict that the addition of Sativex to psychotherapy will double abstinence rates to approximately 44%. This estimate is based upon findings from a laboratory relapse model, in which heavy cannabis users consumed less than half the amount of cannabis (mean 43% less, range 39-48%) following repeated doses of nabilone, relative to placebo treatment.[19] With 80% power (two tailed) and α=0.05, a total of 142 participants (71 per group) are needed to detect the predicted benefits in cannabis abstinence.

3.5 Recruitment procedures

The summary of recruitment procedures is detailed in Figure 6 and more details about recruitment to this project are given in section 4. In brief, participants will initially be screened in a telephone interview by research staff. Those broadly eligible will be medically assessed by an Addiction Medicine Specialist, including a structured clinical history, physical and mental state examination and relevant investigations, including onsite urine testing to exclude pregnancy and to

confirm recent THC use. Eligible participants will attend a research interview for written informed consent, baseline data collection and randomisation.

Participants will be recruited via D&A services of SESLHD, WSLHD or HNELHD. All three LHDs have large D&A services, including Specialist Cannabis Clinics targeting clients with cannabis use disorders. Recruitment will be supplemented by advertisements (flyers) in local primary care services, NGOs and Emergency Departments, and media advertisements in local popular press. Similar procedures in previous cannabis pharmacotherapy trials at these sites have recruited 5 to 8 subjects per month.[8,49] As such we anticipate that this study will recruit the required 142 subjects in 18 months.

3.5.1 Eligibility assessment: telephone screening

Clients interested in participating in the study will undergo a detailed phone screen interview by CIB or his delegate based at the University of Sydney, or the RA at Newcastle, and if eligible, will be scheduled for face to face eligibility assessment by the trial MO's. The detailed phone screen will include information regarding:

- Demographic characteristics (e.g., age, sex, housing, employment, education)
- Whether the potential participant has been mandated by a court diversion program to seek cannabis treatment (in which case they are not eligible).
- Cannabis Severity of Dependence Scale SDS; [50,51]
- Other drug use in last 28 days, including alcohol use
- Drug treatment in last 28 days
- Mental health (anxiety, depression, bipolar & schizophrenia)
- Prior unsuccessful quit attempts
- Pregnancy / contraception status
- Willingness to adhere to study procedures
- Willingness to enter into a blinded placebo vs active drug randomised controlled trial

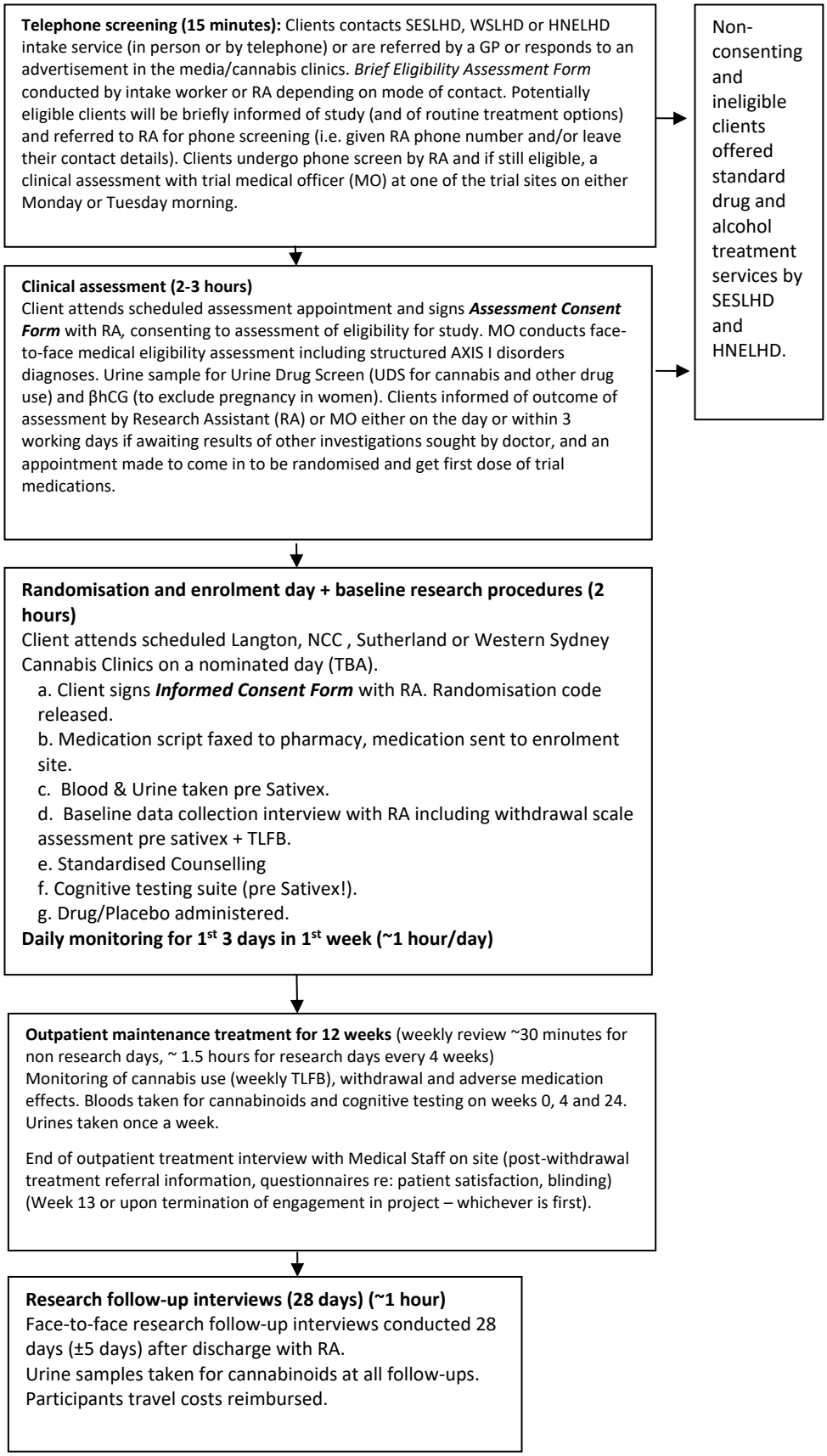
3.5.2 Medical eligibility assessment day (2-3 hours)

On presentation for a clinical assessment, a standard comprehensive clinical assessment using SESLHD, HNELHD or WSLHD D&A Services Assessment Modules will be completed by the assessing clinician. The face to face medical examination and eligibility check will take place at either the Langton Centre, the Cannabis Clinic at Sutherland/St George, the Centre for Addiction Medicine at Westmead, or the Newcastle Community Health Centre (Hunter New England Clinical Drug and Alcohol Services Site). Participants will be met by the RA at each site and will sign informed consent to take part in the medical assessment. All participants will then undergo a medical eligibility assessment by a trial MO including:

- A comprehensive substance use and medical history, including physical and mental state examinations (including psychosis assessment), and completion of ICD10 cannabis dependence criteria checklist,
- clinical diagnoses and special investigations where clinically indicated, including urine samples for UDS and βhCG (to exclude pregnancy in women).

Clients will be informed of the outcome of the assessment (including relevant investigations) immediately by MO or within 3 working days by the Trial Coordinator/RA, and randomisation/ study admission meeting booked (generally within 2 weeks of eligibility assessment). For those patients

990 who are not eligible or choose to not participate in the study, alternative treatment options will be
991 organised as clinically appropriate.
992



993 **Figure 6 Overview of recruitment and trial procedures**

3.6 Informed consent

The details of the clinical trial protocol will be discussed with each potential participant and written informed consent obtained prior to any trial-related procedure being performed. A copy of the *Participant Information Sheet* and signed *Consent Forms* will be provided to each potential participant prior to commencing any trial-related procedure. There will be two consent forms used. The first consent form (*Sativex Participant Medical Screening Consent Form*) will be to provide informed consent for the medical assessment and collection of urine samples for eligibility screening, collected by the trial MO. The second consent form (*Study Consent Form*) will be completed immediately prior to commencement of all subsequent study procedures, and will be completed with a Research Assistant (RA).

3.7 Randomisation and blinding

The study design complies with requirements of the Consolidated Standards of Reporting Trials (CONSORT) statement for conducting randomised controlled trials. The randomisation schedule will be developed by an independent statistician. Eligible participants will be randomised in a 1:1 ratio between groups using variable block randomisation to help maintain blinding,[8] with subjects stratified by site. Sativex and placebo will be packaged in labelled containers with the subjects ID number and site. Aside from trial pharmacists, no other member of the team or clinical staff will know the allocation of treatment condition. Master randomisation lists will be available if the blind needs to be broken.

Participants, clinicians and researchers involved in service delivery, data collection and analysis will remain blinded to study condition (active or placebo medication) by the use of placebos manufactured by the pharmaceutical company providing the medication and placebo, in combination with the trial pharmacists at both sites. All medications will be packaged into identical spray bottles using an alcohol base and peppermint flavouring. Our previous Sativex / placebo study[8] indicated that the blind was effectively maintained using these procedures.

The randomisation schedule will be made available to the trial pharmacists and DSMB only. The trial pharmacists will label medications in sequential and sealed opaque plastic spray vials according to the randomisation schedule. Each vial will be labelled as clinical trials medication, printed with the trial code name (SatCom - for Sativex in the community), HREC approval code (TBA), site principal investigators name (Dr Nick Lintzeris at Langton, Dr Adrian Dunlop in Newcastle, Dr Nghi Phung in Western Sydney), expiry date (listed on batch number form supplied by GW), and Subject ID (which links to the randomisation schedule).

As participants are enrolled in the study at each site, they will be dispensed according to these previously packaged medication containers. Printed details of the container's contents will be removed by the trial pharmacist prior to delivery to trial site to maintain blinding. In this way, clinicians, participants and research staff involved in treatment delivery and data collection will not have access to the randomisation schedule or be able to influence group allocation.

In cases where the allocation needs to be 'unblinded' (e.g. Severe Adverse Event), CIA or CIF (senior trial MO's) or their nominee, will be able to break the blind for that particular participant in consultation with the trial pharmacist holding the unblinded randomisation codes, or the DSMB, who will also hold the unblinded randomization codes.

3.8 Trial interventions

3.8.1 Study sites

The trial is to be conducted at four specialist outpatient D&A services experienced in delivering treatment interventions to cannabis dependent clients. The sites are The Langton centre, St George Hospital, Centre for Addiction Medicine at Westmead, and Hunter New England Clinical Drug and Alcohol Services Site (Newcastle Cannabis Clinic).

3.8.2 Trial medications: Supply, Distribution & Dispense

Active and placebo medications will be provided by GW Pharmaceuticals (UK). Sativex is dispensed in 10 ml containers (bottles), each delivering 90 metered sprays of 100 µL (2.7 mg THC and 2.5 mg CBD). The placebo medication consists of the alcohol base and peppermint oil flavouring present in the active Sativex medication, except all cannabinoids and plant based terpinoids are not present. The placebo looks and smells just like Sativex.

GW Pharmaceuticals will dispatch trial medications in batches as required depending upon recruitment rates at each site. The initial batch will be delivered to Langton Centre (the first clinical site up and running), with a batch size of:

800 vials of Sativex and 800 vials of placebo.

Vials will be packed into 24 cardboard boxes (each box size: 270x165x160mm) – they will be packed as follows:

Active: 11 boxes of 72 vials each + 1 box of 8 vials
Placebo: 11 boxes of 72 vials each + 1 box of 8 vials

This first shipment will be distributed amongst the clinical sites as needed (as they come online with recruitment activity) from the Langton Centre.

The trial pharmacists will be responsible for labelling of medication bottles used in the trial. Trial pharmacists will receive boxes of brown opaque spray bottles, with each box labelled either sativex or placebo. Labelled boxes will be transported from the UK to each of the four study sites (Langton, St George Hospital, Newcastle Community Health Centre, and Cumberland Hospital). A separate Commonwealth license will be issued for each batch consignment in the name of the Chief medical officer at each site.

Sativex and placebo will be labelled by the trial pharmacist and their staff at each site using the label below to identify the bottles (Appendix A). All bottles containing Sativex will be stored in secure S8 refrigerators at each clinical site pending prescription to a patient. Placebo bottles will be stored in non-S8 refrigerated conditions on site.

3.8.2.1 Accountability of trial medications

All medications and placebo medications received and dispensed as part of this trial will be inventoried and accounted for throughout the trial on the study medication log by the clinical trials pharmacists, and by nursing staff administering the medication at each site. Each 10ml vial of Sativex or placebo will be primed when it is the first spray from a new bottle, by pumping a full spray into a paper towel, which will then be discarded. Participants will be instructed on the correct buccal application of the medication.

As the medication and placebo are liquids held in opaque spray bottles, participants will be asked to maintain a daily dosing diary to keep track of the number of sprays delivered from each

bottle (See below). This will also assist in assessing medication use and aberrant behaviours over the trial. Medication bottles will be weighed at each dispensing visit for unauthorised dose escalation or diversion (use of >20% of maximum dose prescribed). Three such instances of aberrant medication use over the course of the trial will result in study termination.

Sativex Trial Drug Register Procedures

Upon randomisation, individual patients will be prescribed a generic study script by the doctor (See Appendix B). The script will be filled on site as the pharmacist receives the named patient script, and will be dispensed to the patient by a study nurse. A dedicated S8 requisition book and a dedicated S8 Drug Register will be used for the study at each of the four clinical sites. The trial pharmacist at each site will be responsible for compiling and maintaining a Drug Register as seen Appendix C.

Return of used or 'complete treatment" containers

Used containers must be returned to the pharmacist once a patient completes medication. Entries in the register should state "Returned to Pharmacy" date and be weighed.

3.8.3 Trial medications & Route of administration: Sativex and placebo

Sativex and Placebo are administered as sprays into the oral cavity whereupon they are absorbed through the oral mucosa.

All medications will be dispensed by trial pharmacists at the participating clinics.

Dosing regimens are described in detail below. Doses of up to 8 sprays will be delivered up to 4 times a day, titrated to individual need. This is based upon the product information,[35] published literature, and our inpatient trial where this dose suppressed withdrawal and was well tolerated.[8] Whilst the dose is higher than recommended for multiple sclerosis (up to 12 sprays per day in total with maximum 7 sprays per individual dose),[35] high doses are required to achieve therapeutic objectives (suppression of illicit cannabis use) in this cannabis dependent population. Sativex is a relatively short acting medication,[28] requiring up to 4 doses per day, preventing complete supervised dosing. Medication will be dispensed once a week from the clinics. Doses will be supervised during weekly clinic visits for compliance and safety assessments.

The spray container should be shaken before use and the spray should be directed at different sites inside the mouth changing the application site each time the product is used. Patients should wait for a period of 2-3 second between sprays to allow time for the medication to be absorbed through the oral mucosa.

It might take up to two weeks to find the optimal dose and that undesirable effects can occur during this time, most commonly dizziness. These undesirable effects are usually mild and resolve in a few days. However, the trial doctor will consider maintaining the current dose, reducing the dose or interrupting, at least temporarily, the treatment depending on seriousness and intensity.

To minimise variability in the effects of the drug Sativex should be taken at approximately the same time each day, standardised as far as possible in relation to food intake (i.e. take 30 minutes before eating). Please allow a minimum of a 2 second time frame between each spray administered into the mouth to allow time for the spray to be absorbed through the lining of the cheeks.

3.8.3.1 Week 1: Induction, dose titration, and risk assessments

As with many psychoactive medications, Sativex doses need to be titrated against individual response, particularly early in treatment as patients become tolerant to the effects of the medication. The first week involves regular review and dose titration, such that the patient has achieved their stable dose by Wk 2. Thereafter, the preferred regimen is in 8 unit daily integers (2 u QID (8/day); 4 u QID (16/day); 6 u QID (24/day); 8u QID (32/day). The proposed dosing regimen for Sativex is shown in following table.

Day	Reviewed by	Prescription	Instruction	Dispense
1	M.O.	Day 1, 2 sprays QID Day 2-3, may increase to 4 sprays QID Day 4-7, may increase to 8 sprays QID	2 sprays QID	2 bottles (Max doses: D 1: 8 D2: 16 D3:16 D4:32 D5:32 D6: 32 D7:32
2	Nurse		Take xx sprays QID Miss dose if intoxicated. Reduce dose at next administration. Maintain dose if comfortable, with minimal cravings or withdrawal. Increase dose if cravings or withdrawal	Weigh bottles & return to client
3	Nurse		Take xx sprays QID Miss dose if intoxicated. Reduce dose at next administration. Maintain dose if comfortable, with minimal cravings or withdrawal. Increase dose if cravings or withdrawal	Weigh bottles & return to client
8	M.O.	Assess dose adequacy. Prescribe either 2, 4, 6 or 8 sprays QID	Take xx sprays QID Miss dose if intoxicated. Reduce dose at next administration. Maintain dose if comfortable, with minimal cravings or withdrawal. Increase dose if cravings or withdrawal	Weigh & keep all used bottles. Dispense as per dose: 1 bottle: 8 - 12 u/day 2 bottles: 16-28 u/day 3 bottles: 30-32 u/day
15 & later weeks	M.O.	Assess dose adequacy. Prescribe either 2, 4, 6 or 8 sprays QID	Repeat as per Day 8	Repeat as per day 8

As per the above table, week 1 doses are: Day 1: up to 2 sprays 4 times a day (QID); Day 2-3: May increase to 4 sprays QID; Days 4-7: May increase up to 8 sprays QID.

Subjects will attend clinics daily during week 1 for clinical review, safety/risk assessments and a supervised dose. Subjects will be monitored for 5 minutes prior (trough effects), and 20-30 minutes after the supervised dose to clinically assess intoxication and dose adequacy. Clinical data collection will include: patient report of number of Sativex/placebo doses and any other substances used since last review; at each review the nurse of medical clinician will rate a 5 point likert scale their global assessment of whether the client is in severe withdrawal (1), mild withdrawal (2), stable (3), mild intoxication (4) or severe intoxication (5). For clients who are assessed as having any withdrawal or intoxication evident, the clinician will conduct a history of recent Sativex dosing and other substance use, and perform the following clinical assessments:

- Blood pressure
- Pulse rate
- Assessment of eye signs (red eyes, dilated or constricted pupils, nystagmus)
- Behavioural features of intoxication (sedation, slurred speech, ataxia, reddened sclera) or withdrawal (e.g. speech, gait, anxiety, restlessness, agitation)
- Breath alcohol concentration
- Urine test if indicated (suggest use instant 'dip sticks' for rapid result but also send for routine UDS – *but exclude cannabis from these tests I order to maintain the study blind*)

Features of withdrawal or intoxication may warrant review of the client's medication and dose.

Clinical review will also asses adverse events; and aberrant medication use. Medication bottles will be weighed at each dispensing visit for unauthorised dose escalation or diversion (use of >20% of maximum dose prescribed). Three such instances of aberrant medication use over the course of the trial will result in study termination.

3.8.3.2 Weeks 2-12 (eleven weeks): Maintenance phase

Doses during the maintenance phase will be based upon the dose determined at the end of week 1, and individually titrated up to a maximum of 8 sprays, four times per day. Subjects should be prescribed either 2, 4, 6 or 8 sprays QID for subsequent weeks, with clinical review, and they will attend clinics weekly to renew medication, have medication bottles weighed for above maximum prescribed dose used, provide UDS, and to undergo case management, clinical review, TLFB and counselling as described above.

In addition to the usual nursing counselling, the routine 6-session manualised CBT program developed by NCPIC will be used for all participants in the trial (Appendix D). Counsellors are to co-ordinate 6 appointments over the 12 week medication course.

Fidelity to counselling: to ensure fidelity with counselling approaches,
(a) all counsellors participating in the trial will participate in training sessions to be organised in early 2016 prior to commencement of the Newcastle, Parramatta and St George sites.
(b) all counselling sessions will be tape recorded using a digital recorder. A random selection (10%) of all scheduled counselling sessions will be selected for fidelity scoring by experienced raters

experienced in delivering cannabis CBT –based interventions. Up to 80 sessions will be monitored in this manner.

3.8.3.3 Week 13: Dose tapering and withdrawal.

The final week of medication, after the maintenance phase (and week-12 outcome assessment) is completed, will involve daily clinic attendance, dose reduction of approximately 10-20% of maintenance dose each day, monitoring of withdrawal severity (CWS)[32] and adverse events. The dose taper should minimise any discontinuation withdrawal effects: our previous study showed that a 3-day dose taper from 32 sprays per day was not associated with significantly rebound withdrawal (Fig. 2A), consistent with other published other reports on Sativex discontinuation.[35]

3.8.3.4 *Table of schedule of events.*

	STUDY PERIOD														
	Screen	Enrol	Post-allocation												Follow-up
TIMEPOINT*	$-t_1$	0	*Wk 1*	*Wk2*	*Wk3*	*Wk4*	*Wk5*	*Wk6*	*Wk7*	*Wk8*	*Wk9*	*Wk 10*	*Wk 11*	*Wk 12*	*Wk 13*	*Week 24*
ENROLMENT:																
Phone screen (Eligibility)	X															
Informed consent for medical screen	X															
Medical screen/assessment (Eligibility)	X															
Informed consent for main study participation		X														
Allocation		X														
INTERVENTION:																
Medication *[Nabiximols or placebo]* dispensed			X	X	X	X	X	X	X	X	X	X	X	X	X	
Nursing clinical reviews			X	X	X	X	X	X	X	X	X	X	X	X	X	
Medical clinical reviews			X	X		X				X				X		
Psychotherapy				X		X		X		X		X		X		
Urine drug screen[2]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ASSESSMENTS:																
Phone screen. Variables include: Demographics, Cannabis SDS, Alcohol SDS, mATOP, Drug treatment, Mental health, Prior unsuccessful quit attempts, Pregnancy/ contraception status	X															
Research Interviews. Variables include: Cannabis & other substance use (TLFB), CWS, AEs, Aberrant medication behaviour (mod ORBIT), SF-6D (QOL), WHO Health and Performance Questionnaire: CT version, SF-36 (Physical and Mental health), DASS-21, PHQ-15, OTI: Crime, Satisfaction & test blind/dose		X				X				X				X		X
Clinical (Nursing/medical) Review variables[1]: ATOP every 4 weeks (recent substance use, risk assess, physical, mental health & QOL), AEs, Aberrant medication behaviour (weigh bottles), dose adequacy			X	X	X	X	X	X	X	X	X	X	X	X	X	
Cognitive assessment[3]. Variables include Blood samples (pre/post cognitive testing), Cognitive testing, Abuse liability (subjective liking, strength, Physiological response)		X				X										X

[1] Once a week nursing clinical reviews. Will coincide with medication dispensing & UDS collection

[2] Collected once a week – coincides with medication dispensed once a week.

16 [3] *During treatment phase, assessments conducted pre (rough) and post (peak) dosing. Single sessions at Wk 24.*

3.8.4 Adjunct medications: Nicotine Replacement Therapy

All participants will be offered prescriptions for nicotine replacement therapy (NRT) either in the form of 16-hour patches (7, 14 or 21mg) and/or nicotine chewing gum or lozengers. NRT patches are to be removed at 8pm daily, to avoid abnormal dreams (Thompson and Hunter 1998). Utilisation of NRT will be documented in the patient's medical records and costs to patients itemised and included in the CEA.

3.8.5 Psychosocial interventions.

All subjects will be provided with a minimum of 6 structured 40-50 minute counselling sessions over the 12 week medication phase, based on CBT and motivation enhancement for relapse prevention, consistent with identified best practice in this area (see Appendix D).[52] Trained nurses or counsellors will deliver the counselling interventions according to a manual that will be created by the CI team in consultation with nurses and counsellors of the various services.

3.8.6 Clinical reviews, case management and monitoring

Subjects will be reviewed daily for the first 3 days during week 1 and at least weekly thereafter by experienced D&A nurses. Medical reviews will occur during weeks 1, 2, 4, 8, and 12 with additional reviews as indicated. Structured clinical assessments will include the ATOP[53] (part of electronic Medical Records documentation and a CRF) conducted 4 weekly – a validated clinician completed instrument that includes client ratings of physical and mental health and assesses a range of clinical risks (e.g. child protection, violence, homelessness). Where a clinician has concerns regarding the client's well-being due to suicidal ideation, they will complete the NSW Health D&A Clinical Documentation eMR CHOC Form "Assessment of Harm to Self or Others", as per routine practice, and escalate the case to the study medical officer, and site investigator as clinically appropriate. Such cases may require referral to appropriate emergency or mental health services, consistent with NSW Health policy directive. Depressive symptoms will be closely monitored at these reviews and if symptoms of depression are observed to clinically significantly worsen, or if suicidal ideation appears, the blind will be broken for that patient and they will be removed from the study (i.e. Sativex or placebo administration will cease under careful clinical care). Participants discontinued from the study for any reason (e.g. withdrawn consent, or due to administrative or medical discharge) will continue to receive clinical services as appropriate. In the case of participants who are discontinued from the study due to deteriorating medical condition, the addiction medicine staff specialist will be responsible for co-ordinating appropriate clinical care – which may involve alternative D&A treatment services, and/or referral to other services as clinically appropriate. Urine Drug Screens (UDS) will be collected once a week over the 12 weeks (at approximately the same time each week relative to dosing – e.g. in the am) to assess illicit cannabis and other substance use and a weekly TLFB self report cannabis use will also be collected. Standard D&A treatment case management will be implemented over the study period.

At each review the nurse of medical clinician will rate a 5 point likert scale their global assessment of whether the client is in severe withdrawal (1), mild withdrawal (2), stable (3), mild intoxication (4) or severe intoxication (5). For clients who are assessed as having any withdrawal or intoxication evident, the clinician will conduct a history of recent Sativex dosing and other substance use, and perform the following clinical assessments:

- Blood pressure
- Pulse rate
- Assessment of eye signs (red eyes, dilated or constricted pupils, nystagmus)
- Behavioural features of intoxication (sedation, slurred speech, ataxia, reddened sclera) or withdrawal (e.g. speech, gait, anxiety, restlessness, agitation)

- Breath alcohol concentration
- Urine test if indicated (suggest use instant 'dip sticks' for rapid result but also send for routine UDS – *but exclude cannabis from these tests I order to maintain the study blind*)

Features of withdrawal or intoxication may warrant review of the client's medication and dose.

3.8.7 Clinical care beyond medication phase.

Usual clinical care (counselling, case management and support) will be available as individually determined by the patient and treatment providers. Sativex will not be available to participants beyond the 13-week medication phase of the trial.

3.9 Urinalysis and blood pathology testing

Blood and urine samples will be collected in accordance with the *National Statement on Ethical Conduct in Human Research (2007).* All blood and urine samples must be taken and stored de-identified using the patients study ID code. The individual pathology services at each unit will create custom order forms and protocols to be used with this study.

Cannabinoid levels. Plasma samples will be taken from all participants on weeks 0, 4 and 24 pre and post cognitive testing to determine serum cannabinoid (THC, 11-OH THC, THC-COOH, CBD. 7-OH CBD) levels .

Blood Samples. Blood specimens (10 ml) to be taken by a nurse or project staff and transported in BD lavender tops (EDTA tubes) from study sites: Stored at 4C and centrifuged within 24 hours (10 min at 1500 g or whatever is standard in the lab). Plasma should be alloquoted into 4 x 1 ml samples, into 1.5 ml eppendorf tubes or similar and stores in a freezer (-20 for 1 month or less, -70 for more than a month storage), until collected for transfer to Sydney University when they reach a total of at least 6 in a batch.

Urine drug screens. Urine samples will be taken weekly during drug treatment to confirm abstinence from cannabis and to chart cannabinoid metabolite profiles through time. Urines will be collected at times that participants attend clinical appointments, research interviews or to collect dispensed medications. All urinalyses will be conducted by the Psychopharmacology lab at Sydney University. Standard Urine Drug Screen instant dipsticks will be used at research interviews on weeks 0, 4, 8, 12 and 24 to verify cannabis use (at week 0 – baseline before any medications are administered) and to check other drug use other than cannabis at subsequent research interviews (i.e. a UDS that does not quantify THC will be used at weeks 4, 8, 12 and 24).

3.10 Cognitive Testing

Cognitive testing takes place 3 times, once at week 0 (baseline, before any drugs are administered), once at week 4, and once again at week 24 (follow-up interview).

Primary objective: To determine the effects of Sativex on cognitive processes relevant to occupational safety among individuals withdrawing from cannabis and on maintenance doses of replacement therapy. A between and within-subjects comparison of cognitive performance at peak- and trough-Sativex will be conducted using an array of cognitive tests that have been validated as sensitive to cannabis effects and as predictive of driving impairment.

Secondary objective: To determine whether administration of Sativex ameliorates cognitive deficits experienced during cannabis withdrawal and during the use of illicit cannabis in the community.

If Sativex is successful in ameliorating symptoms of cannabis withdrawal, then it may conceivably be employed as an outpatient treatment in future. If this is the case, then it becomes important to consider

some of the safety aspects of this medication: one issue of particular importance is the effects of these doses of Sativex on cognition, particularly on those aspects of cognitive processing that are relevant to driving performance.

Cannabis use has been demonstrated to impair cognitive function and real-world driving performance in a dose-dependent fashion (Ramaekers, Berghaus, van Laar & Drummer, 2009). Recently, an international consensus statement has provided guidelines for research on drugged driving (Walsh, Verstraete, Huestis & Morland, 2008), and have provided a framework for selecting cognitive tests for studies seeking to predict risks of crashes and accidents. These types of tasks also have general applicability to safety, and are summarised in Table 1 below.

Table 1: Recommended cognitive measures for assessing potential impacts of medications on driving from the Consensus Statement of Guidelines for Research on Drugged Driving (Walsh et al, 2008).

Behaviour Domain	Specific Activity	Test Applied in this Protocol
Automotive behaviour (well-learned skills)	Vigilance (staying alert for changes over long times)	Rapid Visual Information Processing (RVP)
Control behaviour (maintaining distance, etc)	Motor performance	Reaction Time (from neutral stimuli in Flankers task)
Executive planning (interactive behaviours with ongoing traffic)	Adaptive inhibition (e.g. stopping a lane change when hearing the horn of a car in your blindspot)	Stop Signal Task (SST)
	Information processing	Digit Symbol Substitution
	Freedom from distraction	Flankers task

Importantly, the Guidelines statement also recommends that tests selected should have been validated as sensitive to drug effects on driver performance, and have demonstrated predictive validity of driving impairment (Recommendation B1: Walsh et al, 2008). The SST (or close analogues) have been demonstrated to be sufficiently sensitive to reveal dose-dependent effects of THC across a range of plasma levels (1-20ng/mL) in a double-blind, placebo-controlled, three-way cross-over study of recreational cannabis users (Ramaekers et al, 2006). Moreover, the THC concentration-effect curves for performance impairment on these tasks demonstrate a high correspondence with THC concentration-effect curves for THC-induced culpability risk in epidemiological studies (Laumon et al, 2005), with THC-induced performance deficits and THC-induced culpability risk highly correlated ($r>0.85$) across a range of dose levels (0-20ng/mL). As such, these cognitive tests may be reasonably taken to be valid measures to predict THC-induced crash risk in real-world driving (Ramaekers et al, 2009).

In addition, meta-analyses of the residual effects of cannabis suggest that memory and learning are the two components most strongly affected [54]. As such, standard tests of working memory (N-Back), as well as acquisition, retrieval and storage of memory (RAVLT) will be included. A full description of the cognitive tasks to be employed can be found in Appendix E.

Procedure

Cognitive testing will be performed at five time points.

- week 0 (baseline, before any drugs are administered),
- week 4 trough- and peak- (pre- and post- Sativex dosing)
- week 24 (follow-up interview)

The tasks are largely automated, following a pre-programmed battery for each of the three testing days. Instructions for administering the test will be manualised, providing instructions for workers on site in

relation to how to start and run each of the programs and code participant identification data, as well as a detailed script for exactly how to explain each task so that the administration procedure is standardised.

3.11 Health Economics Data section

The health economic data will be comprised of data collected from participant clinic records for services provided as trial interventions and from participants during research interviews at base line, (0), weeks 4, 8, 12 (maintenance phase) and week 24 (follow-up).

Data to be collected from participants include

- Quality Adjusted Life Years (QALY) measured by the SF-6D
- Productivity through the WHO Health and Performance Questionnaire (Clinical Trials Version) and
- Past four week:
    - Visits to hospitals, emergency department, and GP and specialist visits, etc.
    - Criminal behaviors

All health services will be costed with unit costs obtained from clinics, NSW Health Wages and Salaries, and published data.

3.12 Participant satisfaction with medication and test of blind.

Assessment of dose adequacy and satisfaction with medication (e.g. rating of drug liking, good drug effects, bad drug effects, "would you recommend to a friend" etc) will be assessed at research interviews. Each participant will be asked to indicate whether they received active Sativex or placebo condition at the Week 24 research interview to test the blind.

3.13 Research Interviews (~1.5 hours)

Research interviews will be conducted by the RA on weeks 0, 4, 8, 12 and 24 (day 28 following discharge from study) at either of the four clinical study sites, using CRF D. For each interview, the following will be administered:

- TLFB – daily cannabis use since most recent follow-up
- SDS (cannabis)
- Cannabis Withdrawal Scale (CWS)
- SF-36
- Cannabis Problems Questionnaire
- Reasons for Relapse to Cannabis Use Scale
- Self-efficacy for Quitting Cannabis Questionnaire
- Depression, Anxiety and Stress Scale-21
- Insomnia Severity Index
- Australian Treatment Outcomes Profile (ATOP)
- Fagerstrom nicotine dependence scale
- Physical Health Questionnaire (PHQ-15)
- Brief Pain Inventory (BPI)
- WHO Health and Performance Questionnaire (Clinical Trials Version) and
- Health Services Utilisation Questionnaire
    - Participation in treatment
        - Past four week:
            - Visits to hospitals, emergency department, and GP and specialist visits, etc.
- Participation in criminal activity in preceding 4 weeks (Opiate Treatment Index – OTI)
- Urine samples will be requested at face-to-face research interviews to corroborate self-reported cannabis use via cannabis immunoassay and carboxy-THC:creatinine ratio. A positive cannabis

urinalysis at follow-up will be indicated by the presence of cannabis metabolites in the concentration 50ng/ml or above. [55]

3.13.1 Enhancing research follow-up

Participants will undergo confidential interviews with the research officer at baseline (0), weeks 4, 8, 12 (maintenance phase) and week 24 (follow-up). The team will replicate strategies used in previous research where high follow-up rates have been achieved (80-90% follow-up after discharge in recent cannabis treatment studies).[11,12] Strategies to encourage follow-up attendance include: multiple points of contact being collected for each participant, including home phone, mobile phone and email address and contact details for a nominated contact person. Participants will be posted standardized letters and text messages ahead of follow-up appointments, and staff will attempt to contact participants with up to 5 phone calls before they will be classified as lost to study. Subjects will be reimbursed $40 for travel and related expenses to attend all research interviews.

3.13.2 Remuneration of participants

Subjects will be reimbursed $40 for travel and related expenses to attend all research based interviews.

3.14 Discontinuation criteria

Upon termination of each participant from the trial, the **"Reasons for Discharge CRF"** will be completed by the trial Medical Officer. Categories include involuntary or voluntary termination (as described below).

3.14.1 Involuntary termination

Termination criteria for individuals in the study are:

- Medical reasons: the local trial MO in consultation with the CIA may terminate participation in the event of clear evidence of an adverse event that warrants study discontinuation, or due to deteriorating physical or mental health.
- Administrative discharge for violation of treatment centre rules and conditions (e.g. evidence of diversion or abuse of medication or other substance use; violence (or threats) towards staff or other patients).
- Non-compliance with trial protocol, including persistent refusal to participate in other trial procedures (counselling, clinical reviews, case management urine drug screen (UDS), bloods, monitoring).

The treating team and participant should examine alternative treatment arrangements where practicable prior to involuntary discharge from the trial clinical procedures.

3.14.2 Voluntary termination

Participants are free to withdraw their consent to participate in the trial at any time without fear of reprisal. The site RA should be informed of any voluntary termination.

3.14.3 Discontinuation and data collection

Statistical analyses will be conducted on an intention-to-treat basis. Data from participants withdrawn from the trial will have their data included in statistical analyses. In addition, withdrawn participants will be followed-up with the same instruments and at the same sequencing as participants not withdrawn from the trial. Participants who are withdrawn from the trial will not be replaced if they have consented and received a 1st dose of medication, but will be if they have consented and had no medication.

Participants who are withdrawn from the study either voluntarily or involuntarily may revoke their consent to have their data included in the study. Participants opting to withdraw their consent for data inclusion must complete a *Revocation of Consent Form*. Participants who revoke their consent for inclusion of their data will not be replaced.

3.15 Duration

The project will be completed in 3 years. The study will be conducted at large D&A treatment services from where subjects can be readily recruited. Collectively, SESLHD, WSLHD and HNELHD D&A Services delivered over 1,600 treatment episodes to patients with primary cannabis problems in 2013, and so a target recruitment rate of 80 per year is realistic.

The project stages are:

ACTIVITY	YEAR 1		YEAR 2		YEAR 3	
ESTABLISHMENT: 6 MONTHS (Finalise study protocols& ethics, staff recruitment and training)						
RECRUITMENT, TREATMENT & DATA COLLECTION Staggered recruitment (80/year, 40/site = 18 months), treatment & follow-up of last recruit (6 months)						
DATA ANALYSIS AND DISSEMINATION: 6 MONTHS						

4 Safety Monitoring & Reporting Protocols

4.1.1 Definition & recording of adverse events in this trial

An adverse event is any untoward event that may inconvenience a study participant, staff member or other individual. The event may or may not be related to the treatment received within the framework of the study. This includes the onset of new illness and the exacerbation of pre-existing conditions. Additionally, any event that is associated with or observed in conjunction with a product overdose (whether accidental or intentional) or a product abuse and/or withdrawal is also considered an adverse event.

Each nursing clinical review, the reviewing nursing staff asks an open question (not checklist prompted) about whether the client has experienced any side effects since the last review. The severity of symptoms and the extent of impairment should be asked and documented using the following categories. Any rating of 3 or more should be referred to the study medical officer for review, with grade 4 or 5 requiring immediate notification to the study medial officer for further assessment

Adverse event rating	**Action**
1 = mild and no impairment;	Document & review at next appointment
2 = mild symptom with mild impairment of function that does not require specific treatment or further assessment at this time	Document & review at next appointment
3 = moderate symptom severity with mild impairment of function	Liaise with study medical officer
4 = moderate symptom severity with moderate impairment of function	Liaise with study medical officer
5 = severe symptom severity	Liaise with study medical officer.

At the regular medical officer appointments (Wks 2, 4, 8, 12) the medical officer will review all side effects from previous reviews, and complete the Adverse Event Log, which includes ratings of AE severity, relationship to study medication, course of action and whether the AE has resolved.

Separate to the clinical reviews, the Researcher will also ask at the 4 weekly research interview a structured checklist of possible side effects, which are based upon previous studies involving cannabinoids. These are not subject to further clinical interpretation as they are confidentially reported to the researcher.

4.1.2 Definition of Serious Adverse Event

A Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR) is any untoward medical occurrence that at any dose:

- Fatal or life threatening
- Results in a chronic condition or severe and/or permanent disability
- Results in cancer
- Results in overdose requiring medical attention by ambulance attendants, a doctor or attendance at a hospital
- Results in or prolongs inpatient hospitalisation

Medical and scientific judgment will be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalisation but might jeopardise the participant or might require intervention to prevent one of the other outcomes listed in the definition above.

4.1.3 Definition of Suspected Unexpected Serious Adverse Reaction

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is a SAE for which there is some degree of probability that the event is related to the trial medication, and was not expected to occur with the trial medication (e.g., not listed in product label)

4.1.4 Assessment of adverse event severity and relationship to treatment

All Adverse Events are to be recorded on the clinical CRF at each of the weekly medical review and consultation sessions. The clinical CRF has a specific AE table for each week comprising a list of possible side effects arising from Sativex. This data forms one of the main outcome measures for the clinical trial, as we are primarily interested in the safety profile of the drug for the cannabis withdrawal and relapse indications. Any other AE's that occur that are not listed on the daily AE's table can be recorded on the relevant days AE table in one of the blank "other" spaces at the bottom of the table. The AE's table asks the registered nurse to grade the severity of each event using the following definitions:

None	Not experienced at all.
Mild	Awareness of sign, symptom or event, but easily tolerated
Moderate	Discomfort enough to cause interference with usual activity and may warrant intervention
Severe	Incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention

The project management team have decided that the site MO should be contacted by the RN if any of the AE's recorded on the daily AE's table is rated as either Moderate or Severe. In that instance, the participants will be clinically reviewed as soon as possible by the study MO or their nominee, and a decision made as to the likelihood that the AE is a SAE or related to the study medication.

When a participant is discharged from the study, the trial MO must fill out the "Summary of Adverse Events Log" in the back of the participant file, by reviewing the weekly AE tables for the 12 weeks of sativex maintenance treatment, and summarise the AE's occurrence, severity, start and end dates, whether they were SAE's and what action was taken. The relationship of any adverse event to the use of the trial medication must also be assessed, based on available information, using the following guidelines:

Unlikely related	No temporal association or the cause of the event has been identified, or the drug cannot be implicated
Possibly related	Temporal association, but other etiologies are likely to be the cause. However, involvement of the drug cannot be excluded
Probably related	Temporal association, other etiologies are possible but unlikely

An adverse event liable to be due to the research is defined as an adverse event whose occurrence cannot be reasonably attributed to a cause independent of the research conditions. The expression 'research conditions' includes all the constraints related to the research or imposed by it, particularly the trial medications (including placebo), the investigations conducted and the conditions under which they are conducted.

4.1.5 Recording of SAEs, and SUSARs

When an SAE or SUSAR occurs, CIA and CIF are responsible for reviewing all documentation (e.g., progress notes, laboratory and diagnostic reports) relative to the event. The investigator will then record all relevant information regarding this event(s) in the participant's medical records and on the SAE CRF. The onset and end dates, action taken and outcome (e.g., hospitalisation, discontinuation of treatment), severity and relationship to trial medication will be recorded for each adverse event. The severity of the adverse event and relationship to trial medication will be assessed according to specific guidelines listed above. Follow-up laboratory results will be filed with the participant's source documentation.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In the absence of a diagnosis, the individual signs/symptoms will be documented in the participant's medical records and on the CRF. In addition, all details of any treatment(s) initiated due to the event will be recorded in the medical records and CRF.

For all adverse events that require the participant to be discontinued from the trial, relevant clinical assessments and laboratory tests will be repeated at clinically appropriate intervals until final resolution or stabilisation of the event(s).

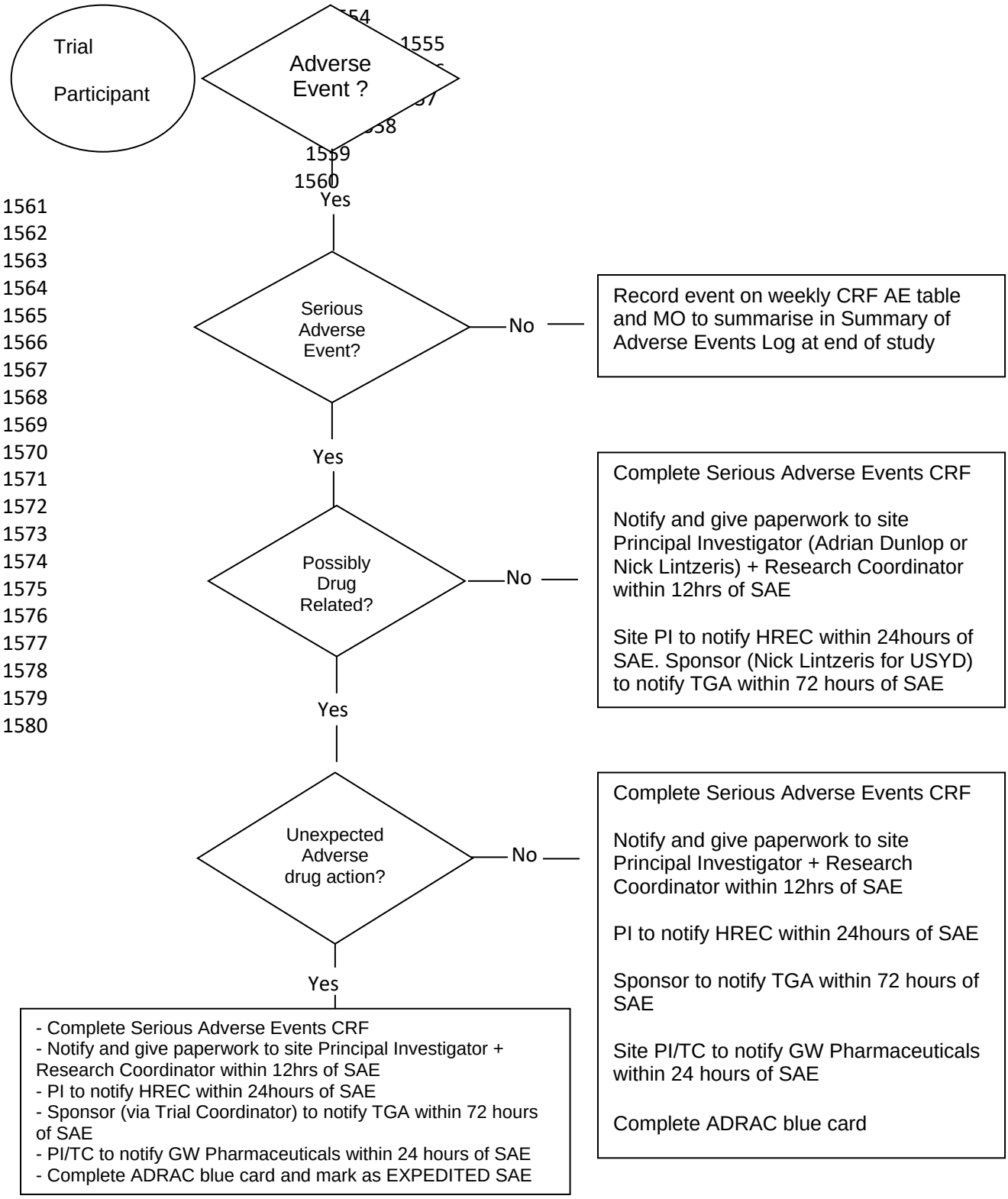


Figure 7. AE, SAE and SUSAR procedural flow chart

4.1.6 Reporting of SAEs and SUSARs

All SAEs must be reported to the on-call physician immediately upon staff being aware of its occurrence. SAE require notification of the site investigator, CIA or CIF and Trial Coordinator within 24 hours of the SAE. The Trial Coordinator is responsible for notifying the relevant HREC on behalf of the sponsor (USYD) if investigator considers the event will impact the research and action is planned as a result (e.g. protocol amendment), or if reporting to institution is required as per jurisdictional requirements, or if required under conditions of HREC approval. The Trial Coordinator will collate all adverse events data as it occurs and be responsible for passing information to the Data and Safety Monitoring Board as an when events are alerted. An annual summary of all SAEs will be provided to the HREC with comment by The Trial Coordinator regarding action in regard to trial, or if no action is planned.

All SUSARs will be reported to the relevant HREC with comment by The Trial Coordinator regarding planned action, or if no action planned. SUSARs will also be reported to the Therapeutic Goods Administration (TGA) in accordance with pharmacovigilance requirements, in line with the GCP guideline as adopted by the TGA. After the TGA report has been issued, the sponsor (USYD) must advise CIA of TGA's decision and, in turn, CIA (via The Trial Coordinator) must notify relevant HREC.

Reports of expected adverse reactions, both serious and non-serious will be provided by The Trial Coordinator to the sponsor. Expected adverse reactions will be reported to the relevant HREC if the event will impact the research and action is planned as a result (e.g., protocol amendment). As a minimum, and as required by the *National Statement*, annual reporting to HREC will occur and will detail all adverse events or adverse reactions occurring during research approved by those HRECs at any site for which the institution conducting the research is responsible.

5 PROTOCOL DEVIATIONS

When circumstances arise which suggest that a departure from this protocol should be considered, the study MO or their nominee must contact the CIB (Allsop) by telephone as soon as possible prior to implementation. Any departure from the agreed protocol will pertain only to the individual participant involved. The CRF will describe the circumstances and identify the pertinent protocol procedure.

In the event that a protocol amendment is proposed for all participants, then the procedure for protocol amendment should be followed. In either case, any modification of the protocol that may become necessary during the course of this trial, other than to protect participants from an immediate hazard must be agreed to by all CIs.

6 STATISTICAL ANALYSES

6.1 Sample size determination

Psychotherapy treatment studies for cannabis achieve abstinence rates of 12 to 23% (mean, 20.8%) over follow-up periods from 2-6 months,[14] and medication studies are similar (~23.1% abstinence).[8,22] We thus base our power analysis on the assumption that the Placebo group will achieve abstinence rates at 12-weeks of ~22%. We predict that the addition of Sativex to psychotherapy will double abstinence rates to approximately 44%. This estimate is based upon findings from a laboratory relapse model, in which heavy

cannabis users consumed less than half the amount of cannabis (mean 43% less, range 39-48%) following repeated doses of nabilone, relative to placebo treatment.[19] With 80% power (two tailed) and α=0.05, a total of 142 participants (71 per group) are needed to detect the predicted benefits in cannabis abstinence.

6.2 Statistical methods

Chi square and ANOVA will identify any baseline covariates that differ between groups for controlling the main analyses. Missing data will be imputed using multiple imputation except for missing urine where cannabis use will be assumed to have taken place. All analyses will use Intention-to-treat, which is defined here as any person who is randomised to one of the study arms and receives at least one dose of study medications. Mixed Models for Repeated Measures (MMRM) will compare groups on changes in outcome variables (cannabis use and secondary outcomes) in the medication phase with the multiply imputed dataset, assuming that Littles Missing at Random test confirms the data to be missing at random). In addition we will perform a sensitivity analysis based on only those with complete data, and compare results to that from the MI dataset analysis. Adverse Events will be analysed using chi-square. A Cox proportional hazards model will compare retention in treatment between study arms, controlling for potential confounds. The impact of the intervention on post-medication outcomes will compare changes in cannabis use outcomes at baseline and at follow up between groups using MMRMs. Family-wise error corrections will control for Type 1 errors where multiple comparisons are performed within a particular analysis where post hoc contrasts are performed to further explore interesting (significant) findings.

7 DATA MANAGEMENT

7.1 Data identification

All Case Report Forms (CRFs) will use participant and site codes, such that individual patient details can not be identified in research records. Original source data from clinical sites (e.g. medical records) must necessarily have patient identification labels on them. A researcher at each site will photocopy original source data, insert participant identification codes (research study specific numeric code), and remove any identifying participant details either by cutting out or blacking out identifiable information.

The only CRFs that will include identifiable participant details will be the Informed Consent CRFs and the *Contact Tracer Forms* (that enable researchers to contact the participants for follow up). These will be kept in a separate filing cabinet to the research participant CRF files.

7.2 CRFs and direct access to source data and documents

Each participant will have a *Participant File* with all relevant CRFs pertinent to their participation in the trial. The *Participant File* will be identified by Study Code, indicating their Trial Site, and participant number, but no identifiable data will be recorded in the participant's file. Only researchers involved in the trial will have direct access to the *Participant Files*. Identifiable data (including participant's name, signed consent forms, and *Contact Tracer Form*) will be stored separately by the researchers in locked filing cabinets, and will only be accessible to the Trial Coordinator and RAs.

The Participant Identification Log of all those enrolled and randomised onto the trial will be kept in the Investigators File at each site, and maintained by the Trial Coordinator. This will include the patient's identification and study number.

The Chief Investigators will permit trial-related monitoring, audits, HREC review, and regulatory inspections, providing direct access to source data and documents.

7.3 Databases, data entry and data management procedures

Trial data will be stored in multiple separate databases which will be linked on an ongoing basis throughout the trial and at analysis by CIB Dr David Allsop. Sativex study databases include: (1) Adverse Events Database, (2) Cannabis Withdrawal Scale database, (3) Baseline Surveys Database, (4) Clinical Data

database (during maintenance), (5) Discharge Database, (6) One month follow up database, (7) Phone screen database.

The Trial Coordinator will be responsible for establishing the study's computerised data bases using PASW® software. Each site will have their own individual databases for the study, which local site based staff (RA and/or Research Nurse) will update on a regular basis according to the following schedule:

Data for each study participant (including baseline surveys and the clinical data collected during the maintenance phase) must be entered at least weekly by site RAs or RNs and transferred electronically to Central Trail Database maintained by Dr David Allsop at USYD for cleaning and merging (electronic data transfer to USYD must take place within 1 week of each participants previous week of data collection activity throughout the maintenance phase of the trial).

This means that the RA/Research Nurse at each site must track each participant's engagement in the study and obtain copies of all CRFs collected as close to the day of discharge as possible, or on an ongoing basis throughout the trial if logistics permits. Any CRF's that needs to be de-identified should be, before being photocopied twice. One copy of the patient's paper CRFs should be transferred to a research file (located at one of the four study sites). The RA/Research nurse can then enter data into the site-specific database according to the schedule and transfer it to Dr Allsop for central merging and storage. The second paper copy of the CRF's should be posted to Dr Allsop to be maintained in the Sponsor data folders at USYD. The second paper copy will be used for periodical data monitoring to ensure the face validity of the data in the electronic databases.

The first five *Participant Files* from each trial site will be assessed by the Trial Coordinator who will assess face validity of the data before data entry.

7.4 Data Monitoring

The study will be internally monitored by the Trial Coordinator. Errors and queries identified on data input and merging will be referred to coordinating staff onsite for correction or comment.

The Data and Safety Monitoring Board will have access to all study data as an unblinded dataset with updates every quarter as supplied by CIB.

8 QUALITY CONTROL AND QUALITY ASSURANCE

The conduct of this study, and the generation, documentation and reporting of data will be conducted in compliance with this protocol, the CONSORT statement for the conduct of clinical trials, and the GCP guidelines. This trial was registered with the Australian New Zealand Clinical Trials Register (ACTRN - TBA) prior to recruitment of the first participant.

8.1 Project Management Team

The Project Management Team (PMT), consisting of CIs will oversee the conduct of the study, be responsible for key decision making for the trial, and ensure that the trial objectives and tasks are being met within proposed timelines, and within budget. It is proposed that the PMT will meet at least every three months.

8.2 Data Safety and Monitoring Board

An independent Data Safety and Monitoring Board (DSMB) has been established to review the ongoing accumulating data arising from this study. The DSMB consists of an independent clinician, cannabis researcher, and biostatistician. The DSMB is primarily responsible for safety monitoring of the trial, involving ongoing reviews of any adverse events arising from the administration of Sativex (unblinded data). The DSMB will also monitor aspects of study integrity and design should any protocol changes need to be made.

The Terms of Reference for the DSMB are:

- To advise on potential strategies in addressing problems or difficulties which arise during the conduct of the trial
- To ensure that the project is consistent with national policy and clinical developments in the field
- Data monitoring

It is proposed that the DSMB will meet every quarter

8.3 Compliance with trial protocol

The Trial Protocol will be kept in the investigators file at each site, and site investigators will sign to acknowledge they have read and understood these protocols. Standing operating procedures for recruitment and the identification and monitoring of adverse events will be kept in the investigators file. Standard operating procedures (SOP) for interviewing procedures will be kept in the Trial Master File. All researchers conducting interviews will be trained by the Trial Coordinator.

A weekly meeting between clinical staff and researchers will be held to identify new referrals, organise appointments for screening and research interviews, clinical assessments, and relevant investigations. Any issues relating to the day-to-day local management of the trial will be discussed at these meetings and minuted. Copies of these minutes will be kept in the Investigators file.

9 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with Australian and international standards of Good Clinical Practice (*The National Health and Medical Research Council's National Statement on Ethical Conduct in Human Research (2007) and the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) annotated with TGA comments).* Applicable government regulations and Institutional research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the lead HREC at SESLHD for formal approval to conduct the study. The decision of the HRECs concerning the conduct of the study will be made in writing to the investigator.

All participants for this trial will be provided with a *Participant Information Sheet* and two *Consent Forms* describing this study and providing sufficient information for participants to make an informed decision about whether to participate in this study. The *Consent Forms* will be submitted with the protocol for review and approval by the HREC. The formal consent of a participant, using HREC-approved *Consent Forms*, will be obtained before that participant is submitted to any study procedure. The *Consent Forms* must be signed by the participant, and the investigator-designated research professional obtaining the consent.

To ensure sensitive data on drug use and the likes is kept confidential, all research material will be kept in a secure building that is only accessible to authorized persons. All consent forms, instruments and data will be stored in locked filing cabinets and in password protected computer files. Only people directly involved with the project will have access. Participants will be deidentified and assigned codes which will be replicated on instruments. The list of codes will be stored separately to data with identification details. All clinical services are familiar with and comply with NSW Health privacy and confidentiality legislation and procedures. All findings will be disseminated as unidentified study average values with standard deviations and appropriate statistics. No names or code numbers will be reported in any result dissemination The only instances where confidentiality are likely to be broken are if the participant reports a risk of committing harm to either themselves or to others (e.g. planned suicide, reports of child abuse, illegal activity etc). Under such circumstances the information will be reported to the appropriate authority after alerting the participant to this fact

10 FINANCING AND INSURANCE

This study is being funded by a 2014 NMHRC Project Grant (#APP1088902). The University of Sydney will be the trial sponsor. This is not a commercially sponsored trial.

11 PUBLICATION POLICY

The trial sponsor, USYD, has no claim over the dissemination of results. GW Pharmaceuticals (UK) are providing the drug materials for this trial, and require to see any commercially sensitive findings at least 60 days prior to submission for publication.

Manuscripts and abstracts will be prepared by all CIs in collaboration with the AIs. Only aggregate data will be reported. Results pertaining to individual participants that could be potentially identifying will not be reported. Authorship of manuscripts arising will be merit based on the extent of contribution to the paper, and agreed upon in "Authorship Meetings" by all CIs.

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1940 **Appendix A. Sativex/Placebo bottle labels**
1941

1942

Keep out of reach of children

Device/kit #

John Citizen
Patient No 3
MRN : 123456

Refrigerate

Do not drive etc

THC 27mg/mL CBD 25mg/mL (Sativex ®) OR Placebo TRIAL

Apply two sprays four times daily. Allow content to be absorbed in the mouth lining. Do not swallow.

Once open may store under 25°C for 42 days only

On first use, prime device by actuating a few sprays into a tissue until a fine spray appears.

Qty: 1 of 2 1 Nov 2015

Exp: Batch:

Dr N Lintzeris
Langton Centre
591 South Dowling St, Surry Hills NSW

Appendix B. Generic Trial Prescription

Clinical Trial site: Langton Centre
SESLHD Drug and Alcohol Services
591 South Dowling Street, Surry Hills NSW

Medication Order Form

RCT of cannabinoid replacement therapy (Sativex®) for the management of treatment-resistant cannabis dependence

Protocol number: 1.3 **Ethics Number**: HREC ref no: 14/289 (HREC/14/POWH/701)

Investigational drug: Nabiximols (Sativex® oromucosal spray)
(Each 100 microlitre spray contains: 2.7 mg THC and 2.5 mg CBD and up to 0.04 g alcohol.)

Patient's name: _____

MRN: _____ DOB _____

Address: _____

Subject ID: _____

Week Number: _____ Arm Number (if applicable): _____

Nabiximols spray or Placebo spray

Instruction: _____
Quantity supplied: _____
Investigator(s): **Professor Nicholas Lintzeris** **Prescriber name**: _____
Prescriber number: _____ Signature: _____
Pharmacist 1 name: _____ Pharmacist 2 name: _____
Signature: _____ Signature: _____
Affix dispensing labels here below (pharmacists to sign and date across label)

Appendix C. Drug Register

SESLHD Drug and Alcohol Services
Site: Langton Centre
Bulk Accountability Log

Ethics No: HREC ref no: 14/289 (HREC/14/POWH/701) Protocol No:___1.3_____

Site No: __Langton_____ Investigator:___Dr Nick Lintzeris_____

Product name:_ Nabiximol buccal spray (Sativex®)

Date	Quantity Received	Quantity Dispensed	Batch & expiry	Patient Number	Patient Initials	Staff initials	Balance
30 Oct 2015	100 devices		B 12345			RN	100
1 Nov 2015	NA	2		456123	TC	RN	98
2 Nov 2015		3	B12345	456111	MM	RN	95

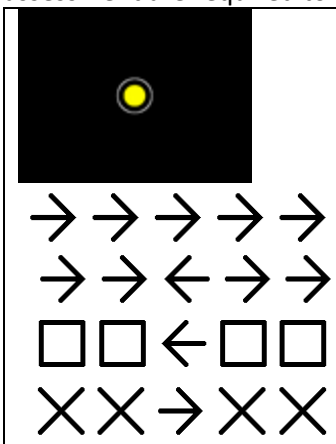
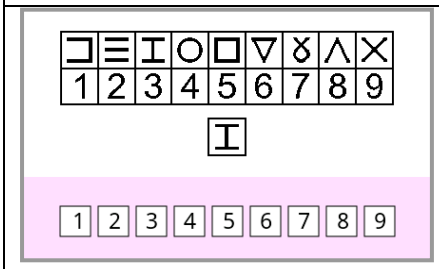
Appendix D. NCPIC 6 Session counselling manual

Refer to attached Appendix D document.

Appendix E. Cognitive testing tasks

Task descriptions

These measures all require simple motor responses for their execution (e.g. pressing a touch pad or computer screen in response to a stimulus). The tasks are all simple to complete, and have been designed so that very elderly or very cognitively impaired individuals can understand and complete the tasks. There is no identifying information required for their completion (names etc) and existing protocol sequence identification numbers will be used in all instances for attributing data to each participant, as per those used in the approved protocol. The batteries are largely automated, and a standardised 'script' for participant instructions (explaining how to complete each task) will be provided. No specific skills in cognitive assessment are required to administer these tests.

	**Flankers Task. This test assesses both choice reaction time and the ability to ignore distracting but irrelevant information.** Sets of five symbols appear on the screen one set at a time. The central symbol (target) is always an arrow, pointing either to the right or the left. The other four symbols (flankers) are either congruent (arrows pointing in the same direction as the target); incongruent (arrows pointing in the opposite direction to the target); neutral (squares); or suppressors (crosses). The task is to press a left or right button corresponding to the direction of the central target arrow as quickly as possible, unless the flankers are crosses, in which case no response should be made. The mean time for correct responses and the number of errors are recorded for each of the three congruence conditions, as well as the number of false positive responses to the suppressor (NoGo) condition.
	***Digit-Symbol Substitution Task*** This is a basic test of speed of information processing. A key is displayed at the top of the screen, matching nine symbols with the digits 1 — 9. Symbols appear in the box below, and the testee responds by tapping on the numeric button corresponding to the digit as quickly as possible. The number of correct and incorrect responses and the mean response time for correct responses is recorded.
	Rapid Visual Information Processing (RVP) This test assesses how well a person can stay alert during cognitively demanding tasks. A series of digits appears one at a time on the screen. The digits appear every 600 msec, that is 100/minute. The task is to respond whenever there are three even digits in a row OR three odd digits in a row. The number of correct responses(more suggests better attention), the number of false positives, and the reaction time for correct responses (faster suggests better performance) are recorded.
	Rapid Visual Information Processing (RVP) This test assesses how well a person can stay alert during cognitively demanding tasks.

	A series of digits appears one at a time on the screen. The digits appear every 600 msec, that is 100/minute. The task is to respond whenever there are three even digits in a row OR three odd digits in a row. The number of correct responses(more suggests better attention), the number of false positives, and the reaction time for correct responses (faster suggests better performance) are recorded
	***Stop signal task*** *(SST)* This test assesses how well an individual is able to suddenly stop a response when situations change. This has direct relevance to driving as when road hazards randomly emerge, a rapid response is required. Participants are presented with a stimulus and are required to press a corresponding key as fast as possible (e.g., left button key press with the presentation of a left arrow). On a minority of trials, a 'stop' signal (a loud 'beep') is presented soon after the stimulus onset (starting between 100 and 500 milliseconds), whereby participants are required to withhold their response to the stimuli. The delay time at which participants can reliably inhibit their responses ('stop' reaction time) is determined using an iterative staircase procedure, where the time between stimuli presentation and the stop signal is steadily reduced (i.e. the task made more difficult) until participants start to make errors, and the task is then made easier: this process repeats for 320 trials in order to make an accurate assessment of 'stop' reaction time. Shorter 'stop' reaction times suggests that participants are more quickly able to adapt to changing situations, and suggests better performance. This task takes approximately 6-8 minutes to complete.
	N-Back This is a test of verbal working memory, and is dependent on the integration of the frontal and temporal regions, two areas particularly affected by THC. Participants are presented with a series of letters on screen, one at a time at the rate of 15 stimuli per 20 seconds. There are three levels of difficulty of the task: in the 1-back condition, participants are asked to respond when the letter presented is the same as the one previously presented; in the 2-back condition, participants are asked to respond then the letter presented is the same as the one presented two letters prior; and the 3-back condition requires participants to respond when the letter presented is the same as the one presented three letters prior. Reaction time to targets (faster suggests better performance) and number of trials correctly identified (more suggests better working memory) are recorded for each level of difficulty.
	Ray Auditory Verbal Learning Task This is the classic test of verbal learning and memory. In this task, participants are read a list of 15 words at the rate of one per second, and, when the list has been read, to say as

	many words as they can remember. The list is read again, and participants again asked to report as many words as they can remember. This process is repeated for 5 presentations of the word list. This allows the assessment of initial memory (immediate memory recall) and learning (improvement over trials). A distractor list of 15 words is then presented for recall; after which the participant is requested to recall the initial list, which examines the degree of interference from new learning and robustness of memory trace. Finally, 20 minutes after the initial learning, the participant is asked to spontaneously recall as many words from the list as possible, as well as identify the targets in a presented sequence of words, which assesses both recall and recognition memory.

A randomised placebo-controlled trial of nabiximols for the treatment of cannabis dependence.

Statistical Plan

Table of Contents

A Note on Data Sets Analysed

For all analyses the primary *predictor* was treatment group (nabiximols vs placebo). The core analyses for this study were performed on a non-imputed modified intention-to-treat basis, i.e. on all valid data from participants who were allocated to a treatment arm and received one or more doses of either nabiximols or placebo. Identical analyses were performed on two alternate datasets: (1) a per-protocol dataset comprising only the participants who finished treatment, (2) a dataset imputed using Longitudinal Multiple Imputation (as outlined in Chapter 9 of *Flexible Imputation of Missing Data*; van Buuren, 2012). Sensitivity analyses, comparing results from the core intention-to-treat analyses to those from the alternate datasets, were performed and are reported in brief in the main manuscript but in detail in the supplementary materials.

Section 1: Baseline Characteristics

Summary statistics (frequency for categorical variables, mean and standard deviation for continuous variables) were calculated for both groups and across the entire sample. To test for pre-existing site differences in relevant biohistorical variables that might bias results, separate regressions, with study site as the sole predictor, were performed on outcomes: (1) participant age, (2) gender, (3) frequency of cannabis use prior to study commencement, (4) quantity of cannabis use prior to study commencement, (5) ICD-10 cannabis dependence score, (6) age of first cannabis use, and (7) duration of regular cannabis.

Section 2: Treatment Characteristics

The purpose of these analyses was to test for between-group differences in variables that could potentially confound the primary analysis: (i) retention in treatment, (ii) dose of medication, and (iii) number of counselling sessions.

2.1 Retention in Treatment

For the purposes of this analysis only, a participant was considered to have exited the study if they ceased collecting medication.

Some participants informed staff of their intention to cease receiving medication or to leave the study. For these participants there was a precise exit day. However, many participants simply stopped attending the study without notifying staff, and were unable to be contacted. Because participants were given a week's worth of nabiximols/placebo medication at the start of each week it was not possible to know how many of each week's dose these participants consumed. Thus the problem for any survival analyses is that there is no way to know exactly what day participants 'exited' the study (i.e. the first day they did not take their medication).

In light of these difficulties a formal decision rule was adopted whereby a participant was considered to have remained in treatment until the last known day of prescribed and dispensed nabiximols/placebo medication. .

Analysis: Between-group difference in time in treatment was analysed using a Cox's proportional hazards regression and a Kaplan-Meier plot, including median treatment retention for each group.

2.2 Dose of Medication

Daily number of sprays, averaged across the maintenance phase (Weeks 2 to 12) was regressed on treatment group. Week 1 was omitted from calculation of this 'average sprays per day' score as participants were still adjusting their dose.

2.3 Counselling Sessions

Choice of the final model used to analyse the effect of treatment group on incidence rate ratio of number of counselling sessions was based on three assessments: (i) comparison of mean number of sessions to standard deviation of number of sessions to assess presence or absence of over- or under-dispersion, (ii) obtaining a dispersion statistic (α), (iii) comparison of models using Vuong's non-nested test (Vuong, 1989). These assessments determined whether Poisson or negative binomial regression was more appropriate.

Section 3: Primary Analysis: Frequency of Illicit Cannabis Use in Days Across the 12-Week Trial

3.1 Rationale for Primary Outcome Measure

There are many ways to measure drug dependence but the most readily quantifiable is drug use, and the most reliable measure of drug use is number of days used. Thus any treatment claiming to reduce dependence on cannabis should be associated with a reduction in number of days of cannabis use if it is to be considered truly effective. We hypothesised that if nabiximols was truly capable of reducing illicit cannabis, its use should lead to a significant reduction in the total number of days participants used illicit cannabis over the course of the 12-week trial. Thus total number of cannabis use days over the 12-week trial was the primary outcome measure for the study. This outcome was a continuous variable, calculated by summing self-reported number of days used in the previous 4 weeks across research interviews at weeks 4, 18, and 12, yielding a single score out of 84 (12 x 7 days) for each participant still participating at 12 weeks who completed all three research interviews.

3.2 Presentation of Summary Data

A box and whisker plot will be used to display the distribution of 84-day cannabis use scores for each group. Group mean scores for each group will be calculated and displayed on the same box plot.

Conducting a multi-site study affords the opportunity to test the generalisability of a treatment by examining its influence within and across each of the study locations. A table will present number of participants at baseline, number of participants who completed all three research interviews, and mean 84-day cannabis use score within each group at each of the four study sites (The Langton Centre, St George Hospital, Western Sydney Centre for Addiction Medicine, and Newcastle Community Health Services) and within each group averaged across all sites.

3.3 Inferential Analysis

The primary analysis was an ANCOVA, with total days of illicit cannabis use across the 12-Week trial as the outcome and predictors (1) Treatment (two-level factor: Placebo vs Nabiximols), (2) Site (four-level factor: Langton Centre, St. George Hospital, Western Sydney, Newcastle), (3) Treatment x Site interaction, and (4) mean-centered days used in the previous 4-weeks at baseline.

In the event of significant omnibus effects for Treatment, Site, or the Treatment x Site interaction, estimates of the difference in average days used between levels of factors, and the corresponding 95% confidence intervals, were obtained by comparing covariate-adjusted means, with *P*-values adjusted for multiple comparisons using the Benjamini-Hochberg procedure for controlling the false discovery rate.

In order to establish the robustness of the observed treatment effect, the primary analysis was also performed on the two alternative datasets (Per-Protocol, and Multilevel Multiply Imputed). These results are briefly reported in the main manuscript, and in more detail in supplementary materials.

3.3 Assumption Testing and Post-Hoc Tests

Frequency of use data in drug dependent populations is often not distributed normally. Fortunately the normality of distribution assumption in regression and ANOVA applies to model residuals, not the outcome variable itself. However, for the primary analysis it was important to check this assumption was upheld via visual inspection of model residuals for normality using Quantile-Quantile (Q-Q) plots[35] and histograms. Our rule for how the outcome of the inspection of residual plots would determine reporting of results was as follows: (1) If model residuals were distributed sufficiently close to normal, the results of the regression would be reported, (2) If deemed not sufficiently close to normal, a non-parametric Wilcoxon-Mann-Whitney rank sum test – testing the null hypothesis that the distributions of the Placebo group and Nabiximols group do not differ in location – would be performed, (3) If there are doubts about whether the departure from normality constituted a violation of the assumptions of ANOVA, results of both the parametric regression and non-parametric Wilcoxon Mann-Whitney tests would be reported.

Section 4: Secondary Analyses

4.1 Abstinence and 50% Reduction in Use

In order to test whether nabiximols affected participants' odds of remaining totally abstinent, a dichotomous abstinence variable was calculated. If participants reported in *any* of the three post-baseline research interviews (weeks 4, 8, and 12) that they were completely abstinent for the previous 4 weeks they were coded as '1'. If participants reported no 4-week periods of total abstinence they were coded '0'. Numbers and proportions of people meeting this criterion are reported. A logistic regression was performed, regressing this dichotomous 'any abstinence' variable on treatment group. A second (less stringent) binary variable was calculated, indicating whether participants had reduced the number of days they had consumed cannabis in the previous 4 weeks by 50% or more from baseline to weeks 9-12 (measured at the week 12 research interview). A logistic regression tested for group differences in the odds of reducing days used by 50% or more from baseline to week 12.

4.2 Longitudinal Analyses of Secondary Outcomes

The fact that the same battery of questionnaires was administered at four equidistant time points across the 12-week trial [0 weeks (baseline), 4 weeks, 8 weeks, and 12 weeks] meant that we could observe the *change* in several important variables during the course of the 12-week trial period. Factorial, random-intercepts mixed models for repeated measures regression (MMRM) testing for between-group differences in change in outcome relative to baseline over the course of the 12-week trial were performed for several outcome variables, including scores on: (1) the Cannabis Withdrawal Symptom (CWS) questionnaire, (2) the Marijuana Craving Questionnaire (MCQ) (3) the Cannabis Problems Questionnaire (CPQ), (3) the Fagerstrom test for Nicotine Dependence, (4) the Alcohol Use Disorders Identification Test (AUDIT), (5) all factors of the Short-Form 36 Quality of Life scale (SF-36) and (6) the OTI drug-related crime scale. The fixed effects in these models were Treatment group (placebo vs nabiximols; a level-2 factor), and Time (0 weeks [baseline], 4 weeks, 8 weeks and 12 weeks; a level-1 factor). Participant ID was the random effect. A block diagonal covariance structure was used to model the within-person error. Maximum likelihood estimates of change in group difference at each time point relative to baseline were obtained, as well as 95% confidence intervals for these estimates. Omnibus tests for main effects of Treatment, main effects of Time, and Treatment x Time interaction were also obtained (Type-3 *F*-tests for continuous variables and Type-3 Wald Chi-square tests for categorical [only OTI crime]) for each MMRM. The *P*-values for these omnibus tests (three tests per variable and 13 variables = 39 tests in total) were corrected using the Benjamini-Hochberg method for controlling the false discovery rate.

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Section 5: Safety

5.1 Adverse events

Adverse events (AEs) were assessed and addressed during clinical assessments with the study medical officer (SMO) at 4-weekly appointments. At the end of study participation, the SMO recorded the severity of each AE (mild, moderate, severe), the outcome (ongoing or resolved, with or without treatment), and attribution to study medication.

Analysis*:* If AE was attributed to study medication then:

(a) Numbers of recorded incidents of each of the different AE categories will be reported for each experimental group.
(b) For the purposes of the inferential analysis AEs were collapsed into a single count variable (i.e. irrespective of type or severity) representing total number of AEs experienced by each participant over the course of the entire 12-week trial period. After examining dispersion, a negative binomial regression was conducted, testing between-group differences in the incidence rate ratios of AEs.

5.2: Abuse Liability: Aberrant Medication Behaviours

Analysis: Aberrant medication behaviors were measured by the modified ORBIT questionnaire at Week 12. Total number of different types of adverse events in each treatment group over the course of the 12-week trial were calculated. A chi-squared test of independence was performed, testing for presence of a between-group difference in proportion of individuals who engaged in *at least one* aberrant behaviour during the 12-week trial.

Section 6: Satisfaction with Medication

Analysis: At the final three research interviews (weeks 4, 8, and 12) participants were asked whether they would recommend their medication to friend seeking treatment (Yes/No response). Participants' last response to this variable (i.e. at last research interview before exiting the study early or at week-12 interview) was the response analysed. Numbers and proportions in each group who indicated they would recommend their medication to a friend was calculated. A logistic regression was performed, regressing this dichotomous 'would not recommend vs would recommend' variable on treatment group.

Section 7: Effectiveness of Blinding

At each follow-up research interview (Weeks 4, 8, and 12) participants were asked to guess what treatment arm (Placebo or Nabiximols), they had been allocated to. A binary variable was obtained for each participant (Guessed Placebo vs Guessed Nabiximols) such that whatever participants guessed in their last research interview before either exiting early or completing the study, was counted as their guess for the study. This guess was compared to their actual allocated treatment group and coded as either incorrect or correct. A logistic regression was performed, regressing this binary 'guessed incorrect vs guessed correct' variable on treatment group. Odds ratios, *P*-values, and 95% confidence intervals are reported for this analysis.

Section 8: Urinalysis

Analysis: Testing the Ability of Self-Reported Days Use to Predict Urinary Cannabinoid Concentration. Urine samples taken at baseline, week 4, week 8, and week 12 were analysed for (−)-*trans*-Δ^9-tetrahydrocannabinol (THC), 11-Hydroxy-Δ^9-tetrahydrocannabinol (11-OH-THC), and 11-Nor-9-carboxy- 9-tetrahydrocannnabinol (THC-COOH). Each cannabinoid was adjusted according to creatinine concentration at the time of measurement using the procedure outlined in Baker and colleagues (2018). Analysis of urine drug tests results was conducted to examine the validity of self-reported illicit cannabis use at baseline and week 4,8 and 12 research interviews, and was therefore be restricted to the Placebo group (the prescribed THC in the Nabiximols group prevents meaningful interpretation of urinary THC or metabolites). Two approaches were taken to the analysis of urinary cannabinoids.

Method 1: This method was a more general test; of whether self-reported days use predicted levels of the three metabolites. Creatinine adjusted urinary THC, 11-OH THC and THC-COOH levels from urine samples from all observations time points from all Placebo participants was compared against self-reported days illicit cannabis use collected on the same day at 4-weekly research interviews. Due to the very large range and heavy positive skew usually observed in this data, creatinine-adjusted cannabinoid concentrations were Winsorized and then log-transformed prior to analysis. The log-levels of the three cannabis metabolites were then regressed on self-reported days use of illicit cannabis in the previous 4 weeks, with participant age and gender entered as covariates. These regressions were performed on data from each of the four measurement points in isolation (baseline, 4 weeks, 8 weeks, and 12 weeks).

Method 2: This approach attempted to verify self-reported cannabis use on a case-by-case basis, via the method described by Baker and colleagues (2018) for assigning recent abstinence from illicit cannabis use based on quantitative creatinine adjusted THC-COOH levels. Change scores were calculated for the THC-COOH variable by dividing Winsorized THC-COOH levels at each time point by Winsorized THC-COOH levels for the same participant at the previous time point (hence there will be no change scores for baseline observations, which will not be included in analysis). A binary variable was then calculated based on these change scores. Observations were recorded as abstinence from recent use (negative or ‘0’) if THC-COOH levels dropped by more than 75% from the previous observation or if THC-COOH observations fell below 200 ng/ml. Any observations that did not meet this criterion were recorded as a positive (‘1’), signifying recent illicit cannabis use.

A binary cannabis use variable was also calculated, where any number of days use was recorded as a positive (‘1’) and zero days use a negative (0). A contingency table was then calculated using these two binary variables. These analyses verified use or abstinence at the observation level. As we were not concerned with trajectory of either cannabis use or THC-COOH levels, time was not included as a factor in these models.

Baker and colleagues also considered 50 ng/ml and 100 ng/ml as cutoff criteria and these were also assessed. ROC analysis was performed using the three cutoff criteria (50 ng/ml, 100 ng/ml, and 200 ng/ml) in combination with the ≥ 75% reduction criterion. Sensitivity, specificity, percentage correctly classified, positive- and negative-likelihood ratios, and area under the curve statistics from these analyses are reported.