

CLINICAL STUDY REPORT

Sativex® for the Treatment of Agitation in Dementia (‘STAND trial’)

Trial long title: A randomised feasibility trial investigating Sativex® for the treatment of the Agitation & Aggression (A/A) in Alzheimer’s Dementia.

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ISRCTN number:	ISRCTN97163562
REC Number:	20/WM/0210
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Indication:	Agitation in Alzheimer’s Dementia
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Study End:	23 rd August 2023
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SIGNATURE PAGE

By signing below I approve the contents of this Clinical Study Report, and confirm that to the best of my knowledge it accurately describes the conduct and results of the study. The clinical trial reported herein was conducted in accordance with the principles contained in the Declaration of Helsinki, Good Clinical Practice (GCP) and all applicable laws and regulations.

Chief Investigator: Professor Dag Aarsland

Signature



Date 17th July 2024

Contents

1	Ethics.....	5
1.1	Independent Ethics Committee or Institutional Review Board.....	5
1.2	Ethical conduct of the study	5
1.3	Subject information and consent	5
2	Data Monitoring	6
3	Sponsors, Investigators and Trial Sites	6
3.1	Co-Sponsors	6
3.2	Chief Investigator	7
3.3	Name and address of Co-Investigator(s), Statistician & expert collaborator(s).....	7
4	Study Synopsis	9
5	Glossary of terms.....	13
6	Publication (reference).....	14
7	Study period (years)	15
8	Phase of development.....	15
9	Objectives	15
9.1	Primary objectives	15
9.2	Secondary objectives	16
10	Background and Context.....	16
11	Methodology.....	19
11.1	Study design.....	19
	Figure 1: STAND Trial CONSORT diagram.....	21
11.1.1	Sample size.....	22
11.1.2	Randomisation and blinding	22
11.2	Participants	22
11.2.1	Inclusion criteria.....	22
11.2.2	Exclusion criteria	23
11.3	Intervention and comparator	24
11.3.1	Investigational medicinal product (IMP) and placebo comparator.....	24
11.3.2	Dosing regimen	25
11.4	Outcomes.....	25

11.4.1	Primary feasibility outcomes:	25
11.4.2	Secondary safety and tolerability outcomes:	26
11.4.3	Future efficacy outcomes	26
11.4.4	Overview of outcome measures and time points	26
12	Statistical Methodology	27
12.1	Descriptive summaries.....	27
12.2	Analysis of primary feasibility outcomes	27
12.3	Analysis of secondary neuropsychiatric outcomes.....	27
12.4	Analysis of safety data	28
13	Summary – Conclusions	28
13.1	Demographic data.....	28
13.2	Feasibility results (Primary outcome)	32
13.3	Safety results (Primary outcome)	36
13.4	Clinical outcome results (Secondary Outcomes)	37
13.5	Conclusion.....	43
14	Date of Report.....	43
15	References	44

1 Ethics

1.1 Independent Ethics Committee or Institutional Review Board

The study protocol and amendments were reviewed and approved by a National Research Ethics Service (West Midlands – Coventry & Warwickshire Research Ethics Committee on the 14th August 2020; reference: 20/WM/0210).

1.2 Ethical conduct of the study

The trial was conducted according to the protocol and in compliance with the principles of the Declaration of Helsinki (1996) as amended, the principles of Good Clinical Practice (GCP) and in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, the Research Governance Framework for Health and Social Care, the Data Protection Act 1998 and other regulatory requirements as appropriate. The trial protocol and substantial amendments were reviewed by the United Kingdom (UK) Medicines and Healthcare products Regulatory Agency (MHRA)

1.3 Subject information and consent

The target sample was primarily recruited through the NIHR Maudsley Biomedical Research Centre Care Home Research Network (CHRN) (1). Approximately 200 care home managers were emailed a brief information sheet and inclusion criteria for the study and asked to consider if any of their residents could be eligible. Follow-up telephone calls were offered to provide further information and clarity. Additionally, we arranged regular workshops and public engagement events with CHRN members to advertise the study more broadly. If they identified potential candidates within their care home, we first asked them to confirm whether they considered the resident to have mental capacity to consider joining the trial themselves. If so, we approached the resident directly to obtain fully informed consent. If not, we asked the care home to contact their next of kin for consideration and consent for us to get in contact directly to discuss. Mental capacity assessments were always conducted by the study team upon receiving a signed consent form. If disagreement found, we reinitiated the correct consenting pathway according to appropriate level of consent. In addition to the CHRN, we conducted regular multistakeholder mapping and engagement exercises with PPI and expert partners to identify additional recruitment channels that accelerated and complemented our recruitment from the CHRN.

2 Data Monitoring

A Trial Management Group 'TMG' consisting of staff from the Co-Sponsors provided management and coordination of the trial. An independent Trial Steering Committee 'TSC' (with nested Data Monitoring Committee 'DMC') was formed consisting of a Chair, clinician, statistician, patient representative, and care home workforce representative.

The Co-Sponsors delegated the delivery of the Sponsor's responsibility for pharmacovigilance (as defined in Regulation 5 of the Medicines for Human Use (Clinical Trials) Regulations 2004) to the King's Health Partners Clinical Trials Office (KHP-CTO). All serious adverse events (SAE), serious adverse reactions (SAR) or unexpected serious adverse reactions (USAR) were reported immediately (and certainly no later than 24hrs) by the Investigator to KHP-CTO and PI for review in accordance with the current Pharmacovigilance Policy. In consenting to the trial, participants are consenting to the trial treatments, trial follow-up and data collection. However, an individual participant could stop treatment early or be stopped early for any of the following reasons:

- unacceptable adverse event as determined by the participant, their care team or the study clinical team
- inter-current illness that prevents further treatment
- any change in the participant's condition that in the clinician's opinion justifies the discontinuation of treatment
- withdrawal of consent for treatment.

Monitoring of this trial to ensure compliance with good clinical practice and scientific integrity was managed and oversight retained, by the KHP-CTO Quality Team

3 Sponsors, Investigators and Trial Sites

3.1 Co-Sponsors

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4 Study Synopsis

Title of clinical trial	A randomised feasibility trial investigating Sativex® for the treatment of the Agitation & Aggression (A/A) in Alzheimer's Dementia
Protocol Short Title/Acronym	Sativex® for the Treatment of AgitationN in Dementia (STAND trial)
Sponsor name	King's College London & South London & Maudsley NHS Trust (SLaM)
Chief Investigator	Professor Dag Aarsland
Eudract number	2020-001056-17
REC number	IRAS Project ID: 272703
Medical condition or disease under investigation	Agitation & Aggression (A/A) in Alzheimer's Dementia
Purpose of clinical trial	Investigating Sativex® as a novel treatment for A/A in Alzheimer's Dementia

Primary objective	To determine the feasibility & safety of Sativex® in the treatment of agitation & aggression in Alzheimer's dementia.
Secondary objective (s)	To estimate the overall symptom response rate to Sativex® in the trial population, including other neuropsychiatric symptoms (sleep, apathy, appetite, anxiety etc) and pain relief.
Trial Design	A randomised, double-blind, parallel group, placebo-controlled trial. Titrated 4-week treatment period, followed by final assessment at 8-weeks.
Qualitative Evaluation sub-study	Qualitative interviews exploring acceptability & feasibility of oromucosal route of administration, & medical cannabis stigma. Conducted with: <ul style="list-style-type: none"> - Resident (where possible) - Residents' designated staff carer
Endpoints	<p>Primary feasibility outcomes:</p> <ul style="list-style-type: none"> - To consent and randomise 60 participants - To follow up at least 75% of those randomised - For a minimum of 80% of participants to demonstrate adherence to the allocation - To <u>estimate</u> a clinically meaningful effect size of at least 0.3 <p>Safety and tolerability:</p> <ul style="list-style-type: none"> - <i>Tolerability:</i> Assessed by self- & carer-report of side-effects, medication discontinuation - <i>Safety parameters:</i> Bloods for Haematology (Full red & white blood cell count and Haemoglobin) and Biochemistry (Urea, liver function test, thyroid function test, lipid profile); Vital signs: Heart rate and Blood pressure; Physical examination - Follow up phone calls for self-reported side effects, including incidence of falls and compliance (week 2 and 6) <p>Future primary Neuropsychiatric Symptom (NPS) endpoint for later study:</p> <ul style="list-style-type: none"> - Change in Cohen-Mansfield Agitation Inventory (CMAI) at 4 weeks at daily dose

	<p>Secondary NPS endpoints:</p> <ul style="list-style-type: none"> - Change in CMAI at 2 & 8 weeks - Neuropsychiatric Inventory – Nursing Home (NPI-NH) 2, 4 & 8 weeks - Standardised Mini Mental State Examination (sMMSE) 4 & 8 weeks - Functional Assessment Staging of Alzheimer’s Disease (FAST) 4 weeks - Clinical Frailty Scale (CFS) 4 weeks - Quality of Life with resident 4 & 8 weeks (QOL-AD care home) - Quality of Life with proxy informant 4 & 8 weeks (QAULID) - Change in pain; Abbey Pain Scale (APS) 4 weeks - Actigraphy data for sleep, physical activity and linked to NPS assessments (exploratory analyses) weeks 4 weeks
Sample Size	60
Summary of eligibility criteria	<p>Inclusion Criteria:</p> <ul style="list-style-type: none"> - Age: 55-95 - Alzheimer’s Disease diagnosis - Clinically significant & persistent agitation & aggression symptoms <p>Exclusion Criteria</p> <ul style="list-style-type: none"> - Evidence of contraindications as specified in Sativex® SmPC - Hypersensitivity to Sativex® - Unstable treatment of ChEIs and/or memantine - Severe, unstable mental and/or physical illness preventing participation - Severe cardiovascular disease - History or family history of schizophrenia, or other psychotic illness; history of severe personality disorder or other significant psychiatric disorder other than depression associated with their underlying condition. - Delirium, pain, or any medical illness as a clear cause of agitation. - Currently using cannabis-based medicines - Females of child-bearing potential - Evidence of suicidality risk - History/current seizure disorder - History/current of alcohol or other substance abuse - History of fall(s) within the last 6 months

IMP, dosage, and route of administration	<p><u>Route of Administration:</u></p> <p>Sativex®/placebo will be administered as an oromucosal spray by qualified clinical nursing staff within the care home.</p> <p><u>Dosage:</u></p> <p>Dosing will be determined by number of sprays per day. Each spray reliably contains 2.7mg (THC)/2.5mg (CBD). Dosage will be titrated up to a maximum dose of 4 sprays per day (10.8mg THC/10mg CBD). Importantly, the placebo group will follow the same dosing schedule.</p>
Active comparator product(s)	Sativex placebo will be administered using the same device (oromucosal spray), and contain ethanol, propylene glycol (50:50), with peppermint oil (.05%) flavourings and colourings.
Maximum duration of treatment of a Subject	4 weeks
Version and date of protocol amendments	V1.0 02.12.19 V2.0 07.08.20 V3.0 07.12.20 V4.0 07.04.21 V5.0 07.02.22

5 Glossary of terms

Abbreviation	Definition
AD	Alzheimer's Disease
AE	Adverse Event
APS	Abbey Pain Scale
AR	Adverse Reaction
ARUK	Alzheimer's Research UK
A/A	Agitation & Aggression
BP	Blood Pressure
BPSD	Behavioural and Psychological Symptoms of Dementia
CB1	Cannabinoid receptor type 1
CBD	Cannabidiol
CH	Care Home
ChEIs	Cholinesterase Inhibitors
CHRN	Care Home Research Network
CI	Chief Investigator
CFS	Clinical Frailty Scale
CMAI	Cohen-Mansfield Agitation Inventory
CRA	Clinical Research Associate
CRF	Case Report Form
DMC	Data Monitoring Committee
DOAP	Department of Old Age Psychiatry
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECS	Endocannabinoid System
FAST	Functional Assessment Staging of Alzheimer's Disease
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General Practitioner
GSTT	Guys & St Thomas Pharmacy Manufacturing Unit
GWP	GW Pharmaceuticals
HR	Heart Rate
IB	Investigator's Brochure
IME	Important Medical Events
IMP	Investigational Medicinal Product
IRAS	Integrated Research Approval System
ISF	Investigator Site File
ITT	Intention-To-Treat
KCTU	King's Clinical Trial Unit
KHP-CTO	King's Health Partners Clinical Trials Office
MAR	Medical Administration Record charts
MHRA	Medicines and Healthcare products Regulatory Agency
MM	Medical Monitor
sMMSE	Standardised Mini Mental State Examination
NPI-NH	Neuropsychiatric Inventory – Nursing Home

NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NINCDSADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NoK	Next of Kin
NPS	Neuropsychiatric Symptoms
PD	Protocol Deviation
PerLR	Personal Legal Representative
PI	Principal Investigator
PlwD	Person/People living with Dementia
POA	Power of Attorney
PPI	Patient and Public Involvement
ProLR	Professional Legal Representative
PV	Protocol Violation
QE	Qualitative Evaluation
QAULID	Quality of Life with proxy informant
QoL-AD	Quality of Life with resident
RCT	Randomised Clinical Trial
REC	Research Ethics Committee
R/F	Relative/Friend
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SDW	Source Data Worksheet
SIV	Site Initiation Visit
SLaM	South London and Maudsley
SmPC	Summary of Product Characteristics
SOPs	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TAU	Treatment as Usual
TC	Telephone call
THC	Tetrahydrocannabinol
TMG	Trial Management Group
TMF	Trial Master File
TSC	Trial Steering Committee

6 Publication (reference)

Albertyn CP, Johar I, Creese B et al. Sativex® for the treatment of Agitation & Aggression in Alzheimer's Dementia in UK nursing homes (STAND): Protocol for a feasibility randomised controlled trial [version 1; peer review: 2 approved with reservations]. Health Open Res 2023, 5:18 (<https://doi.org/10.12688/healthopenres.13311.1>)

7 Study period (years)

Entire study period was from September 1st 2019 to August 23rd 2023.

The end of the trial was defined as database lock plus an additional six-week period.

First Patient First Visit (FPFV) was October 13th 2021.

Last Patient Last Visit (LPLV) was August 28th 2022.

The study experienced significant delays and interruptions because of the covid-19 pandemic. It underwent iterative reviews and amendments between March 2020 until receiving a green light to commence recruitment in September 2021.

8 Phase of development

This was a phase II feasibility pilot randomized controlled trial (RCT).

9 Objectives

9.1 Primary objectives

- To employ a mixed methods approach to explore the feasibility of a definitive multicentre randomized controlled trial (RCT) within residential nursing home settings of Sativex® for treatment of agitation and aggression in AD. Further, our primary objectives were:
 - To explore rate of recruitment and retention in the target population, including determining facilitators and barriers.
 - To investigate the acceptability of an oral mucosal method of administration for this indication in terms of compliance and to care home staff in terms of adherence to the titration schedule.
 - To investigate the acceptability of a cannabinoid-based medicine and explore impact of societal attitudes and stigma within this patient population.

9.2 Secondary objectives

- To estimate the sample size for a later RCT for the treatment effect of Sativex® for agitation and aggression in dementia.
- To estimate the between-group difference in the trial population, including other neuropsychiatric symptoms (such as sleep disturbances and changes in appetite), and pain relief.

10 Background and Context

Dementia is a growing concern for the international healthcare community, with increasing worldwide prevalence and greater associated costs (2,3). Whilst many researchers justifiably focus on potential cures and prevention, a significant proportion of the research priorities identified during consultation with people with dementia, carers and clinicians relate to the challenges of caring for someone with dementia (4). Some of the most challenging aspects of caring are behavioural and psychological symptoms of dementia (BPSD), defined by the International Psychogeriatric Association as “symptoms of disturbed perception, thought content, mood or behaviour that frequently occur in patients with dementia” (5). These symptoms encompass a significant portion of concerns when caring for a Person living with Dementia (PlwD). BPSD are very common, with at least one symptom occurring in 98% of PlwD (6), causing direct distress and risk to the individual and their carers. Agitation, defined as “inappropriate verbal, vocal or motor activity, which is not an expression of unmet need, and encompasses physical and verbal aggression”(7), affects approximately 50% of all PlwD and is persistent (8,9). Agitated behaviours have been reliably associated with: greater caregiver burden, earlier institutionalisation and increased mortality, poorer functioning, accelerated disease progression, greater cost of care and more frequent acute hospitalisations (8,10–14). Current recommended practice in the United Kingdom (UK), as specified by the National Institute for Health and Care Excellence (NICE), involves using non-pharmacological interventions in the first instance, however these are time and resource intensive and can often prove ineffective for those with more severe symptoms; at which point pharmacotherapies are utilised as a last resort (15). In the US there’s no specific designated pharmacological treatment for this indication (16), whereas in the UK only risperidone is indicated for the short-term management of severe aggression in dementia

(17). Other than this, clinicians customarily prescribe off-label antipsychotics, antidepressants, cholinesterase inhibitors, memantine and/or analgesics (18). Unfortunately, these treatments only demonstrate modest efficacy, and come with a myriad of unpleasant and potentially lethal side effects, especially when prescribed in combination, leading to a highly questionable therapeutic cost:benefit ratio (18–20). Therefore, there is a clear and pressing rationale to identify safer novel multitarget pharmacological treatments for agitation in dementia.

There has been growing interest in the endocannabinoid system (ECS) as a potential target to alleviate behavioural symptoms in dementia (21). The ECS is implicated in systems that regulate homeostasis, including domains such as mood, appetite, sleep, and pain, and is typically impacted in the majority of neurological disorders (22). Moreover, a cannabinoid-based medicine (CBM) - typically comprising the constituent cannabinoids: tetrahydrocannabinol (THC), cannabidiol (CBD), or a combination - has the potential to act as a multi-target therapeutic for neuropsychiatric symptoms in Alzheimer's disease, with a much more favourable safety profile than current treatments. For example, a recent large epidemiological analysis of cannabinoid administration for medicinal purposes in older adults ($n = 2736$; mean age = 74.5 ± 7.5 years) found cannabinoids to be well tolerated and safe (23). In a recent systematic review and meta-analysis of 46 randomised controlled trials of CBMs in the elderly with mean age 50 years and over for all indications found that CBMs are generally well-tolerated and safe (24). A recent systematic review of CBMs in dementia found preliminary clinical evidence that THC-only, the primary psychoactive cannabinoid, CBMs may have therapeutic impact for agitation in dementia, however the quality of evidence was rated as very poor due to small sample sizes and questionable trial designs (25). Additionally, there has been interest in the potential of CBD for the same indication, a non-psychoactive cannabinoid with growing evidence for therapeutic anxiolytic potential, but early trials are still underway (e.g. (26)).

STAND differs from these trials as Sativex® uniquely offers a combined THC/CBD 1:1 ratio. There's growing support for a more potent synergistic effect of combined THC/CBD administration (27–29). For example, CBD has been found to increase the antinociceptive potency of THC (30), and that this interactive effect was more potent than THC or CBD

treatment alone. CBD can also attenuate reported adverse effects of higher doses of THC, such as psychotic/paranoia symptoms (31–35) and acute memory impairment (36–39)

Also unique to STAND is that the intervention was administered as an oromucosal spray in nursing homes by resident nurses. An oromucosal route of administration is less common than the typical tablet or oral solution route, however we propose that this format will be highly accessible and well received for residents with dementia, especially those with dysphagia or high likelihood of spitting/refusing medications. Additionally, in comparison to alternative methods of cannabinoids medication administration (inhalation/oral/topical), oromucosal administration demonstrates the fastest onset with the longest duration; 15-45 min and 6-8 hours respectively (40). This is particularly relevant for residents with dementia displaying agitation and aggression, and their primary carers, who would benefit from symptomatic relief that is faster to act and lasts longer.

Recently, Alzheimer's Research UK (ARUK) (41) and the 'Psychiatry Consortium' (PC) in the Medicines Discovery Catapult (42), commissioned the development of a 'Target Product Profile' (TPP) for agitation in Alzheimer's disease. A TPP is considered a cornerstone of precision drug development. It outlines the optimal criteria that are most desirable for a novel therapeutic to be considered effective and fit-for-purpose for a particular condition, including what systems drugs should target; how they are administered; how to measure clinically significant impact; which patient populations should be targeted; and more. Drug development pipelines that use TPPs have a higher chance of translational success from compound to market as they demonstrate a more targeted and efficient approach (43). ARUK and PC's TPP has been developed in collaboration with expert clinical researchers and clinicians, health economists, and crucially with members of the patient and carer population living with Alzheimer's disease.

While this trial was prospectively registered prior to the publication of this TPP (see <https://www.isrctn.com/ISRCTN97163562>), it is noteworthy that it meets many of the proposed essential criteria. For example, STAND meets the following key recommendations from the TPP:

- Using the ‘gold standard’ psychometric scales to measure agitation symptoms in Alzheimer’s disease (Cohen-Mansfield Agitation Inventory, ‘CMAI’; Neuropsychiatric Inventory, ‘NPI’),
- Including additional measures of quality of life, cognition, and caregiver burden,
- Having a drug candidate capable of immediate impact to address acute agitated episodes (fast symptom reduction) and suitable for patients with swallowing difficulty (oral spray),
- Low risk of drug-drug interactions, abuse liability, and better side-effect profile compared to current treatments,
- Including frequent or continuous data collection, such as diaries or remote assessment (e.g. using wearables).

We believe that findings resulting from this research will have a substantial impact for: clinicians prescribing medication for agitation and aggression in dementia in the UK; a future confirmatory clinical trial of Sativex® for A/A; the professional and clinical practice of nurses and care staff in nursing homes; and ultimately alleviate BPSD and improve quality of life for people living with dementia. Unfortunately, the modest benefits of current medications are massively offset by their increased risk of mortality, stroke and heart attacks, driving the search for safer alternatives. A combined THC/CBD CBM such as Sativex® fits this remit and many of the key criteria recommended by the recently published TPP, and offers a unique and novel opportunity to investigate augmented beneficial effects, whilst potentially representing a much safer and more tolerable pharmacological treatment option for agitation in dementia.

11 Methodology

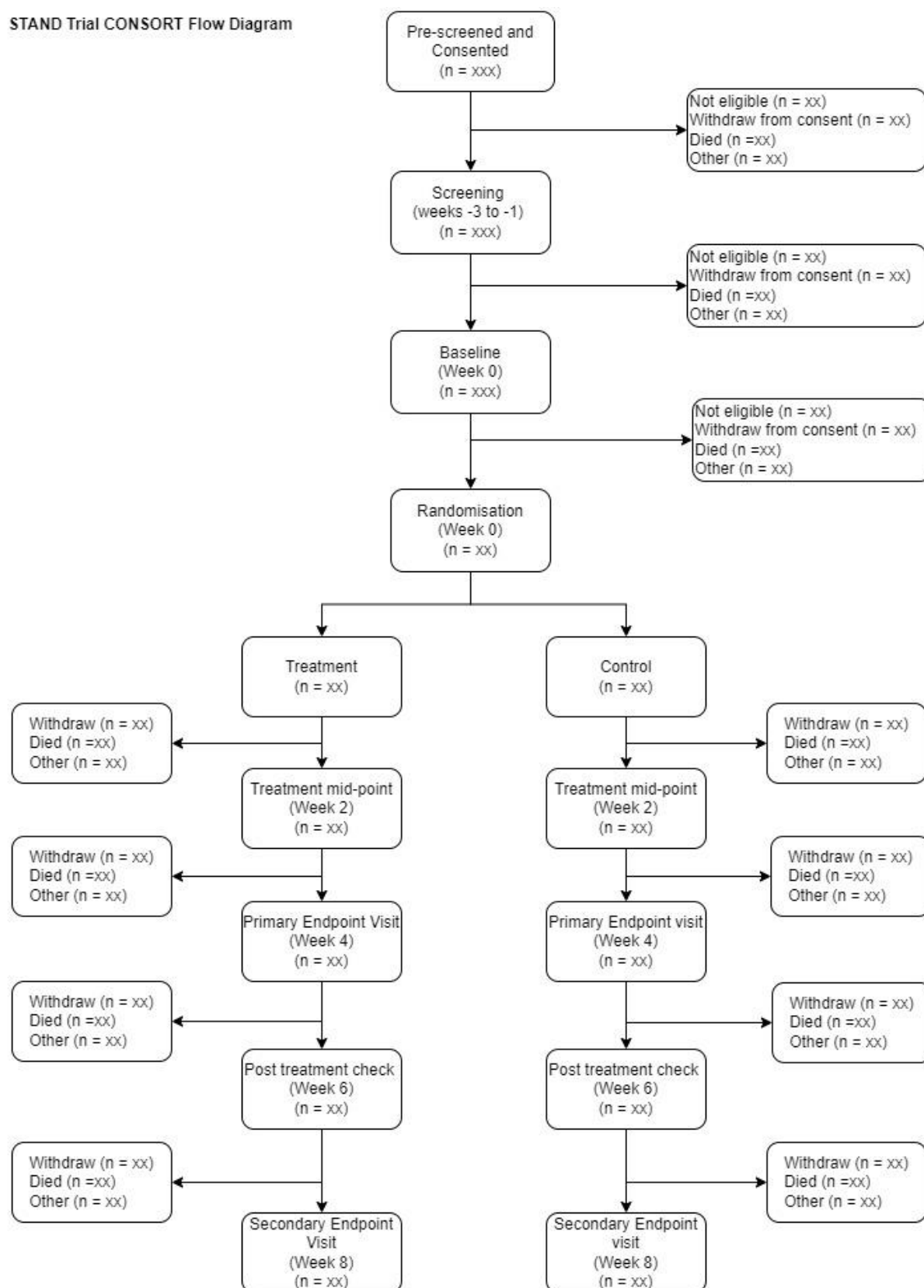
11.1 Study design

STAND is a double-blind, parallel group, randomised, placebo-controlled feasibility trial of Sativex® versus placebo to reduce A/A symptoms in AD. We aimed to conduct recruitment over a period of 12 months. On average we aimed to maintain a recruitment rate of 5 new participants a month. If a participant successfully completed screening, they were enrolled on to the trial according to the CONSORT diagram below (Figure 1). Following baseline assessments, the participants were randomised to either ‘Treatment as usual’ (TAU) +

Placebo; or TAU + Sativex®. The intervention was up-titrated over 4 weeks, with a mid-point safety check. The participants were then checked 2- and 4-weeks post-treatment for safety and other outcome measures.

Figure 1: STAND Trial CONSORT diagram

STAND Trial CONSORT Flow Diagram



11.1.1 Sample size

This feasibility study was not powered to detect important clinical differences between the intervention and the TAU groups. Instead, we aimed to provide strong evidence for the feasibility of recruitment, safety of the medication and adherence to treatment to inform a larger phase III confirmatory trial. With a sample size of 60, we will be able to estimate a drop-out rate of 20% to within a 95% confidence interval of +/- 10% (43,44).

11.1.2 Randomisation and blinding

The randomisation service was provided by the bespoke online randomisation system managed by the independent King's Clinical Trials Unit (KCTU) such that randomisation information was concealed from the study researchers. The sequence was held within a web-based system and concealed from the investigators including the Chief investigator and trial statistician. As a double-blind trial, all study personnel (with the exception of pharmacy staff), care home staff, and participants were blinded to the treatment allocation. Side effects were dealt with on the assumption that the patient is on active treatment. It was the treating physician's responsibility in an emergency to decide if breaking the code is necessary, based on clinical judgement.

11.2 *Participants*

Participants were recruited and screened according to the following criteria:

11.2.1 Inclusion criteria

- **Age: 55-95**
- **Probable Alzheimer's disease diagnosis** according to the criteria of National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDSADRDA)
- **Clinically significant A/A** that requires treatment, defined by CMAI ≥ 45 (46) and/or NPI-NH Agitation total score ≥ 4 (1)
- Residential within a nursing home at recruitment to the study with a history of **at least 2 weeks behavioural disturbance**
- **Written and witnessed informed consent** from **participant** (if deemed having mental capacity), or from **personal legal representative** (next of kin/power of attorney), or

from **professional legal representative** (non R/F member who can attest to knowing prospective participant for significant period of time)

- Informed consent was sought in this order from these potential sources.

11.2.2 Exclusion criteria

- Anti-psychotic, anti-epileptic, antidepressant, benzodiazepine, lithium or hypnotic **dosage alteration in the 2 weeks** prior to the start of the study (and expected to maintain dosage throughout study).
- **ChEIs** (donepezil, rivastigmine or galantamine) and/or **memantine**, dosage alteration in the 6 weeks prior to the start of the study.
- Currently using cannabis-based medicine(s) (defined as being a UK-licensed product prescribed by a doctor)
- **Concomitant treatment with strong enzyme inducers** (rifampicin, carbamazepine, phenytoin, phenobarbital, St John's Wort) and/or CYP3A4 inhibitors
- **Hypersensitivity to Sativex®** or any of the excipients in the formulation (ethanol anhydrous, Propylene glycol, peppermint oil)
- Severe **cardiovascular disease**, recent myocardial infarction ('recency' determined by study doctor according to clinical significance), uncompensated congestive heart failure and uncontrolled hypertension
 - QT interval by Fredericia (QTcF) greater than 450 were excluded if ECG conducted.
- Severe, unstable or poorly controlled medical illness
- If diagnosed with **severe kidney disease/impairment** (as deemed by study doctor/PI), a blood test (taken within 12 months) was required to assess severity of **renal impairment**
 - **Renal impairment** is defined by estimated glomerular filtration rate (eGFR) less than 45ml/min.
- If diagnosed with **severe liver disease/impairment** (as deemed by study doctor/PI), a blood test (taken within 12 months) was required to assess severity of **hepatic impairment**
 - **Hepatic impairment** is defined by alanine **aminotransferase** (ALT)/ aspartate **aminotransferase** (AST) levels 3 times greater than reference value of laboratory (165 IU/L+ for ALT; 150 IU/L+ for AST).

- Any disability that may interfere with the patient completing the study procedure
- History or family history of schizophrenia, or other psychotic illness; history of severe personality disorder or other significant psychiatric disorder other than depression associated with their underlying condition
- Delirium, pain or any medical illness as a clear cause of agitation
- Females of child-bearing potential, defined as 'having experienced menarche and are not permanently sterilised (e.g. by hysterectomy, bilateral salpingectomy and bilateral oophorectomy) or post-menopausal (defined as at least 1 year since last regular menstrual period)'
- Evidence of 'suicidality risk' determined by >0 on Columbia-Suicide Severity Rating Scale (C-SSRS)
- History/current **seizure disorder**
- History/current of **alcohol or other substance abuse**
- History of **fall(s) within the last 6 months.**

11.3 Intervention and comparator

11.3.1 Investigational medicinal product (IMP) and placebo comparator

The investigational medicinal product (IMP) was Sativex® (Jazz Pharmaceuticals). Sativex® is an oromucosal spray of a formulated extract of the cannabis sativa plant that contains the principal cannabinoids delta-9- tetrahydrocannabinol (THC) and cannabidiol (CBD) in a 1:1 ratio. Sativex® has been developed to be administered as an oromucosal spray, whereby the active ingredients are absorbed in the lining of the mouth, either under the tongue or inside the cheek. Each microliter spray (i.e. single dose) contains 2.7mg delta-9-tetrahydrocannabinol (THC) and 2.5mg cannabidiol (CBD), flavoured with peppermint oil. The placebo treatment contained ethanol, propylene glycol (50:50), with peppermint oil (.05%) flavourings and colourings. Identical to active drug, the placebo will be given as per active drug titration regime. Sativex®/placebo will be administered in an incrementally titrated dose over a period of 4 weeks, with a subsequent follow up after a 4 week wash out period at 8 weeks.

11.3.2 Dosing regimen

Dosing was determined by number of sprays per day. Each spray reliably contains 2.7mg (THC)/2.5mg (CBD). Dosage was titrated up to a maximum dose of 4 sprays per day (10.8mg THC/10mg CBD). Importantly, the placebo group followed the same dosing schedule.

Table 3: STAND titration schedule

Week	No. of Sprays (morning)	No. of sprays (afternoon)	No. of sprays (Evening)	Total no. of sprays per day
1 (Days 1 & 2)	0	1	0	1
1 (Days 3 – 7)	0	1	1	2
2	0	1	2	3
3	1	1	2	4
4	1	1	2	4

'Morning', 'afternoon' and 'evening' loosely refer to nursing home typical prescribing times. Further, it was anticipated that these times were between 8-10am, 12-2pm and 6-8pm respectively. This has the added benefit of being concurrent with nursing home meal and tea times to mitigate mild dry-mouth and increased appetite side effects. Sativex® Summary of Product Characteristics (SmPC) licensed product states the starting dose should be one spray daily for the first two days then increase to two sprays daily. Further, our titration schedule reflects this precaution.

11.4 Outcomes

11.4.1 Primary feasibility outcomes:

- To consent and randomise 60 participants as measured by number of participants randomised at trial close
- To follow up at least 75% of those randomised as measured by the number of participants completing each follow up to and including the secondary endpoint
- For a minimum of 80% of participants to demonstrate adherence to the allocation. Adherence defined by participants receiving at least one dose per week during treatment phase.
- To estimate a clinically meaningful effect size of at least 0.3.

11.4.2 Secondary safety and tolerability outcomes:

- Tolerability: Assessed by self- & carer-report of side-effects and medication discontinuation
- Follow up phone calls for AEs/SAEs and self-reported side effects (including incidence of falls)
- Change in Columbia-Suicide Severity Rating Scale (C-SSRS) (47).

11.4.3 Future efficacy outcomes

- Cohen-Mansfield Agitation Inventory (CMAI) (6)
- Standardised Mini Mental State Examination (sMMSE) (48)
- Quality of Life in Late Stage Dementia (QUALID) (49)
- Quality of Life – Alzheimer’s Disease - Care Home (QOL-AD) (50)
- Abbey Pain Scale (APS) (51)
- Functional Assessment Staging (FAST) (52)
- Clinical Frailty Scale (CFS) (53).

11.4.4 Overview of outcome measures and time points**Table 2.** The variable list, with the primary function of the variable and collection points

Variable	Primary function	Time Points					
		Screen	W0	W2	W4	W6	W8
CMAI	Primary outcome	x	x	x	x	x	x
NPI-NH	Secondary outcome	x	x	x	x	x	x
sMMSE	Secondary outcome		x		x		x
QUALID	Secondary outcome		x		x		x
QOL-AD	Secondary outcome		x		x		x
APS	Secondary outcome		x		x		x
FAST	Secondary outcome		x		x		
CFS	Secondary outcome		x		x		
EAT & CH measures	Environment outcome		x				
C-SSRS	Safety	x			x		
AEs	Safety		x	x	x	x	x

Screen: screening, W0: Baseline, W2: Mid-point, W4: Primary endpoint, W6: Post treatment check, W8: Secondary endpoint

12 Statistical Methodology

12.1 Descriptive summaries

Demographic measures and secondary neuropsychiatric outcome scales were summarized using descriptive statistics (means and standard deviations [SDs] for normally distributed continuous variables, medians and quartiles for skewed continuous variables, numbers and proportions for discrete variables). No formal comparisons between arms on baseline characteristics was done.

12.2 Analysis of primary feasibility outcomes

Feasibility parameters such as recruitment, retention, and adherence rates were estimated along with 95% confidence intervals (CIs) using the `cii proportions` command in Stata specifying exact binomial distributions. No significance testing was done.

12.3 Analysis of secondary neuropsychiatric outcomes

Adjusted trial arm differences for continuous secondary neuropsychiatric outcomes were estimated using mixed linear models. Post-randomisation measurements of outcomes were predicted by the following fixed effects:

- Baseline measurement of the outcome
- Baseline stratification factor (disease severity: 1/Low, 2/Moderate, 3/Severe) with the largest group (Severe) serving as the reference group
- Trial arm (0=placebo, 1=Sativex)
- Time (categorical)
- Time * trial arm interaction term

A random intercept was fitted at the participant level to account for repeated measurements, except in the case when the outcome was only measured once post-randomisation (i.e. FAST and CFS). In these instances, the outcome at 4 weeks was predicted by the fixed effects of trial arm, baseline measurement, and baseline stratification factor (no time or time*arm term, no random effects) in adjusted analyses. Since baseline FAST was used to stratify participants by disease severity, the only fixed effects for the adjusted FAST model were stratification factor and trial arm. Estimated trial arm differences for continuous outcomes

were standardized by dividing the difference by the pooled group baseline standard deviation of the outcome. No significance level was set and no p-values are reported as these estimates are only meant to show a range of potential treatment effects.

For continuous outcomes determined to be heavily skewed, the relevant score categories were used instead in appropriate logistic regression models.

12.4 Analysis of safety data

Safety data was summarized by system organ class (SOC), relationship to study intervention, and severity. Summaries were presented as counts of events and counts of unique reporters.

13 Summary – Conclusions

13.1 Demographic data

Table: Baseline demographics for randomised participants

Baseline demographic	Control (N= 14)	Sativex (N= 15)	Overall (N= 29)
Age at randomisation (years) - median (IQR)	81.0 (75.0-87.0)	83.0 (77.0-86.0)	83.0 (75.0-86.0)
Sex - n (%)			
Male	9 (64%)	6 (40%)	15 (52%)
Female	5 (36%)	9 (60%)	14 (48%)
Disease severity – n (%)			
Low (FAST ≤ 5)	0 (0%)	0 (0%)	0 (0%)
Moderate (FAST = 6)	4 (29%)	5 (33%)	9 (31%)
Severe (FAST = 7)	10 (71%)	10 (67%)	20 (69%)
Race - n (%)			

Black	1 (7%)	0 (0%)	1 (3%)
White	13 (93%)	15 (100%)	28 (97%)
Religious affiliation - n (%)			
Christian	10 (71%)	8 (53%)	18 (62%)
Other	0 (0%)	1 (7%)	1 (3%)
No Religion	3 (21%)	4 (27%)	7 (24%)
<i>Not done/unknown (%) = 3 (10%)</i>			
First language - n (%)			
English	14 (100%)	15 (100%)	29 (100%)
Marital status - n (%)			
Single	1 (7%)	1 (7%)	2 (7%)
Married	8 (57%)	8 (53%)	16 (55%)
Widowed	4 (29%)	5 (33%)	9 (31%)
Long-term partnership	1 (7%)	1 (7%)	2 (7%)
Friend/family visits per month - median (IQR)	2.0 (1.0-5.0)	4.0 (2.0-8.0)	4.0 (1.0-5.0)
Physical disabilities - n (%)			
No	9 (64%)	11 (73%)	20 (69%)
Yes	5 (36%)	4 (27%)	9 (31%)
Visual disabilities - n (%)			
No	11 (79%)	15 (100%)	26 (90%)

Yes	3 (21%)	0 (0%)	3 (10%)
Auditory disabilities - n (%)			
No	12 (86%)	13 (87%)	25 (86%)
Yes	2 (14%)	2 (13%)	4 (14%)
Other disabilities - n (%)			
No	14 (100%)	15 (100%)	29 (100%)
Smoking history - n (%)			
Current smoker	0 (0%)	2 (13%)	2 (7%)
Ex-smoker	1 (7%)	2 (13%)	3 (10%)
Never smoked	7 (50%)	8 (53%)	15 (52%)
<i>Not done/unknown (%) = 9 (31%)</i>			
Alcohol history - n (%)			
Currently used	0 (0%)	4 (27%)	4 (14%)
Used in past but not currently	9 (64%)	10 (67%)	19 (66%)
Never used	1 (7%)	1 (7%)	2 (7%)
<i>Not done/unknown (%) = 4 (14%)</i>			
History of illicit recreational cannabis use - n (%)			
Never used	8 (57%)	10 (67%)	18 (62%)
<i>Not done/unknown (%) = 11 (38%)</i>			
History of legal cannabis product use - n (%)			

Never used	8 (57%)	10 (67%)	18 (62%)
<i>Not done/unknown (%) = 11 (38%)</i>			

At baseline the median participant was aged 83 (Control=81.0, Sativex=83.0) with an approximately equal ratio of males to females. The study sample was English-speaking (100%) and majority White (97%) with no visual (90%) or auditory (86%) disabilities. Over two-thirds (69%) of participants reported no physical disabilities. Of the 18 participants that provided responses on cannabis use, all 18 reported never using illicit recreational cannabis use or legal cannabis product use. About half (55%) of participants were married.

No participants were in the 'low' disease severity category. Over half of randomised participants were in the 'severe' disease severity category.

The participant characteristics were approximately balanced across arms. This was confirmed by the Trial Steering Committee. The sample, albeit small, was interpreted to be typical of an agitated nursing home population. Thus, any internal validity may be assumed to offer external generalisability.

13.2 Feasibility results (Primary outcome)

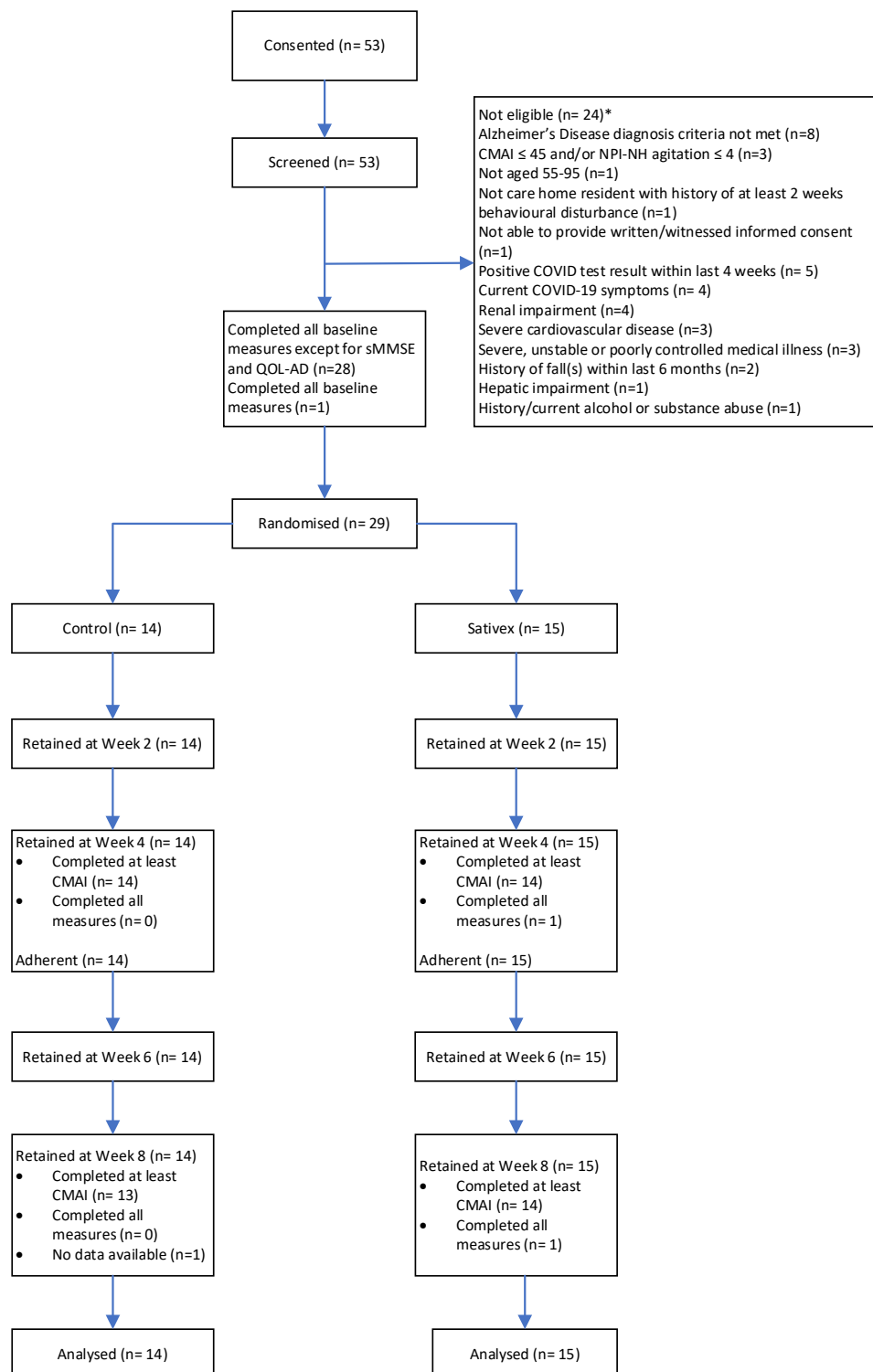


Figure: CONSORT diagram for STAND pilot trial

Table: STAND primary feasibility progression criteria

Primary feasibility metric	Estimate	Pass / Fail
To consent and randomise 60 participants as measured by number of participants randomised at trial close	29 randomised by trial close	Fail
To follow up at least 75% of those randomised as measured by the number of participants completing each follow up to and including the secondary endpoint (Week 8)	29/29 retained at Week 4, 29/29 retained at Week 8: Retention: 100% (95% CI: 88% - .)	Pass
For a minimum of 80% of participants to demonstrate adherence to the allocation. Adherence defined by participants receiving at least one dose per week during treatment phase (Weeks 1 – 4)	29/29 had at least 1 dose/week. Adherence: 100% (95% CI: 88% - .)	Pass
To estimate a clinically meaningful effect size of at least 0.3 for CMAI (Using Cohen's d) Note: an effect size in favour of Sativex for CMAI would be a negative value (i.e. Cohen's d of -0.3) when the control arm is the reference group. Given the baseline imbalance these findings need to be interpreted with caution, as this metric is unclear	Adjusted analyses (control as reference group): Wk 4: 0.23 (95% CI: -0.2 to 0.7) Wk 8: 0.08 (95% CI: -0.4 to 0.5)	Fail

The primary feasibility criterion of consenting and randomising 60 participants was not met, but this should be considered in the context of study recruitment occurring during the COVID-19 pandemic. The study exceeded its feasibility progression criterion for a minimum of 80% of participants to demonstrate adherence to the allocation. However, the definition of adherence as receiving at least 1 dose each week may be too easily achieved if the total number of planned doses each week ranges from 12 to 28.

All 29 randomised participants were retained at the primary endpoint (Week 4). The study exceeded its goal of following up at least 75% of those randomised at 4 weeks. In addition, the completion rates for the future primary outcome (CMAI) were excellent. All 29 randomised completed the CMAI at Week 4, and only one participant did not provide responses to the CMAI at Week 8. The effect size estimates are discussed in the Secondary Outcomes section.

The following tables give more details into the recruitment, retention, and adherence metrics.

Table: Recruitment and retention capability estimates

Feasibility parameter	Estimate [95% CI]
Eligibility rate (# eligible / # screened)	29/53 is 55% [40% - 68%]
Randomisation rate (# randomised / # eligible)	29/29 is 100% [88% - .]*
Follow-up rates (# retained at timepoint / # randomised):	
At Week 4 (primary endpoint)	29/29 is 100% [88% - .]*
At Week 8 (final timepoint)	29/29 is 100% [88% - .]*
CMAI completion rates (# completing CMAI / # randomised):	
At Week 4	29/29 is 100% [88% - .]*
At Week 8	28/29 is 97% [82% - 99.9%]

*One-sided 97.5% CI given if proportion is 100%.

About half of participants screened were found eligible and subsequently randomised. From the first randomisation on 17 November 2021 to the last randomisation on 04 July 2022, this represents 29 randomisations over a recruitment period of 7.5 months. On average, 3.9 participants were randomised per month (95% CI: 2.6 – 5.6).

Table: Summaries of intervention experiences by trial arm and overall

Intervention experience	Control (N= 14)	Sativex (N= 15)	Overall (N= 29)
Number completing titration schedule as planned (%) [95% CI]	6 (43%) [18 – 71%]	10 (67%) [38 – 88%]	16 (55%) [36 – 74%]
Week 1 (12 total)			
Missed doses	5 (36%)	4 (27%)	9 (31%)
Took total scheduled doses	8 (57%)	11 (73%)	19 (66%)
Took more doses than scheduled	1 (7%)	0 (0%)	1 (3%)
Week 2 (21 total)			
Missed doses	4 (29%)	3 (20%)	7 (24%)
Took total scheduled doses	10 (71%)	12 (80%)	22 (76%)
Week 3 (28 total)			
Missed doses	3 (21%)	5 (33%)	8 (28%)
Took total scheduled doses	11 (79%)	10 (67%)	21 (72%)
Week 4 (28 total)			
Missed doses	3 (21%)	4 (27%)	7 (24%)
Took total scheduled doses	11 (79%)	11 (73%)	22 (76%)

*one-sided 97.5% CI given if proportion is 100%

Although all participants were defined as adherent, just over half of all randomised participants completed the titration schedule as planned. There was one participant in the control arm that was accidentally given additional evening doses during the first two days.

13.3 Safety results (Primary outcome)

Table: Summary of adverse events by trial arm

Adverse event info	Control (N= 2)	Sativex (N= 4)	Overall (N= 6)
Category			
Hepatobiliary disorders	1	2	3
Respiratory disorders	0	1	1
Eye disorders	1	0	1
Skin/tissues disorders	0	1	1
Severity			
1. Mild	2 (100%)	4 (100%)	6 (100%)
Relationship to study intervention			
4. Remote	0 (0%)	1 (25%)	1 (17%)
5. Not related	2 (100%)	3 (75%)	5 (83%)

If a single number is presented, the number of events and number of unique reporters are the same. In this case, all events were reported by different participants. All events were of mild severity, and no events were deemed to be related to study intervention.

Table: Summary of serious adverse events by trial arm

Serious adverse event info	Control (N= 2)	Sativex (N= 1)	Overall (N= 3)
Category			
Respiratory, thoracic, and mediastinal disorders	1	0	1
Renal and urinary disorders	0	1	1
Unknown category	1	0	1
Severity			
2. Moderate	0 (0%)	1 (100%)	1 (33%)
3. Severe	2 (100%)	0 (0%)	2 (67%)
Relationship to study intervention			
5. Not related	2 (100%)	1 (100%)	3 (100%)

No SAEs were deemed to be related to study intervention, and there were no deaths reported. No falls were reported. No withdrawals were reported. The event description for the 1 SAE of unknown system organ class was 'Atrial Fibrillation'. The two SAEs in the control arm were reported for the same participant.

Overall, 6 patients (21%) patients experienced at least one AE. The proportion that experienced at least one SAE was 6.9% (n=2).

13.4 Clinical outcome results (Secondary Outcomes)

Table: Secondary neuropsychiatric outcome data by trial arm and timepoint

	BASELINE			WEEK 4 (PRIMARY ENDPOINT)			WEEK 8 (FINAL TIMEPOINT)		
Outcome	Control (N=14)	Sativex (N=15)	Overall (N=29)	Control (N=14)	Sativex (N=15)	Overall (N=29)	Control (N=14)	Sativex (N=15)	Overall (N=29)
CMAI total – median (IQR) [missing (% of N)]	65.0 (53.0-78.0)	84.0 (78.0-109.0)	78.0 (63.0-106.0)	49.5 (45.0-61.0)	81.0 (57.0-93.0)	61.0 (48.0-83.0)	44.0 (43.0-64.0) [1 (7%)]	62.0 (49.0-94.0)	59.5 (43.5-75.5) [1 (3%)]
CMAI total – mean (SD) [missing (% of N)]	71.5 (26.3)	95.5 (29.0)	83.9 (29.8)	58.2 (23.9)	77.0 (24.5)	67.9 (25.6)	55.5 (21.4) [1 (7%)]	70.5 (24.2)	63.6 (23.8) [1 (3%)]
NPI-NH total – mean (SD) [missing (% of N)]	30.2 (20.9)	58.5 (24.3)	44.8 (26.6)	22.5 (16.7)	36.6 (18.2)	29.8 (18.6)	18.7 (15.0) [1 (7%)]	32.6 (20.7)	26.1 (19.3) [1 (3%)]
NPI-NH disruptiveness – mean (SD)	10.2 (8.4)	16.3 (11.4)	13.4 (10.4)	7.3 (5.5)	13.3 (6.2)	10.4 (6.5)	6.8 (4.4) [1 (7%)]	11.5 (7.5)	9.3 (6.6) [1 (3%)]

	BASELINE			WEEK 4 (PRIMARY ENDPOINT)			WEEK 8 (FINAL TIMEPOINT)		
Outcome	Control (N=14)	Sativex (N=15)	Overall (N=29)	Control (N=14)	Sativex (N=15)	Overall (N=29)	Control (N=14)	Sativex (N=15)	Overall (N=29)
<i>[missing (% of N)]</i>									
QoL-AD total – mean (SD)	. (.)	43.0 (.)	43.0 (.)	15.0 (.)	36.0 (1.4)	29.0 (12.2)	23.0 (.)	38.0 (4.2)	33.0 (9.2)
<i>[missing (% of N)]</i>	<i>[14 (100%)]</i>	<i>[14 (93%)]</i>	<i>[28 (97%)]</i>	<i>[13 (93%)]</i>	<i>[13 (87%)]</i>	<i>[26 (90%)]</i>	<i>[13 (93%)]</i>	<i>[13 (87%)]</i>	<i>[26 (90%)]</i>
QUALID total – mean (SD)	29.9 (9.4)	33.3 (8.4)	31.6 (8.9)	27.4 (9.6)	29.8 (8.9)	28.6 (9.2)	28.5 (10.6)	28.4 (7.5)	28.5 (8.9)
<i>[missing (% of N)]</i>							<i>[1 (7%)]</i>		<i>[1 (3%)]</i>
APS category – n (%)									
No pain	12 (86%)	14 (93%)	26 (90%)	14 (100%)	15 (100%)	29 (100%)	12 (86%)	12 (80%)	24 (83%)
Mild pain	2 (14%)	1 (7%)	3 (10%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	3 (20%)	4 (14%)
Moderate pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Severe pain	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
<i>[missing (% of N)]</i>							<i>[1 (7%)]</i>		<i>[1 (3%)]</i>

	BASELINE			WEEK 4 (PRIMARY ENDPOINT)			WEEK 8 (FINAL TIMEPOINT)		
Outcome	Control (N=14)	Sativex (N=15)	Overall (N=29)	Control (N=14)	Sativex (N=15)	Overall (N=29)	Control (N=14)	Sativex (N=15)	Overall (N=29)
sMMSE total – mean (SD) <i>[missing (% of N)]</i>	. (.) <i>[14 (100%)]</i>	17.0 (.) <i>[14 (93%)]</i>	17.0 (.) <i>[28 (97%)]</i>	. (.) <i>[14 (100%)]</i>	18.0 (.) <i>[14 (93%)]</i>	18.0 (.) <i>[28 (97%)]</i>	. (.) <i>[14 (100%)]</i>	16.0 (.) <i>[14 (93%)]</i>	16.0 (.) <i>[28 (97%)]</i>
FAST (stratifier categories) - n (%)									
Low	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)			
Moderate	4 (29%)	5 (33%)	9 (31%)	4 (29%)	7 (47%)	11 (38%)			
Severe	10 (71%)	10 (67%)	20 (69%)	10 (71%)	8 (53%)	18 (62%)			
CFS summary category – n (%)									
Living with very mild frailty	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (7%)	1 (3%)			
Mild frailty	0 (0%)	4 (27%)	4 (14%)	1 (7%)	0 (0%)	1 (3%)			

	BASELINE			WEEK 4 (PRIMARY ENDPOINT)			WEEK 8 (FINAL TIMEPOINT)		
Outcome	Control (N=14)	Sativex (N=15)	Overall (N=29)	Control (N=14)	Sativex (N=15)	Overall (N=29)	Control (N=14)	Sativex (N=15)	Overall (N=29)
Moderate/severe frailty	14 (100%)	11 (73%)	25 (86%)	13 (93%)	14 (93%)	27 (93%)			

The CMAI, NPI-NH, FAST, CFS, APS, and QUALID measures were completed at all timepoints, except where one participant in the control arm did not have available responses for any measures collected at Week 8.

Almost no responses were collected for the QOL-AD or sMMSE at any timepoint due to multiple refusals from care home residents to conduct the assessments. At baseline, only 1 participant provided responses to the QOL-AD and sMMSE. At Weeks 4 and 8, only 3 participants had scored responses for the QOL-AD. At Weeks 4 and 8, there was only 1 participant that had scored responses for the sMMSE. If a future trial is planned in the same population, it may be inadvisable to include the QOL-AD and sMMSE as study measures.

There may be some baseline imbalance between arms for the total CMAI and NPI-NH scores. No significance testing was carried out to formally assess baseline imbalance, only visual inspection of boxplots.

All participants reported APS scores falling in the 'No pain' or 'Mild pain' categories at each timepoint.

There were 4 participants in Sativex that reported worsened CFS scores at Week 4, all 4 of these participants had high enough scores to be categorised in a higher frailty category (from 'Mild frailty' at baseline to 'Moderate/severe frailty' at Week 4). One participant in the Sativex arm reported improved frailty, moving from the 'Moderate/severe frailty' category at baseline to the 'Living with very mild frailty' category at Week 4. One participant in the control arm reported improved frailty, moving from the 'Moderate/severe frailty' category at baseline to the 'Mild frailty' category at Week 4.

Results from adjusted analyses are presented in the following table.

Table: Results of adjusted analyses for secondary neuropsychiatric outcomes

Outcome	N in analysis model	Mean difference (95% CI)	Cohen <i>d</i> (95% CI)
CMAI	29		
4 weeks		6.77 (-6.71 , 20.25)	0.23 (-0.23 , 0.68)
8 weeks		2.43 (-11.23 , 16.10)	0.08 (-0.38 , 0.54)
NPI-NH	29		
4 weeks		3.15 (-9.46 , 15.76)	0.12 (-0.36 , 0.59)
8 weeks		2.53 (-10.2 , 15.26)	0.10 (-0.38 , 0.57)
QOL-AD	0		
4 weeks		N/A	N/A
8 weeks		N/A	N/A
QUALID	29		
4 weeks		-0.25 (-4.21 , 3.7)	-0.03 (-0.47 , 0.42)
8 weeks		-2.61 (-6.63 , 1.41)	-0.29 (-0.75 , 0.16)
APS*	29		
4 weeks		1.08 (0 , .)**	N/A
8 weeks		3.82 (0.28 , 52.09)**	N/A
sMMSE			

4 weeks		N/A	N/A
8 weeks		N/A	N/A
FAST at 4 weeks	29	-1.22 (-2.23 , -0.21)	-0.71 (-1.30 , -0.12)
CFS at 4 weeks*	19	1.13 (0.06 , 21.09)***	N/A

*Odds ratios (ORs) reported instead of mean differences for APS and CFS measures.

**All participants had reported APS scores in the 'No pain' category at Week 4, there were no values in the 'Mild pain' cells. There were only 4 participants reporting APS scores in the 'Mild pain' category at Week 8.

***Only 2 participants reported CFS scores in either the 'Living with very mild frailty' or 'Mild frailty' categories at Week 4 and some observations were omitted because they perfectly predicted being in the combined lower categories.

The effect estimates for each measure are imprecise with very wide 95% CIs. APS and CFS ratings in this sample were similar across arms and timepoints. The results of the adjusted QUALID analyses suggest that there may be no clear treatment effect. For the continuous FAST outcome, the adjusted analyses suggest that participants randomised to Sativex may have a lower staging level (indicating less severe impairment) at Week 4 compared to participants randomised to placebo control. However, only 2 participants in the Sativex arm actually improved enough at Week 4 to move from the 'severe' disease category to the 'moderate' disease category.

There was no association between treatment and total CMAI at Week 4 with an adjusted mean difference (aMD) of 6.77 (95% CI -6.71 to 20.25; Cohen's $d=0.23$). It should be noted that for this future primary outcome, an aMD of 6.77 indicates higher agitation in the Sativex arm at the end of the 4-week treatment period. The intraclass correlation (ICC) from the adjusted CMAI model was 0.36 (95% CI 0.19 to 0.57). After adjusting for covariates, about a third of the total variance in CMAI scores was due to clustering at the participant level.

The adjusted analyses for NPI-NH total score found no association between treatment allocation and severity of neuropsychiatric symptoms at Week 4 (aMD=3.15, 95% CI -9.46 to 15.76; Cohen's $d=0.12$) or at Week 8 (aMD=2.53, 95% CI -10.2 to 15.26; Cohen's $d=0.10$).

13.5 Conclusion

The study was not able to randomise the target 60 participants, but this should be considered in the context of a pandemic and a shortened recruitment period. Despite the challenges of conducting a trial in nursing homes during COVID, retention was 100% and data completion for key neuropsychiatric outcomes was excellent. There were very few safety reports reported. Overall adherence to the titration schedule was decent, although the definition of adherence should be revisited in a future trial. Adjusted analyses indicated no clear association between Sativex and key secondary neuropsychiatric outcomes. However, the small sample size and lack of precision should be considered.

14 Date of Report

This is version 1.0 of the Clinical Study Report, dated 3rd July 2024.

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