STUDY PROTOCOL

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: 1 approved with reservations]

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Abstract

Background: People living with dementia often experience a myriad of behavioural and psychological symptoms of dementia (BPSD). Agitation is highly common within BPSD, negatively impacting their health, accelerating dementia progression, and is distressing both to patients and those caring for them. It also costs society a great deal, with increased hospitalisations, cost of care and earlier institutionalisation. Unfortunately, current treatments for these symptoms do not work very well and have a lot of unwanted side-effects. Recently, cannabinoid-based medicines have emerged as potentially safer alternative candidates for agitation in dementia. However, there is little systematic and robust evidence to support these encouraging early reports. Therefore, we specifically hope to investigate Sativex®, administered as an oral-spray, containing 50% delta-9-tetrahydrocannabinol (THC) and 50% cannabidiol (CBD) for agitation in dementia.

Methods: STAND is a mixed-methods, randomised, double-blind, parallel group, placebo-controlled feasibility clinical trial, recruiting 60 people living with Alzheimer’s disease displaying behavioural symptoms from UK nursing homes.

Conclusions: We aim to assess the safety, feasibility and acceptability
This article is included in the Alzheimer's Research UK gateway.

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Introduction

Background and rationale

Dementia is a growing concern for the international healthcare community, with increasing worldwide prevalence and greater associated costs\(^1\). 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\(^1\). 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”\(^2\). 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\(^3\), 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”\(^4\), affects approximately 50% of all PlwD and is persistent\(^4\). 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\(^5-8\). 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\(^9\). In the US there’s no specific designated pharmacological treatment for this indication\(^1\), whereas in the UK only risperidone is indicated for the short-term management of severe aggression in dementia\(^10\). Other than this, clinicians customarily prescribe off-label antipsychotics, antidepressants, cholinesterase inhibitors, memantine and/or analgesics\(^1\). 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\(^10-12\). 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\(^13\). 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\(^13\). 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\(^14\). 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\(^15\). 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\(^16\). 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. \(^25\)).

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\(^26-28\). For example, CBD has been found to increase the antinociceptive potency of THC\(^29\), 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\(^30-32\) and acute memory impairment\(^33-35\).

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\(^36\). 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)\(^37\) and the ‘Psychiatry Consortium’ (PC) in the Medicines Discovery Catapult\(^38\), 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\(^39\). 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 BPDS 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.

Research objectives

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.

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.

Methods

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.

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%.

Recruitment strategy

The target sample was primarily recruited through the NIHR Maudsley Biomedical Research Centre Care Home Research Network (CHRNR). 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 reintimated 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.
Figure 1. STAND Trial CONSORT diagram.
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.

Participants
Participants were recruited and screened according to the following criteria:

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 and/or NPI-NH Agitation total score >/= 4
- 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.

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.

Intervention and comparator
Investigational medicinal product (IMP) and placebo comparator
The investigational medicinal product (IMP) was Sativex® (GW 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.

Dosing regimen
Dosing was determined by number of sprays per day (Table 1). 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.

‘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.

Outcomes
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.

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)

Future efficacy outcomes
- Cohen-Mansfield Agitation Inventory (CMAI)
- Standardised Mini Mental State Examination (sMMSE)
- Quality of Life in Late Stage Dementia (QUALID)
- Quality of Life – Alzheimer’s Disease - Care Home (QOL-AD)
- Abbey Pain Scale (APS)
- Functional Assessment Staging (FAST)
- Clinical Frailty Scale (CFS)

Environment outcomes
- Care Home Level measures
- Environmental Audit Tool (EAT)

Overview of outcome measures and time points (Table 2)

Qualitative evaluation
This trial includes an embedded qualitative evaluation (QE) to evaluate contextual factors that may impact a future phase III trial, implementation in real-world practice. This is facilitated via recorded semi-structured interviews with nursing home staff, relatives of the participants, and the participant themselves (when possible). Staff interviews are conducted 1-to-1 with the researcher, whereas interviews with the residents can include a staff member and/or a relative present for support. The interviews can be conducted virtually or in-person at a

Table 1. STAND titration schedule.

<table>
<thead>
<tr>
<th>Week</th>
<th>No. of Sprays (morning)</th>
<th>No. of sprays (afternoon)</th>
<th>No. of sprays (Evening)</th>
<th>Total no. of sprays per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (Days 1 &amp; 2)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>1 (Days 3 – 7)</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
</tr>
</tbody>
</table>
Table 2. The variable list, with the primary function of the variable and collection points.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Primary function</th>
<th>Time Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Screen</td>
</tr>
<tr>
<td>CMAI</td>
<td>Primary outcome</td>
<td>×</td>
</tr>
<tr>
<td>NPI-NH</td>
<td>Secondary outcome</td>
<td>×</td>
</tr>
<tr>
<td>sMMSE</td>
<td>Secondary outcome</td>
<td>×</td>
</tr>
<tr>
<td>QUALID</td>
<td>Secondary outcome</td>
<td>×</td>
</tr>
<tr>
<td>QOL-AD</td>
<td>Secondary outcome</td>
<td>×</td>
</tr>
<tr>
<td>APS</td>
<td>Secondary outcome</td>
<td>×</td>
</tr>
<tr>
<td>FAST</td>
<td>Secondary outcome</td>
<td>×</td>
</tr>
<tr>
<td>CFS</td>
<td>Secondary outcome</td>
<td>×</td>
</tr>
<tr>
<td>EAT &amp; CH measures</td>
<td>Environment outcome</td>
<td>×</td>
</tr>
<tr>
<td>C-SSRS</td>
<td>Safety</td>
<td>×</td>
</tr>
<tr>
<td>AEs</td>
<td>Safety</td>
<td>×</td>
</tr>
</tbody>
</table>


Remote continuous measurement of BPSD using wearables

BPSD are notoriously difficult to objectively observe and measure. Previous research has primarily relied on proxy-report and observational metrics to determine presence and severity of BPSD. However, these methods are relatively flawed due to their reliance on subjective report – often leading to spurious and irreproducible results making it difficult to generalise treatments and therapies to a wider patient population.

There are currently no validated objective measures of BPSD that can provide 24hr feedback in every situation in nursing homes (even during night-time and personal care); further, wearables present a succinct opportunity to measure stress-related biomedical variables, such as: (aberrant) physical activity, skin temperature, heart rate variability, blood volume pulse and skin conductance; in addition to environmental conditions such as exposure to light and temperature. These variables could be mapped on to a BPSD matrix; and interpreting the data. A succinct description of FA is described by Gale & Colleagues (2013)\(^5\).

Summary qualitative results will be included within the main study report, and an in-depth qualitative report including the COREQ 32-item checklist and reflexivity sub-section\(^6\) will be produced separately.

In particular, the QE intends to explore the following topics:

- attitudes towards cannabis-based medicines
- issues/benefits of administering via an oromucosal method
- feasibility and acceptability of wrist-worn actigraphy devices
- factors that facilitate or inhibit engagement with research in care homes.

The initial topic guide, including example questions and prompts, was developed with advice from the King’s College London Department of Old Age Psychiatry PPI group\(^7\). Additional questions that arise in interviews will be considered and added on a case-by-case basis with consultation within the trial team and the PPI advisory group. Interviews are being audio-recorded and transcribed for analysis. Transcripts will be analysed using the thematic ‘codebook’ analysis method\(^8\), specifically ‘framework analysis’ (FA). FA involves a 7-stage process: transcription; familiarisation with the interview; coding; developing a working analytical framework; applying the analytical framework; charting data into the framework matrix; and interpreting the data. A succinct description of FA is described by Gale & Colleagues (2013)\(^9\).
phenotype, providing an objective digital signature that can be collected passively. Moreover, exploring the feasibility of wearables in this population would engender significant value for money, nursing home care practices, and ultimately overall patient well-being.

We incorporated wearables into the STAND trial; assessing feasibility and acceptability in a nursing home context and evaluating methods to map wearable raw data to BPSD phenotypes. Participants were required to wear the device for the whole 4 week intervention period. Summary acceptability and feasibility results will be included within the main study report, and an in-depth actigraphy methods and analysis report will be produced separately.

**Activinsights GeneActiv Original watch**
The device that was used is the ‘GeneActiv Original’ watch. The GeneActiv (CE marked) is designed for 24 hour wear, has been described in detail previously, is one of the most widely used accelerometers for the assessment of physical activity and sedentary behaviour (see 60), and has been tested in an older adult population. Raw data output can be directly extracted from the device and is provided in open source format and transformed into acceleration in 3 axes, ambient light/temperature, physical activity intensity and sleep/wake measurements, which can be analysed with software developed by Activinsight (https://activinsights.com/support/geneactiv-support/) that is open to the public.

**Data collection and management**
The Principal Investigator acted as custodian for the trial data. Patient data was collected directly from care home participants, staff and records and pseudonymised on bespoke STAND data worksheets. These paper worksheets were stored securely on King’s College London premises in a locked cabinet. The data was entered into a digital database, ‘InferMed MACRO’, managed by King’s Clinical Trials Unit. The system is compliant with FDA 21 CFR part 11 and Good Clinical Practice (GCP). It is an appropriate system to use for medicinal trials falling under the Medicines for Human Use (Clinical Trials) Regulations 2004 and its subsequent amendments and has also been used for other complex intervention trials. The web-based system can be accessed 24 hours a day. All trial data is stored in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 and the Data Protection Act and archived in line with the Medicines for Human Use (Clinical Trials) Amended Regulations 2006 as defined in the Kings Health Partners Clinical Trials Office Archiving SOP.

**Data analysis**
Statistical analyses will be performed in STATA 17. This feasibility trial will estimate parameters needed for planning an efficacy trial in future including estimating various rates (e.g., recruitment, randomisation capability, sample characterisation, acceptability of intervention, follow-up rates, and description of the primary and secondary of the outcome measures) and estimating the within-trial arm means, standard deviations, confidence intervals, the pre-post correlation and for possible outcome measures to inform the sample size calculation of a future randomised control trial. Outcome measures will be assessed for their understanding and acceptability and the mean scores summarised for each outcome by trial arms. Intervention effect sizes (e.g., incidence rate ratios for the count outcome and mean differences for continuous outcome measures) will be estimated for various outcome measures, but no formal hypotheses testing will be carried out. Descriptive statistics for patient symptom scores and clinician grades included means (SDs) and frequencies of each response category will be presented by arm and follow-up visits. Prior to any data analysis and reporting, data will be checked for quality.

A full statistical analysis plan (SAP) is available as extended data.

**Missing data**

**Missing baseline data**
All efforts will be made to avoid missing baseline data (i.e., requiring completion of baseline data before randomisation), but if this occurs, missing values will be imputed using mean imputation as per the recommendations of White and Thompson [White, 2005].

**Missing items in scales and subscales**
Where available we will use missing value guidance provided for scales. Where this is not available, we will prorate missing items only when there are no more than 20% missing items (i.e., for a ten-item questionnaire, prorate only where one or two items are missing) by replacing the missing item values with the mean value of the complete items for each individual. See 55 for further details. If after prorating there are still missing total questionnaire scores at baseline, these will be imputed as described in the paragraph just above. Details of how to deal with missing items for each measurement are presented in 55.

**Missing outcome data**
To check for the introduction of bias because of any withdrawals or missed to follow-up, the following evaluations will be performed: 1) Comparing the percentage of participants between two arms who withdraw from the treatment prematurely, 2) Comparing the percentage of participants between two arms who missed to follow-up for any reason.

In the case of missingness at 4 weeks, the data from 8 weeks follow-up will be used in a mixed model using maximum likelihood methods (by including the random effect of participants and fixed effect of time) to have a better estimate at 4 weeks despite missingness. Such an approach provides valid inferences under the assumption that the missing data mechanism is ignorable (or Missing At Random).

**Trial governance and 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.

Patient & public involvement & engagement (PPI)

The NIHR Maudsley Biomedical Research Centre Dementia theme PPI group (MALADY) and SLaM Mental Health of Older Adults Service User and Carer Group (SUCAG) were consulted during the development of this proposal on design, feasibility, and social acceptability. The project was also presented to our annual Care Home Research Network (CHRNR) May 2019 conference for informal feedback. The trial received positive and supportive feedback from these PPI channels.

Throughout the trial we consulted members of the CHRNR via our departmental monthly CHRNR webinars and workshops, and MALADY group members when needed for operational and ad-hoc advice. We also sought the involvement of MALADY and CHRNR members to assist in identifying, approaching and developing the optimal public dissemination channels, mediums and materials.

Ethics and dissemination

This trial has been approved by the West Midlands – Coventry & Warwickshire Research Ethics Committee on the 14th August 2020 (REC reference: 20/WM/0210), authorised by the Medicines and Healthcare products Regulatory Agency (MHRA) on 12th August 2020, and given final approval by the Health Research Authority (HRA) on the 4th September 2020.

For every trial participant, written informed consent was sought and capacity to consent assessed, and in those not having capacity a personal or professional legal representative were sought. Full duty of care remained the participants’ primary physician for the duration of the trial, except for instances that were a direct result of trial activity. Full duty of care returned to the participants’ primary physician upon their completion of the trial.

The results of the trial will be disseminated in peer-reviewed academic journals and presented at conferences (local, national and international), regardless of the direction of effect. Ownership of the data arising from the study resides with the trial team. The publication policy will be in line with rules of the International Committee of Medical Journal Editors. The STAND TMG will prepare a structured publication policy.

Study status

Primary recruitment and data collection opened September 2021, and finished June 2022, with the final participant finishing their final follow-up on 29th August 2022. At the time of this report, we are currently conducting the qualitative evaluation, and estimate to complete this phase by June 2023. All members of the study team, including the statistical team members, remain blinded to treatment allocation. The database is due to be locked and analysis expected to start in summer 2023.

Trial identifiers

EudraCT Number: 2020-001056-17
IRAS Project ID: 272703
ISRCTN registry: 97163562
Protocol Version number and date: V5 07.02.22

Trial Co-sponsors: King’s College London & South London & Maudsley NHS trust (contact via corresponding author).

Data availability

Underlying data

No underlying data are associated with this protocol.

The Principal Investigator (PI) will determine if and when to make the data accessible to new users or specifically to an organisation or institution. Investigators who wish to access the data once the study is finished/published would have to contact STAND PI and request permission. A formal application will be required indicating the question to be addressed and methods to be applied. No hypothesis testing regarding the main aims of the study will be allowed to the new users of the data as part of the data sharing agreement.
Extended data

This project contains the following extended data:

- STAND form_QE Topic Guide.pdf (interview topic guide)
- STAND PIS (Short) V2 07.04.21.pdf (participant information sheet)
- STAND PIS_V4.0 07.02.22.pdf (participant information sheet)
- STAND trial Participant ICF V4.0 07.02.22.pdf (participants consent form)
- STAND trial PerLR ICF V4.0 07.02.22.pdf (persona legal representative consent form)
- STAND trial ProLR ICF V4.0 07.02.22.pdf (professional legal representative consent form)
- STAND-SAP v1.0_clean_sign.pdf (statistical analysis plan)

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

Reporting guidelines

References


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Publisher Full Text


Open Peer Review

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This study describes the protocol for an RCT that will consider the treatment of cannabinoid based medication (CBM) on agitation and aggression on individuals living with Alzheimer’s Dementia in UK nursing homes. Overall, I would like to commemorate the authors for designing and undertaking this type of trial and really support this work to be considered for passing peer review. I think the study has been well written and clearly described. I have included a couple of suggestions for the authors to consider. Overall, the language used throughout the manuscript changes ‘as though the study has been conducted’ to ‘as though it will be done’. I would suggest the authors chose one methods of writing style and adjust this throughout. Currently it makes it difficult to understand what has been done and what is still to come.

Some specific comments include;

Introduction
  ○ Cite US in full
  ○ The authors discuss that the medication will be administered using an oromucosal spray. This method has been tested and is effective, however does come with its limitations if the participant is not compliant to taking additional medication or opening their mouth. Have the authors considered some alternatives in how they could administer this medication in these instances?
  ○ Is the Neuropsychiatric inventory that has been selected, the nursing home version? This seems to have been described in the methods. Could this be clarified in the introduction?

Methods
  ○ The authors have described that AEs will be reported, but they have not outlined what specifically or how this will inform the titration of the medication. Could further information be included here? I would also suggest to the authors that they collect AEs at baseline to see if there are any AEs already been experienced by the participants which could be taken into
consideration when they are monitoring the titration phase (Table 2).

○ Could the authors expand and include some justification on how they have come to a double-blind, parallel group RCT, instead of another RCT method? Eg, cross-over RCT design?

○ TAU – I understand why the authors have selected TAU for the medication participants may already be taking. However what steps will be taken to ensure that this does not influence the effects of Sativex? I can see they are excluding participants taking CYP3A4 inhibitors (great start!) however the number of medications that these participants may already be taken could potentially influence the effect of CBM.

○ Also could the authors describe who will be completing the surveys and who will be administering the medication and completing the AEs? Currently they have only mentioned self and carer-report. Eg. Does the carer mean a staff member in the aged care facility or a family member or both?

Participants
○ Could the authors clarify if they are including those in the study at different stages of dementia (mild to severe)? I am assuming so if they are including those who can consent and next of kin consent. Following on from this comment, will the stage of dementia be compared during the analysis? The difficulty with this is that as the dementia severity increases, the ability to observed changes due to CBM become more complex. Will the CMAI and NPI-NH be sensitive enough to detect a change?

Intervention and comparator
○ Could the authors explain why they have included peppermint oil in the formulation? From my understanding, sweet/sugar is the taste bud that lasts the longest as a patient ages. Why did the authors not select a sweet taste to add? What if the participant does not like the taste of peppermint oil?

○ Also will the spray be administered with something to eat and who will administer this?

Future efficacy outcomes
○ Why is the NPI-NH – not mentioned in this section?

Qualitative evaluation
○ This is an important phase to include, however will this be completed while the researcher and participants are still blinded? This will make it difficult to tease out if any observed changes are due to the effects of the medication. Could further information be included as to when this component of the study will be completed.

○ In this section this is the first-time the authors mention of Actigraphy devices (larger study)? Could the qualitative evaluation section be placed after the Remote continuous measurement of BPSD using wearables? As I am assuming this will theoretically happen before the qualitative evaluation?

○ If the authors agree with this, then could the time period of the Actigraphy measures not be included in Table 2?

Is the rationale for, and objectives of, the study clearly described?
Yes

**Is the study design appropriate for the research question?**
Yes

**Are sufficient details of the methods provided to allow replication by others?**
Partly

**Are the datasets clearly presented in a usable and accessible format?**
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Cannabinoid based medication, active aging

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.