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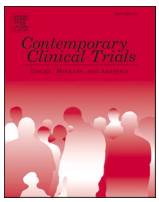

Evaluating the effect of cannabidiol on sleep quality in patients with multiple sclerosis using 15 aggregated N-of-1 trials: A study protocol

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ABSTRACT

Background: Sleep disorders, including insomnia, are highly prevalent in individuals with multiple sclerosis (MS), significantly impacting quality of life. Patients frequently use cannabidiol (CBD) as an alternative to standard medical treatments for sleep disorders, yet its efficacy has not been rigorously investigated.
Methods: This study comprises 15 randomized, placebo-controlled N-of-1 trials evaluating the effect of pure CBD oil (10 % g/v) on sleep quality in MS patients. Each N-of-1 study consists of a two-week run-in period, followed by four treatment periods of three weeks, separated by a one-week washout. Participants receive both CBD and placebo twice in a randomized order. Treatment starts at 150 mg daily, increasing to 300 mg from week 2. Study outcomes are assessed during the final two weeks of each block. The primary outcome is sleep quality, measured by the Insomnia Severity Index (ISI). Secondary outcomes include patient-reported outcome measures of sleep recorded in a sleep-wake diary, and scores on the Checklist Individual Strength Fatigue-subscale (CIS-F), the Fatigue Severity Scale (FSS), and the Epworth Sleepiness Scale (ESS). Additionally, as a continuous proxy for fatigue, smartphone keyboard interactions will be collected using the Neurokeys application. Results from the individual N-of-1 trials will be aggregated for group-level analyses.
Discussion: This study aims to provide insight into the effects of a controlled CBD product on sleep quality in MS patients through an N-of-1 trial design. Given the substantial variability in sleep quality and the anticipated interindividual differences in CBD response, an N-of-1 design is considered a suitable methodological approach.

List of abbreviations

AE	Adverse event
CBD	Cannabidiol
CIS-F	Checklist Individual Strength Fatigue-subscale
ESS	Epworth Sleepiness Scale
ECRF	Electronic case report form
FSS	Fatigue Severity Scale
ISI	Insomnia Severity Index
MS	Multiple Sclerosis
OTC	Over-the-counter
PROM	Patient-reported outcome measure
THC	Delta-9 tetrahydrocannabinol

1. Background

Impaired sleep quality is a common problem among individuals with multiple sclerosis (MS) and has a significant impact on disease burden and quality of life. More than 70 % of MS patients experience sleep disturbances, which are often multifactorial in origin (Fig.1) [1]. Insomnia is a prevalent complaint among adults with MS and is characterized by difficulty initiating or maintaining sleep and/or early awakenings [2]. A meta-analysis by Zeng et al. (2023) showed that more than half of adults with MS self-report poor sleep quality, and 22 % meet the diagnostic criteria for insomnia [2]. Furthermore, MS-related symptoms like pain, spasticity, bladder problems, and mood disorders, alongside MS-related drugs, contribute to impaired sleep quality.

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Daytime consequences include especially increased physical fatigue, present in ≥75 % of MS patients (Fig.1) [3,4]. Despite their prevalence and clinical impact, sleep disorders often remain underdiagnosed and undertreated, exacerbating the challenges faced by patients.

The treatment of impaired sleep quality requires a comprehensive approach, ranging from advice on sleep hygiene to cognitive and pharmacological interventions, depending on the type and severity of sleep disturbances and associated comorbidities. Cognitive behavioral therapy for insomnia (CBT—I) is considered the gold standard treatment for insomnia, but is not readily available and labor-intensive [5]. Pharmacotherapy, including the use of benzodiazepines, can be problematic as its long-term efficacy is limited, and its use is associated with tolerance, dependence, and adverse effects, the latter including an increased risk of falls, cognitive decline, and delirium, particularly in older adults. Given these limitations, patients with MS frequently use medicinal cannabis or cannabinoid products, such as cannabidiol (CBD), as an alternative approach to manage impaired sleep quality. CBD belongs to the phytocannabinoids, which comprise a group of specialized ('secondary') metabolites, of which more than 100 compounds have been characterized in the *Cannabis* genus. Depending on the strain, CBD is one of the dominant components, next to delta-9 tetrahydrocannabinol (THC). THC is responsible for its psychotropic effects. Conversely, CBD is non-hallucinogenic, has a better safety profile, and a low abuse potential.

The few studies that examined the effects of CBD on sleep quality mostly used relatively low doses. While 160 mg CBD improved self-reported sleep in insomniacs, lower doses (40–150 mg) showed no effects in placebo-controlled trials [6,7]. Previous studies were further limited by poor methodology, including small sample sizes and the evaluation of sleep as a secondary outcome [8,9]. A recent review confirmed the need for well-designed clinical trials with higher CBD doses to assess the potential clinical benefit of CBD [10]. Given the expected inter- and intra-individual variability in both sleep quality and the CBD treatment effects, an N-of-1 trial design can provide valuable insights into the therapeutic potential of a treatment. The repeated crossover allows each individual to serve as their own control, reducing confounding of between-subject covariates. In addition, it enhances the precision of measurements, minimizes random error in outcomes, and reduces the required sample size to detect an effect.

Despite the limited clinical evidence, there is significant patient-initiated use of cannabis products by MS patients. Surveys indicate a prevalence between 10 and 66 % [11,12]. Next to poor sleep, reasons for use that were reported include pain, spasticity, muscle spasms, anxiety, and bladder dysfunction, which align with indications suggested in clinical research. Most of the respondents consumed freely available, uncontrolled cannabis-based products, often sold as supplements and tolerated as such by authorities in most EU countries [12–14]. The composition, concentration, and quality of these products are not controlled. Most of these over-the-counter (OTC) products contain a small quantity of CBD, less than 100 mg per dose, and in some cases only a fraction of that [15]. Besides OTC products, CBD is also an ingredient in regulatory-approved (Food and Drug Administration and European Medicines Agency) medicinal products, primarily used for neurological indications. The oral CBD product Epidyolex® is used to treat patients from the age of two years with certain forms of refractory epilepsy, Lennox-Gastaut syndrome, and Dravet syndrome [16,17]. Recommended doses range from 2.5 mg/kg twice daily as a starting dose to a maximum of 10 mg/kg twice daily during maintenance therapy. The oromucosal spray Sativex®, containing both THC and CBD, has been approved as an adjuvant therapy to alleviate symptoms in adult patients with moderate to severe spasticity resulting from MS [18]. There is a significant need for controlled studies on the effects of CBD on sleep in MS patients. These studies should adopt a controlled and individualized approach, utilizing pharmaceutical-grade CBD products at doses currently considered pharmacologically active, generally starting at 300 mg.

2. Methods

2.1. Study design

The CanISleepinMS study comprises 15 double-blinded, randomized, placebo-controlled N-of-1 trials. Each N-of-1 trial starts with a two-week run-in period, followed by four treatment periods of three weeks, separated by a one-week washout, with a total study duration of 18 weeks. The design of a single N-of-1 trial is depicted in Fig. 2.

2.2. Study population

This study aims to include 15 Dutch-speaking adult MS patients (≥ 18 years) with chronic impairment of sleep quality, as quantified by an ISI score of at least 15 (threshold for clinical insomnia). The sample size of 15 is based on a sample size calculation (see Section 2.9). Eligible participants must have a diagnosis of relapsing-remitting, secondary

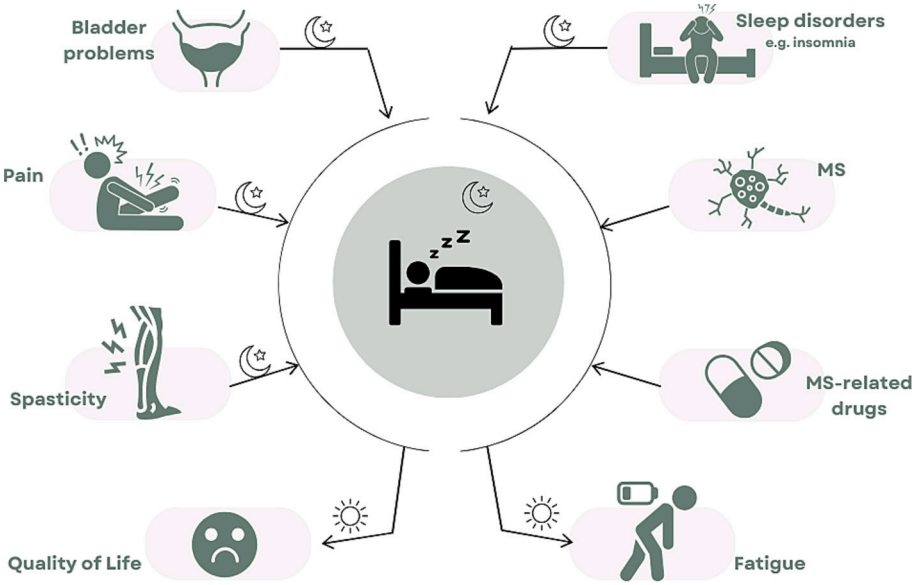

Fig. 1. Factors influencing sleep quality in individuals with MS, impacting quality of life and increasing disease burden.

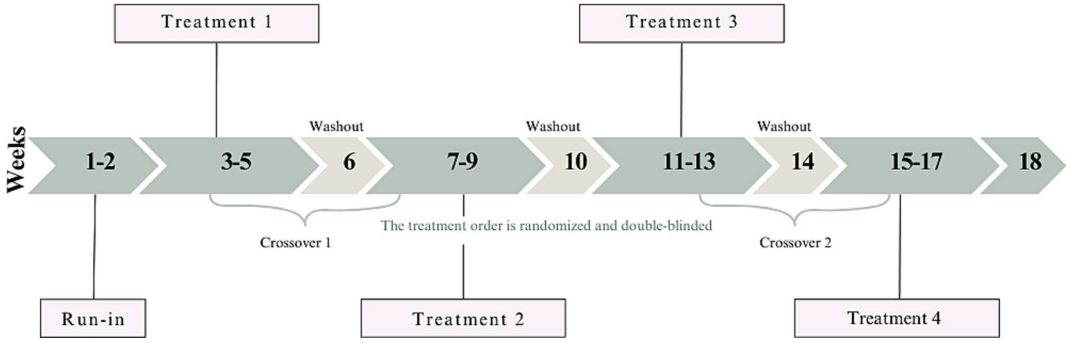

Fig. 2. Design of 1 N-of-1 trial: a two-week run-in period, followed by four treatment periods of three weeks, separated by a one-week washout.

progressive, or primary progressive MS, with an Expanded Disability Status Scale (EDSS) score below 7.5 and a stable medical condition. For a complete list of inclusion and exclusion criteria, see the Supplementary Material (SM1).

2.3. Recruitment and screening

Individuals with MS will be recruited through the Neurology outpatient clinic of Rijnstate Hospital, the sleep medicine outpatient clinic of Kempenhaeghe, and online via the Dutch National MS Foundation, MS patient association, and their social media. Interested MS patients receive detailed written study information (patient information folder (PIF)) and a phone call to acquire more details and to address any questions. Participants have at least seven days to consider participation. If the participant decides to continue, the screening process will be initiated. During screening, potential participants are screened according to the inclusion and exclusion criteria (SM1). The screening process consists of three sequential steps, as illustrated in Fig. 3 below.

2.4. Treatments

The investigational products include an investigational medicinal product (IMP) consisting of purified CBD (10 % g/v) in almond oil, an investigational placebo, and a run-in placebo. The products are administered using a plastic syringe for oromucosal delivery 30 min before bedtime. For detailed instructions concerning the study product and administration, see Supplementary Material (SM2,3) During the first week of each treatment block, trial participants will take an oral dose of 1.5 mL (equivalent to 150 mg CBD) of the investigational product (CBD or placebo). In weeks two and three, the dosage will be increased to 3 mL (equivalent to 300 mg CBD). If signs of intolerance occur, the dosage will be reduced to 1.5 mL and maintained for the remainder of that treatment block. In the subsequent treatment period, the target study dose will again be 3 mL if tolerated.

2.5. Study parameters

2.5.1. Primary outcome measure

The ISI score serves as the primary outcome measure, with a 5-point change in ISI score indicating slight clinical improvement [19]. The ISI is a validated tool sensitive to detect insomnia and treatment responses, including its use in online assessments [19,20]. The ISI evaluates insomnia over the previous 2 weeks. Study participants rate 7 items on a 5-point scale (0 = no, 4 = severe problem). A total ISI score between 0 and 7, 8–14, 15–21, and 22–28 is categorized as no, sub-threshold, moderate, and severe insomnia, respectively.

2.5.2. Secondary outcome measures

2.5.2.1. Sleep-wake diary. Participants will fill in the sleep diary daily throughout the trial. The recorded sleep-related parameters include time of attempting to fall asleep, time needed to fall asleep, number and duration of awakenings during the night, and final wake-up time in the morning. These measurements will be used to calculate the following sleep outcomes: Sleep Onset Latency (SOL), number of awakenings (NA), Wake time After Sleep Onset (WASO), Total Sleep Time (TST), and

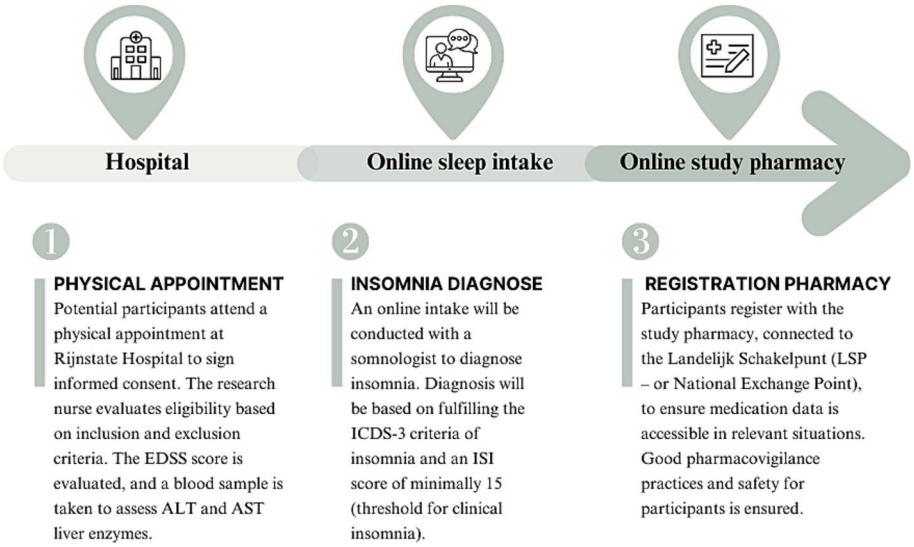

Fig. 3. Overview of the screening process of the CanISleepinMS trial.

Sleep Efficiency (SE). Additionally, adverse events (AEs) will be recorded in the diary as a non-sleep outcome.

2.5.2.2. Questionnaires (CIS, FSS, ESS). The CIS-F is a validated questionnaire that measures fatigue and related behavioral aspects over the past week. It consists of 20 statements, rated on a 7-point Likert scale, and assesses four subcategories of fatigue: subjective fatigue, concentration, motivation, and activity. A total score of $\geq$27 indicates abnormal fatigue, and a total score of >35 indicates severe fatigue [21,22]. The FSS is a validated questionnaire to assess subjective fatigue in patients with multiple sclerosis [23]. The FSS comprises 9 statements, scored on a 7-point Likert scale. The score is reflected by the average of the responses, and a total score $\geq$ 36 suggests suffering from fatigue [24]. The ESS is a frequently used questionnaire to assess excessive daytime sleepiness in patients. It consists of 8 items, each scored on a 0–3 point scale. A total score of 0–10, 11–14, 15–17, and 18–24 indicates no, mild, moderate, and severe daytime sleepiness, respectively [25,26].

2.5.2.3. Smartphone application (Neurokeys). The Neurokeys application will be installed on a participant's smartphone to collect continuous data during daily smartphone use in a real-world setting. This keyboard application has been validated in previous studies with MS patients [27] and enables digital monitoring of various health-related parameters. Typing on a smartphone keyboard requires a combination of coordinated hand movements and higher-order cognitive functions such as focus and information processing. Additionally, smartphones are used in a social context, allowing Neurokeys technology to provide an integrated indication of the physical, mental, and social aspects of patients' health status [27]. Additionally, daily pop-up questions on the Neurokeys keyboard will be used to collect self-reported data on pain, cramps, fatigue, and nocturnal voiding frequency, using a 7-point rating scale. For more details about the collected Neurokeys data, see Supplementary Material (SM4).

2.5.2.4. Other study parameters. The Expanded Disability Status Scale (EDSS) questionnaire is applied to quantify disability by MS. A candidate participant is allowed to have a maximum score < 7.5. Blood is tested for the liver enzymes aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Elevated levels of transaminases (AST, ALT) up to twice the Upper Limit of Normal (2× ULN) are allowed, as elevation of these levels is a common finding in MS patients.

2.6. Trial timeline and measurements

Table 1 provides an overview of study measurements throughout the N-of-1 trial. The trial begins with a two-week run-in period, during which participants self-administer a placebo (1.5 mL during week 1 and 3 mL during week 2) 30 min before bedtime. During the run-in, participants record sleep-related and non-sleep-related outcomes in a diary, and the Neurokeys app continuously collects smartphone data. Week 1 ends with the completion of the CIS-F, FSS, and ESS. In week 2, participants complete these questionnaires in addition to the ISI. Missing one day of treatment and/or a day of diary registration is allowed. Non-compliance will be discussed to decide whether a participant can proceed with the trial. During the 16-week treatment phase, participants continue taking the investigational products as scheduled. The questionnaires CIS-F, FSS, and ESS will be completed in the second and third week of each treatment period, while the ISI questionnaire will be completed solely in the third week. The sleep diary is completed daily, and the Neurokeys app remains active throughout the trial for continuous smartphone data collection. Additionally, blood samples for AST and ALT measurements are collected in weeks 10 and 18. Elevated levels of transaminases (AST, ALT) up to twice the Upper Limit of Normal (2× ULN) are allowed, as elevation of these levels is a common finding in MS patients. Throughout the trial, the research assistant will contact the participant twice weekly to monitor progress, discuss diary data, and ensure protocol compliance.

2.7. Randomization and blinding

Once participants complete the screening (and meet the inclusion criteria), they will be enrolled, and the treatment order will be randomized. Participants receive CBD or a placebo in two crossover cycles. In case of dropouts, a replacing participant will receive the same treatment order as the individual they replace. To ensure blinding, the randomization will be done by an independent researcher, not involved in the study, and trained in blinding and randomization. The respective blinded codes will be shared with the dispensing pharmacy to enable labeling of the treatment products. The decrypted randomization list will be securely digitalized at Wageningen University and sent in a sealed envelope to the participating hospital.

2.8. Safety reporting

All adverse events (AEs) reported spontaneously by the patient or observed by the research assistant or study physicians will be recorded

Table 1
Overview of study timeline and outcome measures in the CanISleepinMS trial.

Timeline	Study phase	Intake study product	Blood	ISI	Diary	CIS-F	FSS	ESS	Neurokeys
			3×	5×	1×/day	1×/wk	1×/wk	1×/wk	24/7
Week 0	Screening		X						
Week 1	Run-in	X			X	X	X	X	X
Week 2	Run-in	X		X	X	X	X	X	X
Week 3	Treatment 1	X			X				X
Week 4	Treatment 1	X			X	X	X	X	X
Week 5	Treatment 1	X		X	X	X	X	X	X
Week 6	Washout 1								X
Week 7	Treatment 2	X			X				X
Week 8	Treatment 2	X			X	X	X	X	X
Week 9	Treatment 2	X		X	X	X	X	X	X
Week 10	Washout 2		X						X
Week 11	Treatment 3	X			X				X
Week 12	Treatment 3	X			X	X	X	X	X
Week 13	Treatment 3	X		X	X	X	X	X	X
Week 14	Washout 3								X
Week 15	Treatment 4	X			X				X
Week 16	Treatment 4	X			X	X	X	X	X
Week 17	Treatment 4	X		X	X	X	X	X	X
Week 18	Last contact		X						

in the electronic case report form (eCRF). Serious adverse events (SAEs) will be reported by the study nurse or research assistant to the sponsor without undue delay. The sponsor will report SAEs through the web portal ToetsingOnline (research portal) of the accredited METC within 7 days of first knowledge of SAEs that result in death or are life-threatening, followed by a maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within 15 days after the sponsor becomes aware of the event. As of January 31, 2025, individual case safety reports (ICSRs) will be submitted via the EVWEB application.

2.9. Sample size

The sample size calculation is based on the primary endpoint, the ISI score. Previous studies in other populations estimated the standard deviation (SD) for the ISI difference between two time periods of a cross-over trial between 5.3 and 5.7 points [28,29]. Given that each participant undergoes two crossover cycles, the SD can be expected to be smaller. A change in ISI score of 5 points is considered a slight clinical improvement. Assuming a conservatively chosen SD of 5.0, an alpha of 0.05 (two-sided testing), and a power of 80 % to detect a minimum difference in ISI score of 5 points, at least 10 patients are required to complete the study. Allowing a dropout rate during the trial of 33 % means that 15 patients need to be initially included.

2.10. Statistical analyses

ISI scores as primary outcome measurements will be analyzed using mixed models and paired *t*-tests. The mixed models allow us to account for the repeated measures within individuals and to estimate both average (group-level) effects and individual treatment responses. In mixed models, we will adjust for period and, if necessary, carryover effects. Age and sex will be included as fixed effects when they improve the fit of the model, as determined by the likelihood ratio test. To assess potential carry-over effects, we will include two dummy variables in the model: one for the current treatment and one for the treatment received in the previous period, using placebo as the reference category. If the carry-over variable (previous treatment) is neither statistically significant nor clinically meaningful, it will be excluded from the final model. The treatment variable will be included both as fixed and random effects. This enables estimation of the group-level treatment effect while accounting for variation in treatment response: random intercepts and random slopes are included to account for individual baseline differences and individual treatment effects, respectively. Best Linear Unbiased Predictions (BLUP) for individual patients will be derived from the final model to estimate individual treatment effects. These will be used to assess the proportion of participants with a clinically relevant reduction of $\geq$5 points in ISI score (on which the sample size calculation was based). In addition, we will estimate the probability that an individual participant experiences such a reduction in ISI score. In sensitivity analyses, we will conduct the same analyses for the clinically meaningful reduction of $\geq$5 points in the ISI score.

The same statistical approach will be followed for the secondary outcome parameters: the scores of the CIS-F, FSS, and ESS questionnaires, diary-recorded sleep-related outcomes SOL, NA, WASO, TST, SE, and the scores for pain, cramp, fatigue, and nocturnal voiding. Smartphone metrics will be statistically analyzed by Neurokeys.

2.11. Ethics

The study will be conducted following the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013, https://www.wma.net/policies-post/wmadeclaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) and with the Dutch Medical Research Involving Human Subjects Act (WMO).

The study protocol (NL83212.091.22) was approved by an accredited Medical Research Ethics Committee (METC Oost-Nederland) on November 20, 2023, and by the National Competent Authority of the Netherlands (Central Committee on Research Involving Human Subjects), January 2, 2024. The study is registered as a Phase II trial in the Clinical Trials Information System (CTIS) (2024-518280-35-00).

3. Discussion

To the best of our knowledge, this will be the first CBD intervention study focusing on sleep quality as a primary outcome measure in MS patients. N-of-1 trials are gaining interest in the investigation of personalized treatments, particularly for neurological disorders. These trials are especially relevant for chronic conditions characterized by substantial intrapersonal variability and that remain (relatively) stable over time [30]. Given the nature of the included MS types (relapsing-remitting, primary progressive, or secondary progressive MS) and the substantial intra- and inter-individual variability in both sleep quality and the expected response to CBD, such a design offers several important advantages. Therefore, the present study can provide novel insights into the short-term effects of a standardized pharmaceutical-grade CBD oil on sleep quality in MS patients at an individual level and may potentially improve quality of life. The study is designed as a first step to investigate the safety and efficacy of 300 mg CBD within a controlled n-of-1 design. Results from this study may contribute to more informed decision-making by both patients and health professionals regarding the use of CBD.

Repeating the crossover within one participant reduces the random error in outcomes, makes the measurements more precise, and reduces the number of participants needed to detect an effect. Another strength of this study is the combination of an accurate, validated assessment of subjective sleep quality (ISI) with an innovative approach measuring clinical outcomes based on the dynamics of smartphone interaction through the Neurokeys Application. This technology has been validated in MS patients and has demonstrated good responsiveness to variations in disease activity and fatigue [27]. Starting the trial with a two-week run-in period enables participants to establish consistent routines—such as using the diary, completing the questionnaires, and taking the study product daily. Lastly, calling participants twice weekly allows us to guide them through the study, ensure close monitoring, and support adherence to the protocol. This facilitates the accurate registration of AEs and increases compliance.

A potential limitation of this trial is the highly variable bioavailability of orally administered CBD, in which an extensive first-pass metabolism plays a role. In addition, as CBD is a highly lipophilic compound, its absorption can be significantly increased when taken with a high-fat meal [31–33]. Although this would argue in favor of combining CBD with the consumption of a (standardized) high-fat meal to improve bioavailability, our methodological choices focus on minimizing patient burden, preventing the introduction of new factors into patients' lives, and maintaining day-to-day routines. Daily consumption of a high-fat meal at a fixed time before going to bed is not a sustainable long-term habit that reflects actual use in practice. Including pharmacokinetic measurements to provide insight into individual variability in CBD metabolism would be helpful; however, considering the patient's perspective, these methodological choices aimed to minimize patient burden and time investment for participants. Although polysomnography is considered the gold standard to assess sleep, previous research indicated that PROMs of sleep are more predictive of insomnia burden and patients' quality of life than polysomnographic measures of sleep, which do not correlate well with subjective sleep quality [34]. The inclusion of actigraphy as a more objective measurement of sleep quality may provide additional insights in future studies, as technological advances will increase the performance of these devices. However, in the context of insomnia and MS, currently available wearables present important limitations (e.g., underestimating quiet wakefulness) [35,36]

and were therefore not included in the present study.

Despite the current lack of clinical evidence supporting the use of CBD, there is significant patient-initiated use of these products among MS patients. This study aims to support more rational decision-making by patients and healthcare professionals regarding the use of CBD, also taking dosage, quality, and potential efficacy into account. If the results of the present study are positive, this would warrant more extensive and longer-term studies to provide more insight into the long-term clinical impact of CBD on insomnia management.

CRediT authorship contribution statement

Bo A.D.F. Saals: Writing – original draft, Visualization, Project administration, Methodology, Investigation. **Renger F. Witkamp:** Writing – original draft, Supervision, Methodology, Conceptualization. **Anne Claire B. van Orten-Luiten:** Writing – review & editing, Methodology, Conceptualization. **Heleen A. Kuijper-Tissot van Patot:** Writing – review & editing, Investigation. **Lonneke M. van der Meijden-Erkelens:** Writing – review & editing. **Angelique Pijpers:** Writing – review & editing, Methodology. **Sebastiaan Overeem:** Writing – review & editing, Methodology. **Jop P. Mostert:** Writing – review & editing, Investigation.

Trial status

The study started and is currently recruiting participants.

Funding

The Dutch National MS Foundation funded the study.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

The Dutch National MS Foundation is the funder of this study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2025.108071.

Data availability

No data was used for the research described in the article.

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