Cannabidiol impact on challenging behaviour in adults with intellectual disability with Lennox-Gastaut syndrome, Dravet syndrome and tuberous sclerosis complex (CANABID-LD): a prospective observational cohort study

CANABID-LD

PROTOCOL

Version 1.2 22.10.2025

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This protocol has regard for the HRA guidance and order of content.

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and in accordance with the UK Policy Framework for Health and Social Care Research, the Data Protection Act 2018), the principles of Good Clinical Practice (GCP) and the Sponsor's (and any other relevant) standard operating procedures (SOPs).

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

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Position: Head of Research Strategy and Governance	

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Trial Statistician:

Signature: 	Date (dd/mm/yyyy): 10/9/2025
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PROTOCOL AMENDMENT HISTORY

Amendment No.	Protocol version no.	Date issued	Author(s) of changes	Details of changes made
AM01-NSA01	1.2	23.10.2025	Abbey Tufft	Removal of Trial Statistician. Updated PenCTU address. Updated follow-up timepoint wording throughout protocol from 3-months/6-months to 90 days/180 days. Primary outcome measure clarified in Section ii, 4 and 13.3.2 as changes to the ABC-2 Irritability subscale between baseline and 180 days. Updated Study Timescale (Section iii). Section 9.2.1 heading updated to 'Assessing capacity to consent'. Section 9.3 baseline data updated: remove year of birth, chronic medication and OTC CBD use. Collection of CBD estimated start date. Seizure type examples provided and seizure diary provision clarified. Section 9.4 updated: seizure type examples provided, clarification that caregiver will report seizures experienced over the last 90 days, addition of 'Clinician reported outcome measures' section, including CGI and side effects. Section 9.4.1 updated that participant will receive £10 voucher. Section 13.1 removal of recruitment rate information. Section 13.2 recruitment rate information updated that it is difficult to predict rate due to sporadic prescribing, estimate updated to 2-6 per site, recruitment period updated to approximately 7-months, clarification that recruitment will be monitored and additional sites/extension would be considered, if required.

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ii. LIST OF ABBREVIATIONS

ABC-2	Aberrant Behaviour Checklist-Second Edition
ADHD	Attention deficit hyperactivity disorder
ADL	Activities of Daily Living
ALCOA+	Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, Available
CB1R	Cannabinoid Type 1
CBD	Cannabidiol
CGI	Clinical Global Impression
CI	Chief Investigator
CI*	Confidence Intervals
CIDER	Cornwall Intellectual Disability Equitable Research
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
CSRI	Client Service Receipt Inventory
CTU	Clinical Trials Unit
DIRUM	Database of Instruments for Resource Use Measurement
DMP	Data Management Plan
DS	Dravet Syndrome
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
EEG	Electroencephalogram
EQ-5D-5L	EuroQol Group 5 Dimensions 5 Level
GCP	Good Clinical Practice
GDPR	UK General Data Protection Regulation
GP	General Practitioner
HONOS-ID	Health of the National Outcome Scale for People with Intellectual Difficulties
HRA	Health Research Authority
HRQoL	Health Related QUality of Life
ICF	Informed Consent Form
ICH-GCP	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice
ID	Intellectual Disability
IQR	Inter-quartile Range
ISF	Investigator Site File
ISRCTN	International Standard Registered Clinical Trials Number
LGS	Lennox-Gastaut Syndrome
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health and Care Research
PAG	Patient Advisory Group

PenCTU	Peninsula Clinical Trials Unit
PI	Principal Investigator
PIS	Participant Information Sheet
PPI	Patient and Public Involvement
QA	Quality Assurance
QALY	Quality-Adjusted Life-Year
QoL	Quality of Life
R&D	Research & Development
REC	Research Ethics Committee
REDCap	Research Electonic Data Capture
SAP	Statistical Analysis Plan
SD	Standard Deviation
SMG	Study Management Group
SOC	Service Organisation Control
SOP	Standard Operating Procedure
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
SHEAP	Statistical and Health Economic Analysis Plan
TAND	TSC-Associated Neuropsychiatric Disorders
THC	Delta-9-Tetrahydrocannabinol
TMF	Trial Master File
TRPV1	Transient Receptor Potential Vanilloid Type 1
TSC	Tuberous sclerosis complex
TSC*	Trial Steering Committee
UKCRC	UK Clinical Research Collaboration
VAS	Visual Analogue Scale
WP	Work package

iii. STUDY SUMMARY

Study Overview		
Study Title	Cannabidiol impact on challenging behaviour in adults with Intellectual Disability with Lennox-Gastaut syndrome, Dravet syndrome and tuberous sclerosis complex (CANABID-LD): a prospective observational cohort study	
Study Acronym	CANABID-LD.	
Study Design	A prospective cohort study divided into WP1 (a prospective observational study), and WP2 (an embedded qualitative study).	
Work Package 1 (WP1)	WP1 is a prospective observational study. All patients with LGS/DS/TSC who will be prescribed cannabidiol (CBD) clinically, and meet the inclusion criteria in participating centres, will be invited to join the study. It does not involve any change in treatment plans or deviations to routine care. Baseline data will be collected, and participants will be followed up 90 days and 180 days after CBD treatment commenced, using validated data collection tools focused on behaviour, seizures, and quality of life.	
Work Package 2 (WP2)	WP2 is an embedded qualitative study. Semi-structured interviews with primary caregivers and clinicians will explore treatment acceptability, including the perceived impact of CBD on seizures and challenging behaviours.	
Planned Sample Size	WP1: 60 WP2: 25 (15 primary caregivers and 10 clinicians).	
Planned Number of Sites	10	
Overall Protocol Aim	To examine the relationship of prescribed Cannabidiol for pharmaco-resistant seizures on challenging behaviours, seizure frequency and quality of life, among adults with LGS, DS or TSC with co-occurring ID.	
	Objectives	**Outcome Measure(s)**
Primary	To determine if cannabidiol affects challenging behaviours in patients with ID and epilepsy, determined by changes to the ABC-2 Irritability subscale score between baseline and 180 days post initiation of treatment.	Aberrant Behaviour Checklist-Second edition (ABC-2)[1] Irritability subscale (baseline, 180 days)
Secondary (WP1)	To determine if cannabidiol affects other behavioural, clinical and psychological outcomes associated with cannabidiol prescribing at 90 days and 180 days post-treatment initiation.	Health of the Nation Outcome Scale for People with Intellectual Difficulties (HONOS-ID)[2] (baseline, 90 days, 180 days) Clinical Global Impression (CGI)[3] (180 days/routine follow-up visit)

		ABC-2 (baseline, 90 days, 180 days)
	To explore the association between cannabidiol dose and change in challenging behaviour.	Cannabidiol daily dose (mg/kg/day) (baseline, 90 days, 180 days) ABC-2 (baseline, 90 days, 180 days)
	To determine any changes in seizure type/frequency at 90 days and 180 days post-treatment initiation.	Seizure type/frequency (baseline, 90 days, 180 days)
	To test methods to economically evaluate the provision of cannabidiol and its impact on quality of life.	EQ-5D-5L Proxy Version 2[4] (baseline, 90 days, 180 days) Resource use questionnaire (baseline, 90 days, 180 days)
	To explore differences in changes to challenging behaviour between those who meet the threshold for moderate to severe challenging behaviour at baseline (Group A) and those who do not meet threshold for moderate to severe challenging behaviour - i.e., no challenging behaviour or mild challenging behaviour at baseline (Group B).	ABC-2 (baseline, 90 days, 180 days)
Secondary (WP2)	To gain a deeper understanding of participant/primary caregiver/clinician's experience of cannabidiol on challenging behaviours and seizures, including treatment acceptability (WP2).	Semi-structured interviews 180 days after treatment initiation
Study Population		
Study Participants	Adults with LGS, DS or TSC with co-occurring ID.	
Inclusion Criteria	• ≥ 16 years of age at the time of enrolment. • Confirmed clinical diagnosis of LGS, DS or TSC. • Confirmed clinical diagnosis of an ID. • Patient is scheduled to start cannabidiol treatment as part of their usual clinical care, prescribed by their practitioner for seizure management. • Participant has the capacity to be able to provide consent for themselves, or a personal/professional consultee is able to provide an opinion on the views and feelings of the participant.	

	• Participant has a primary caregiver who is willing and able to complete caregiver reported outcome measures. • Willing and able to complete all scheduled follow-ups.
Exclusion criteria	• Patient previously or already on prescribed regulatory approved cannabidiol (not including over the counter CBD).
Study Timescales	
Follow Up Timepoints	90 days and 180 days.
Planned Study Period	Total 24 months (approximately 6-month set-up period, 6-month recruitment period, 6-month follow-up period, 6-month analysis period).
Planned Date to Open Recruitment	01/10/2025
Planned Recruitment End Date	30/04/2026
Planned Follow-up End Date	31/10/2026
Planned Study End Date	31/01/2027

iv. FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL SUPPORT GIVEN
Jazz Pharmaceuticals	$483,179.65

v. ROLE OF STUDY SPONSOR AND FUNDER

The Sponsor for this study, University of Plymouth, assumes overall responsibility for the initiation and management of the study. The Sponsor may delegate specific tasks to any other individual or organisation that is willing and able to accept them. Any delegated tasks will be clearly recorded in a matrix of task allocations. Although tasks may be delegated, the overall responsibility remains with the Sponsor.

The Sponsor and funder will not have direct involvement in study design, conduct, data analysis and interpretation, manuscript writing, and dissemination of results.

The study was designed by the Chief Investigator and co-applicants with support from Peninsula Clinical Trials Unit (PenCTU).

vi. ROLE OF THE COORDINATING CLINICAL TRIALS UNIT (CTU)

PenCTU is a fully registered clinical trials unit in the UK Clinical Research Collaboration (UKCRC) with National Institute for Health and Care Research (NIHR) CTU support funding. PenCTU is a leading academic clinical trials unit with expertise in designing, developing, supporting and co-ordinating high quality, multi-centre trials and other well-designed studies that influence clinical and healthcare practice. PenCTU has an extensive track record in delivering feasibility studies. The Sponsor of the study has allocated tasks associated with overall Study management and data management to the Peninsula

Clinical Trials Unit (PenCTU). A detailed breakdown of tasks undertaken by CTU on behalf of the Chief Investigator (CI) and trial Sponsor is described in the task allocation matrix.

vii. ROLES OF TRIAL OVERSIGHT COMMITEES AND GROUPS

The **Study Management Group (SMG)** is chaired by the CI and comprises co-applicants, trial statisticians, a Patient and Public Involvement (PPI) representative, CTU staff and sponsor representatives The SMG will meet monthly to review study progress and to ensure appropriate management of the study. Any problems with study conduct and participating sites will be raised and addressed during SMG meetings.

Trial oversight will be provided by an independent **Trial Steering Committee (TSC*)**. The Trial Steering Committee (TSC*) is an executive oversight body operating and will oversee and make decisions as to the future continuation (or otherwise) of the trial and ensure the trial is being conducted according to International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (ICH-GCP). The TSC* is comprised of an independent chair, independent expert(s), (clinician/pharmacist), a PPI representative and independent statistician. The TSC* will meet at least yearly in accordance with an agreed set of terms of reference, detailed in the TSC* Charter, to review the progress of the trial and will report to the Sponsor and Funder. The roles, constitution and composition of the TSC* is in accordance with NIHR Research Governance Guidelines[1]. Independence of committee members will be as defined in the NIHR Research Governance Guidelines.

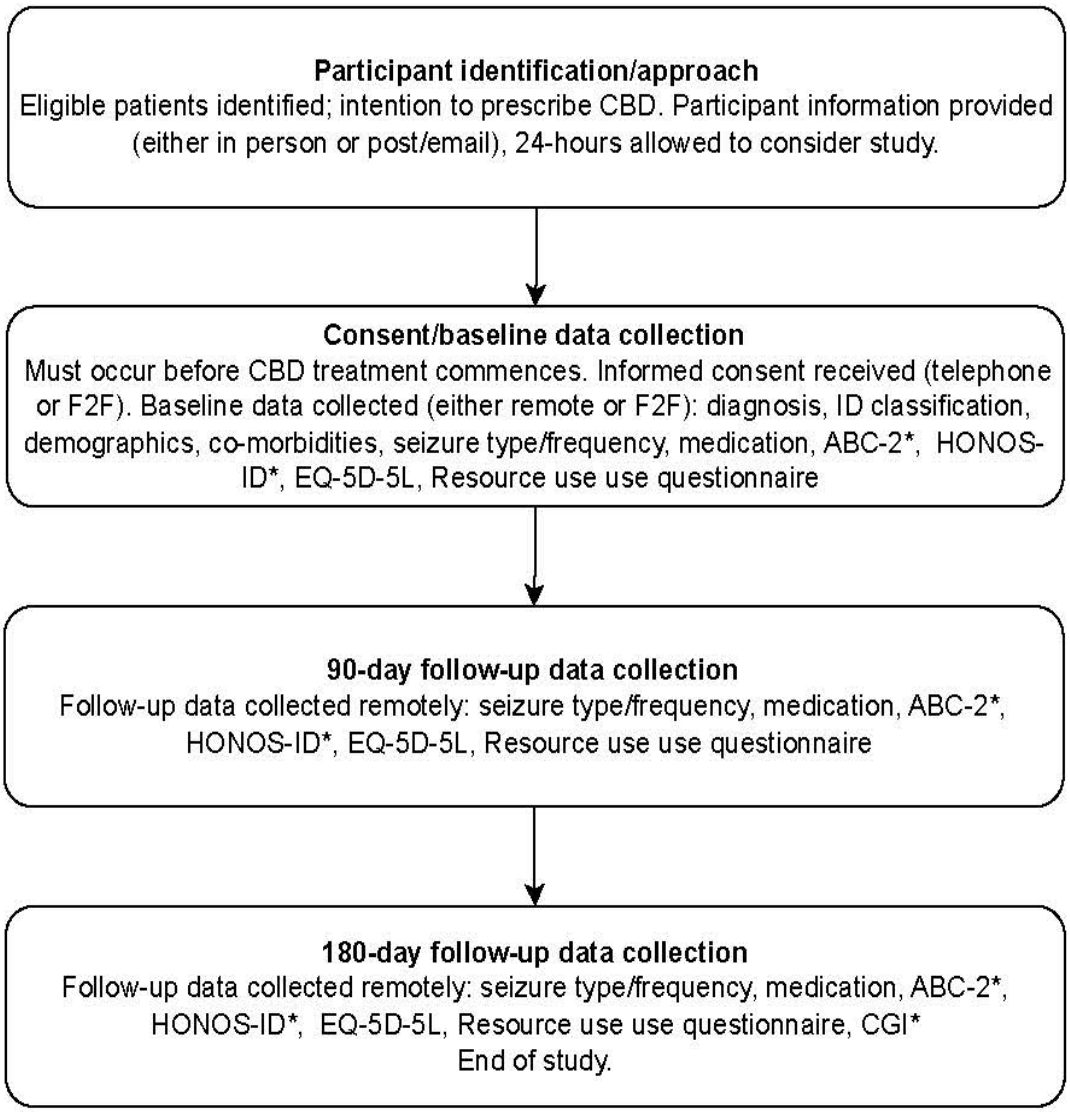
A **Patient Advisory Group (PAG)** comprising of 4-5 public members (patients or family members/ carers) and led by Claire Eldred (Director of Dravet UK) will meet twice yearly to review study progress and provide input on participant/public facing study documents and dissemination materials. They will also advise on study processes and recruitment.

viii. KEY WORDS

Cannabidiol; Epidyolex; Intellectual Disability; Challenging Behaviour; Seizures; Dravet Syndrome; Lennox-Gastaut Syndrome, tuberous sclerosis complex.

[1] NIHR Research Governance Guidelines: https://www.nihr.ac.uk/documents/research-governance-guidelines/12154

ix. PATIENT JOURNEY FLOW CHART



*ABC-2: Aberrant Behaviour Checklist-Second edition (ABC-2 Irritability subscale primary outcome measure)
HONOS-LD: Health of the Nation Outcome Scale for Intellectual Disabilities
CGI: Clinical Global Impression

Figure 1. Participant flow chart and data collection.

1. BACKGROUND

Intellectual Disability

Intellectual disability (ID) is defined by the 5th edition of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) as a disorder characterised by deficits in both intellectual functioning and adaptive functioning, with onset during the developmental period (first 18 years of life)[1]. Intellectual functioning encompasses domains such as reasoning, problem solving, and abstract thinking, whereas adaptive functioning refers to the ability to navigate activities that are part of daily life for most individuals, such as self-care, communicating with others, and living independently[5] . People with ID are also at heightened risk of mental illness compared to their peers; a meta-analysis by Mazza and colleagues estimated a pooled prevalence of 33.6% (95% confidence interval [CI] = 25.2-43.1%) of co-occurring mental illness among adults and adolescents with ID[6]. On average people with ID have 12 physical health conditions[7]. It is recognized that 63% of people with ID die before the age of 65 in England[8]. There is significant public and political concern on the standards of care and support for people with ID. ID is strongly associated with both Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS) and tuberous sclerosis complex (TSC) (described further in the protocol).

Behaviours that challenge (challenging behaviours), people with ID and epilepsy

Challenging behaviour is defined as 'culturally abnormal behaviour of such an intensity, frequency, or duration that the physical safety of the person or others is likely to be placed in serious jeopardy, or behaviour which is likely to seriously limit the use of, or result in the person being denied access to, ordinary community facilities[9] . Examples of challenging behaviours include self-harming, physical aggression towards other persons or property, stereotypic behaviours, verbal aggression, smearing faeces, and exposing oneself in public[10]. More demanding challenging behaviour (defined as 'occurring daily, restricting engagement, requiring physical intervention, or causing injury') is present in around 3.8-10% of adults with ID[11].

Numerous biological, psychological and social factors that increase the likelihood of an adult with ID presenting with challenging behaviour have been identified, including male sex, a more severe level of ID, co-occurring neurodevelopmental disorders such as autism and attention deficit hyperactive disorder (ADHD), deficits in receptive and expressive communication, genetic disorders, age (challenging behaviour is most prevalent in teenage years to thirties), physical restraint, physical illness, particularly epilepsy (22.5% prevalence in people with ID with 70% or more treatment resistant[12]), and mental illness[9,10]. Further, recent investigations have shown there is significant polypharmacy, including the overuse of psychotropics particularly antipsychotics in specific sub-populations such as people with ID and epilepsy, to manage behavioural concerns[12].

Currently, there is a lack of effective pharmacological treatments for challenging behaviour. Guidelines by the National Institute for Health and Care Excellence (NICE) discuss the potential use of antipsychotic medications, when both non-medication-based approaches and treatment of any co-occurring physical and mental illness have proven insufficiently effective, and in addition there is a very severe risk to the patient and/or other persons[10]. However, there are significant concerns about antipsychotic medication use in people with ID[15], principally related to concerns about a relative lack of evidence for their use[16], the side effect burden, and the potential for longer-term metabolic complications, such as diabetes, obesity, and hyperlipidaemia.

Challenging behaviour in people with ID is associated with poor outcomes. People with challenging behaviour are often exposed to restrictive practices such as limited access to activities of daily life, seclusion, physical restraint and polypharmacy without a strong evidence base. Limited ability to access physical health care interventions due to their challenging behaviour is associated with poor

health outcomes. As a result, health outcomes and quality of life of people with challenging behaviour are poor compared to their peers. Furthermore, current interventions are limited in scope and not always effective[17]. This highlights the need for new and effective treatments for challenging behaviour for adults with ID to improve quality of life. Currently there are no significant evidence-based strategies to manage challenging behaviour. This reflects the heterogenicity of aetiology and complexity of the presentation.

Dravet Syndrome, Lennox-Gastaut Syndrome and tuberous sclerosis complex

DS is described as 'an epilepsy syndrome that begins in infancy or early childhood and can include a spectrum of symptoms ranging from mild to severe'[18]. Patients with DS experience multiple different types of seizure, including convulsive seizures, generalized tonic-clonic seizures, alternating unilateral clonic seizures, atypical absence seizures, focus seizures, and tonic seizures[19]. The seizures are treatment-resistant, and accompanied by developmental delay in early life, leading to ID[19]. The incidence of DS has been estimated as being approximately 1 in 33,000 live births (95% CI 1 in 20,400 - 1 in 56,200)[20]. Most people with DS have co-occurring ID estimated as 86% in a systematic review of 29 studies[21], who also reported that almost two thirds of patients had a moderate to profound level of ID (defined as an Intelligence Quotient below 50). Older people living with DS had lower intellectual functioning. In addition, there were noted neurodevelopmental co-morbidities. The prevalence of autism in studies that used autism-specific instruments was 22%-46%. The prevalence of behavioural difficulties on standardized instruments ranged between 37% and 100%. Behavioural difficulties were associated was with low health-related quality of life (HRQoL), with better HRQoL associated with fewer behavioural difficulties.

LGS is another epileptic syndrome, characterised by a triad of 'several epileptic seizures (atypical absences, axial tonic seizures and sudden atonic or myoclonic falls); diffuse slow interictal spike waves in the waking electroencephalogram (EEG) (< 3 Hz) and fast rhythmic bursts (10 Hz) during sleep; slow mental development associated with personality disturbances[22] . The prevalence of confirmed LGS ranges from 2.9-2.8 per 100,000 people[23] , and over 90% of children with the condition have intellectual impairment[24]. ID is found in about half of patients at onset, usually associated with abnormalities at neuroimaging, and worsens over time, severely affecting more than two thirds of patients five years after diagnosis. A minority of patients with intellectual functioning at the lower limits of the normality show important difficulties in everyday life due to the slowing down of their mental processes.

In addition to cognitive impairment, behavioural disorders are often part of the clinical picture of patients making it even more difficult to manage. Challenging behaviour is prevalent in both DS[17] and LGS[25]. Hyperactivity, aggression, and autism spectrum disorders are present in about 50% of patients with LGS[25]. These disturbances have a multi-factorial pathogenesis in which the epileptic activity, through the activation of specific abnormal networks, and the use of many comedications seems to play a key role. Nocturnal seizures, by causing frequent sleep interruption, may deeply interfere with the memory learning process, leading to adverse cognitive and behavioural effects. In addition, some anti-seizure medications may also exacerbate comorbidities (ID, depression, mood alterations) either directly, or via interacting with other drugs, severely affecting the quality of life (QoL) of patients and their caregivers.

Tuberous sclerosis complex (TSC) is a genetic disease caused by mutations in either the *TSC1* or *TSC2* gene that causes lesions to grow in the brain and other areas of the body; symptoms typically begin in infancy or childhood and include seizures (infantile spasms, focal seizures and tonic-clonic seizures), kidney issues (cysts and angiomyolipomas), developmental delay and TSC-associated neuropsychiatric disorders (TAND)[26]. The incidence of TSC is estimated between 1:6,000 and

1:10,000 live births[27]. Approximately 50% of individuals with TSC have a co-occurring intellectual disability, ranging from mild to profoundly impaired[28]. Autism spectrum disorders (25%-50%) and ADHD (30%-60%) and challenging behaviours are commonly observed in people with TSC[29] and higher seizure frequency and increased severity of intellectual disability increase the risk of behavioural problems.

Cannabidiol and its impact on challenging behaviour in people with LGS, DS and TSC

Cannabidiol is now a recognised licenced treatment option for pharmaco-resistant epilepsy in people with LGS, DS and TSC.

One potential therapeutic option for challenging behaviour in people with ID may be medicinal cannabis, particularly cannabidiol (CBD) which lacks the psychoactive effects of delta-9-tetrahydrocannabinol (THC), the other notable chemical derived from the cannabis plant. Cannabidiol has been found to demonstrate multiple therapeutic benefits, demonstrating anti-epileptic, anxiolytic, and analgesic effects[30,31].

Theoretical Framework of action of cannabidiol in challenging behaviours

The endocannabinoid system has an important role in both neurodevelopment as well as the mature nervous system, where it 'modulates neuronal activity and network function[32]. The underlying pharmacological mechanism for medicinal cannabis is unclear, but possible modes of action include alterations in neurotransmission and calcium homeostasis, as well as anti-inflammatory and antioxidant effects[30,33,34] (Campbell *et al.*, 2017; Korb *et al.*, 2023; Poleg *et al.*, 2019). Neurotransmitter-based effects could be exerted via the serotonin 5-HT1A, cannabinoid type 1 (CB1R), and/or transient receptor potential vanilloid type 1 (TRPV1) receptors[30,35].

2. RATIONALE

In 2019, the Royal College of Psychiatrists published a Position Statement on cannabis-based medicinal products[36]. They acknowledged the suggested therapeutic potential for cannabidiol for a range of forms of mental illness, but described the current evidence base as 'scarce,' emphasising the 'pressing need for more high-quality research examining the efficacy of these substances for specific psychiatric indications' and recommended that 'key organisations must act to reduce the barriers that exist to this research.' Furthermore, if shown to be effective in clinical trials, cannabidiol may reduce the need for polypharmacy in adults with ID and challenging behaviour, which has been linked to significant patient harm[30,37].

Cannabidiol, when used in combination with Clobazam, is recommended as a treatment option for seizures in patients with LGS[38] , DS[39] and TSC. Thus, patients with these conditions represent an ideal group to assess the impact of Cannabidiol on challenging behaviours, as many will be initiated on this as part of their epilepsy treatment.

3. ASSESSMENT AND MANAGEMENT OF RISK

The study incurs limited risk to participants because it is a prospective observational study that does not involve an intervention; participants usual care will not be affected as a result of study participation.

There may be some psychological risk to the participant and/or their personal consultees relating to being asked to consent to participate in research and the processes associated with this (i.e., providing informed consent) and the requirement to complete patient reported outcome measures which may involve sensitive topics, which would be completed in additional to their standard care. Although aligned with the standard clinic appointment as much as possible, the clinic appointment is likely to be slightly different to the normal routine, which might cause some stress to potential participants in this study population.

In an attempt to manage this risk, the study pack will be provided in advanced of discussions around consenting to participate to allow the patient and/or personal consultee to read through the study documentation and decline, if they wish. They will also be provided with the local site research team contact details if they wish to talk through study participation. Staff members receiving consent will be fully trained in the study's procedures and will be trained to act sensitively and follow the potential participant's/personal consultee's pace during the consent process in an attempt to alleviate as much stress as possible. If it is not appropriate to receive consent at a routine clinic appointment, telephone consent may also be received at a more suitable time.

A detailed risk assessment, including databases associated risks, will be developed by the trial management team at PenCTU and will be regularly updated throughout the study. The risk assessments will consider all potential risks associated with the study which may include study participants, reliability of the study results, data confidentiality and study organisation. The risk assessments will report on the total risk score and category of each risk and any management/mitigation strategies.

4. OBJECTIVES AND OUTCOME MEASURES / ENDPOINTS

4.1. Overall Protocol Aim

To examine the effect of prescribed Cannabidiol for pharmaco-resistant seizures on challenging behaviours, seizure frequency and quality of life among adults with LGS, DS or TSC with co-occurring ID.

4.2. Primary objective

1. To determine if cannabidiol affects challenging behaviours in patients with ID and epilepsy, determined by changes to the ABC-2 Irritability subscale score between baseline and 180 days post initiation of treatment.

4.3. Secondary objectives

1. To determine if cannabidiol affects other behavioural, clinical and psychological outcomes associated with cannabidiol prescribing at 90 days and 180 days post-treatment initiation, as measured by the ABC-2, Health of National Outcome Scale for people with ID (HONOS-ID) and Clinical Global Impressions (CGI) scales.
2. To explore the association between cannabidiol dose and change in challenging behaviour, as measured by ABC-2 and HONOS-ID.
3. To determine any changes in seizure type/frequency at 90 days and 180 days post-treatment initiation.

4. To test methods to economically evaluate the provision of cannabidiol and its impact on quality of life, as measured by the EuroQol Group 5 Dimensions 5 Level (EQ-5D-5L) Proxy Version 2 and resource use questionnaires.
5. To explore differences in changes to challenging behaviour between those who meet the threshold for moderate to severe challenging behaviour at baseline (Group A) and those who do not meet threshold for moderate to severe challenging behaviour - i.e., no challenging behaviour or mild challenging behaviour at baseline (Group B), as measured by ABC-2 and HONOS-ID.
6. To gain a deeper understanding of participant/primary caregiver/clinician's experience of cannabidiol on challenging behaviours and seizures, including treatment acceptability (work package 2 (WP2) - see section 10).

4.4. Work Package 1: Outcome measures

4.4.1. Primary outcome

Table 1. Primary outcome overview

Outcome	Measurement tool	Measured by	Timepoint		
			Baseline	90 days*	180 days*
Challenging behaviour	ABC-2 score	Primary caregiver	X	X**	X
58-item checklist rated on a 0-3 scale. Includes 5 subscales: irritability, social withdrawal, stereotypical behaviour, hyperactivity/non-compliance and inappropriate speech. Include prompts such as "injures self on purpose," "temper tantrums/outbursts," "cries and screams inappropriately," and "irritable and whiny." Takes approximately 15 minutes to complete. Total score range from 0 to 174; this can be further divided into score per subscale. **ABC-2 score at 90 days relates to secondary objectives. ABC-2 at 180 days relates to the primary objective.					

*Days post-treatment initiation.

4.4.1.1. Rationale for primary outcome

The Aberrant Behaviour Checklist (ABC) is one of the few empirically developed scales designed to measure behavioural disturbance exhibited by individuals with ID across 5 domains[40]. It was designed as a problem behaviour rating scale to assess treatment effects in people with a learning disability and has internal consistency ranging from good to excellent for people with ID[41,42]. The Aberrant Behaviour Checklist (ABC) was originally developed to evaluate interventions and is a well-established assessment tool for challenging behaviours in people with intellectual disabilities. The ABC is frequently used in research evaluating interventions and treatment, including pharmacological treatment, for people with intellectual disabilities[43-45]. The ABC-2 was released in 2023; extensive psychometric assessment of the ABC-2 has indicated that the subscales have high internal consistency, good reliability and well-established validity. It has become the standard in the ID field, for assessing challenging behaviours.

4.4.2. Secondary outcome measures (WP1).

Table 2. Secondary outcomes overview

Outcome	Measurement tool	Measured by	Timepoint		
			Baseline	90 days*	180 days*
Behavioural and psychological outcomes	HONOS-ID	Clinician, with support from primary caregiver	X	X	X
18 item scale relating to various behaviours (behavioural concerns, attention/concentration, memory/orientation, communication problems, hallucinations/delusions, mood disturbances, problems with sleeping/appetite, physical problems, seizures, activities of daily living (ADLs), self-care, relationships and meaningful activity). Rated 0-4 based on severity. Takes approximately 10 minutes. Scores range from 0 to 72.					
Clinical outcome/response	CGI	Clinician			X**
2 item observer rated scale measuring illness severity (CGI-S) and global improvement (CGI-I). Rated on two 0-7 scales. Global improvement will relate to challenging behaviours. Takes approximately 5 minutes to complete; completed by clinician. **Completed at the participant's next routine clinical follow-up appointment; this typically occurs 180 days after treatment commences, but there is variability between different NHS Trusts. This measure will be recorded at the next routine follow-up, as per local Trust guidelines.					
Cannabidiol daily dose	Daily dose (mg/kg/day)	Clinician at baseline. Reported by primary caregiver at 90 days/180 days	X	X	X
Cannabidiol starting daily dose (mg/kg/day) will be recorded by the prescribing clinician at baseline. Changes to the daily dose will be recorded at 90 day and 180 day follow-up timepoints, as reported by the primary caregiver.					
Seizures	Seizure type/ frequency	Primary caregiver	X	X	X
At baseline, the primary caregiver will be asked to provide an estimate of the average number of seizures the participant experienced per month over the last 180 days and the type(s) of seizures experienced. At 90 days and 180 days, the primary caregiver will report the number of seizures experienced since the last data collection timepoint (i.e. if the 90 day follow-up timepoint is missed, they will be asked to provide seizures experienced over the last 180 days at the 180 day timepoint). Primary caregivers will be provided with a seizure record at baseline to help them to keep track of seizures the participant experiences during the study period. Seizure types will be classified as: tonic clonic/tonic/atonic/absence/focal/myoclonic.					
Quality of life	EQ-5D-5L Proxy Version 2	Primary caregiver	X	X	X
5 items/dimensions relating to mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each item is scored between 1-5. One visual analogue scale (VAS) recording					

self-rated health. Takes approximately 5 minutes to complete. The EQ-5D-5L Proxy Version 2 will be used for all participants; the primary caregiver will always complete this measure to ensures data is collected consistently across all participants. Research suggests that EQ-5D-5L results vary depending on whether it is completed by the individual or a proxy. In the unlikely situation where a participant has capacity to complete questionnaires themselves, the primary caregiver will still complete the EQ-5D-5L Proxy.					
Resource use	Resource use questionnaire	Primary caregiver	X	X	X
5 questions relating to services the participant has used over the last 90 days and the approximate contact hours with each service. This includes inpatient services, outpatient services, day activity services, community care and contact with other professionals. Takes approximately 10 minutes to complete.					

*Days post-treatment initiation.

4.5. Secondary outcome measure (WP2)

- **Semi-structured interviews-** interviews with a sub-sample of participant's primary caregivers and clinicians about experiences with cannabidiol. Interviews will take place 180 days post-treatment initiation for primary caregivers and at the end of participant follow-up for clinicians. Interviews will take approximately 60 minutes for caregivers and 30 minutes for clinicians. See Section 10 for further information.

5. STUDY TREATMENTS

This is an observational study with no treatment intervention. Participants will be prescribed cannabidiol (Epidyolex) as part of their usual care.

Epidyolex is a prescription medication that is used to treat seizures associated with LGS, DS and TSC; it can significantly reduce seizures for those whom multiple previous antiseizure medications were ineffective. Epidyolex is an oral solution that is typically taken twice daily.

6. STUDY DESIGN

A prospective observational cohort study, with an embedded qualitative component, to examine the impact of cannabidiol on challenging behaviour, seizure type/frequency and quality of life when prescribed for clinical indicated reason of seizure management in people with LGS/DS/TSC.

7. STUDY SETTING

This is a multicentre study based at approximately 10 NHS healthcare trusts across the United Kingdom that prescribe cannabidiol. All participating sites will have the same roles and same requirements for recruiting/data collection/follow-up and will follow the same eligibility criteria and study processes. Sites will be overseen by the principal investigator and will have the resources to recruit and collect data, including research nurses, pharmacists and clinical research practitioners.

Participating sites have been selected who meet specific feasibility criteria including the routine prescription of cannabidiol and sufficient recruitment potential.

8. PARTICIPANT ELIGIBILITY CRITERIA

8.1. Inclusion criteria

- ≥ 16 years of age at the time of enrolment.
- Confirmed clinical diagnosis of LGS, DS or TSC.
- Confirmed clinical diagnosis of an ID.
- Patient is scheduled to start cannabidiol treatment as part of their usual clinical care, prescribed by their practitioner for seizure management.
- Participant has the capacity to be able to provide consent for themselves, or a personal consultee is able to provide an opinion on the views and feelings of the participant.
- Participant has a primary caregiver who is willing and able to complete caregiver reported outcome measures.
- Willing and able to complete all scheduled follow-ups.

8.2. Exclusion criteria

Patients who meet any of the following criteria will be excluded from study participation:

- Patient previously or already on prescribed regulatory approved cannabidiol* (not including over-the-counter cannabidiol variants).

**Please check with the participant/primary caregiver whether Epidyolex has ever been prescribed privately; it may not appear on their NHS medical records during screening if received privately.*

9. STUDY CONDUCT

9.1. Participant recruitment

9.1.1. Participant identification and eligibility screening

At each site, patients meeting the eligibility criteria will be identified by either the direct clinical care team or the local site research team. Eligibility should be confirmed as much as possible *via* the use of medical notes prior to participant approach. Sites will be required to identify patients who will be prospectively prescribed cannabidiol but have not yet commenced treatment. Baseline data must be collected before treatment commences. Therefore, it will be necessary for the clinical team/prescribers to liaise closely with the local site research team to ensure potential participants are identified promptly before treatment begins.

Potential participants can be screened from a variety of sources, including:

- Routine neurology/epilepsy/neuropsychiatry appointments
- Existing and new referrals to the service.

Eligibility should be confirmed as much as possible prior to participant approach.

Site Principal Investigators (PIs) will be responsible for promoting the study amongst relevant staff at the sites to optimise participant identification.

Identifiable information will not be accessed by those outside of the direct clinical care team.

For WP2 (qualitative component), a sample of primary caregivers from the WP1 study population will be invited to take part in a qualitative interview by a researcher at the University of Leicester. Personal consultees will be asked an optional consent point when consenting to WP1 if they wish to be considered to take part in the qualitative interviews. The qualitative researcher will contact the local study team at sites to request contact information of personal consultees who consent to taking part in WP2; local sites are not required to carry out any further activity relating WP2 (see Section 10 Qualitative Component - Work Package 2 for further information).

9.1.2. Participant approach and eligibility confirmation

Efficient participant approach and recruitment is important as consent and the collection of baseline data needs to occur prior to the commencement of cannabidiol treatment. There are two potential routes in which participants and their personal consultees may be approached and recruited to the study.

Prospective approach during routine clinic appointment:

A potential participant may be identified as having an upcoming routine appointment (face-to-face or remote) to discuss medication changes and potential cannabidiol prescription. If the decision to prescribe cannabidiol is made at the appointment, the primary caregiver/potential participant may be introduced to the study and provided with the recruitment pack, if they are interested (in-person or via email/post if the appointment is remote). The recruitment pack contains an invitation letter, consultee information sheet, pictorial Participant Information Sheets (PIS), copies of the study questionnaires and seizure/key events records.

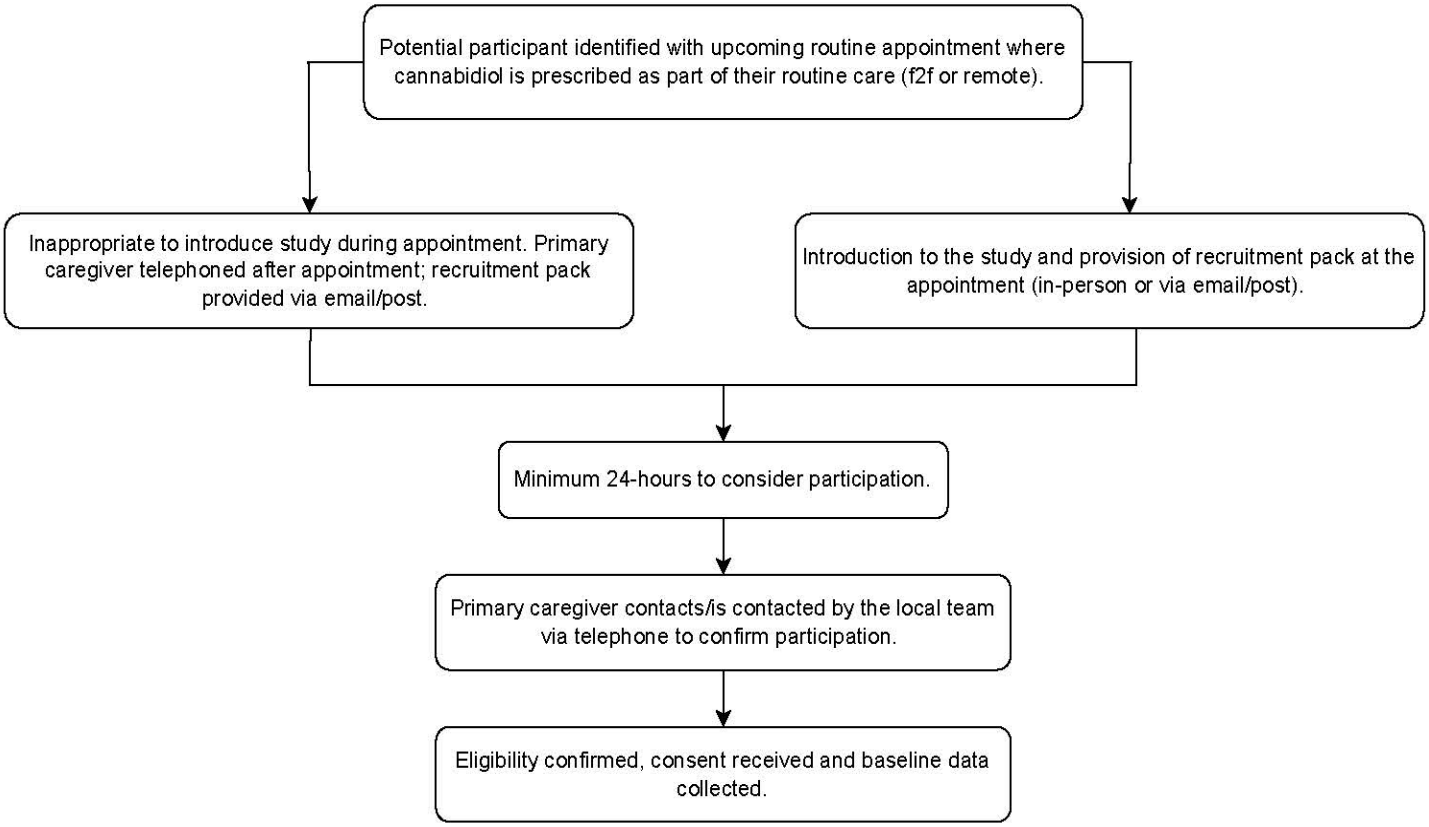
It may be inappropriate to introduce the primary caregiver/potential participant to the study during the clinic appointment, for example the patient or carer may be experiencing some distress or there may be time constraints. In this case, the local study team (who are part of the patient's clinical team) will telephone the primary caregiver after the appointment to introduce the study at a more suitable time and provide the recruitment pack via email or post, if they are interested.

The primary caregiver/potential participant should be allowed a minimum of 24-hours to read the study information and consider participation. If they are interested in participating or have any questions, they can use the contact information in the PIS to telephone the local study team and inform them. If the study team has not heard anything from the primary caregiver/potential participant within a few days, they may contact the primary caregiver to see if they are interested in the study.

During this call any further questions will be discussed and if the patient/carer is interested in progressing their eligibility will be confirmed and documented, which will take approximately 5 minutes. Confirmation of eligibility should be fully documented in the participant's medical notes and entered directly on the Research Electronic Data Capture (REDCap)[45a]. Paper Case Report Forms (CRFs) will also be provided as a data collection aid, which can be entered onto the database retrospectively by the research team. Following eligibility, informed consent/consultee declaration will be received. Baseline data will then be collected.

If the participant has another routine appointment scheduled before treatment commences, then it is permittable to confirm eligibility, receive informed consent and collect baseline data in-person rather than via telephone. This is unlikely, but patient flow and routine appointments can vary between different NHS Trusts.

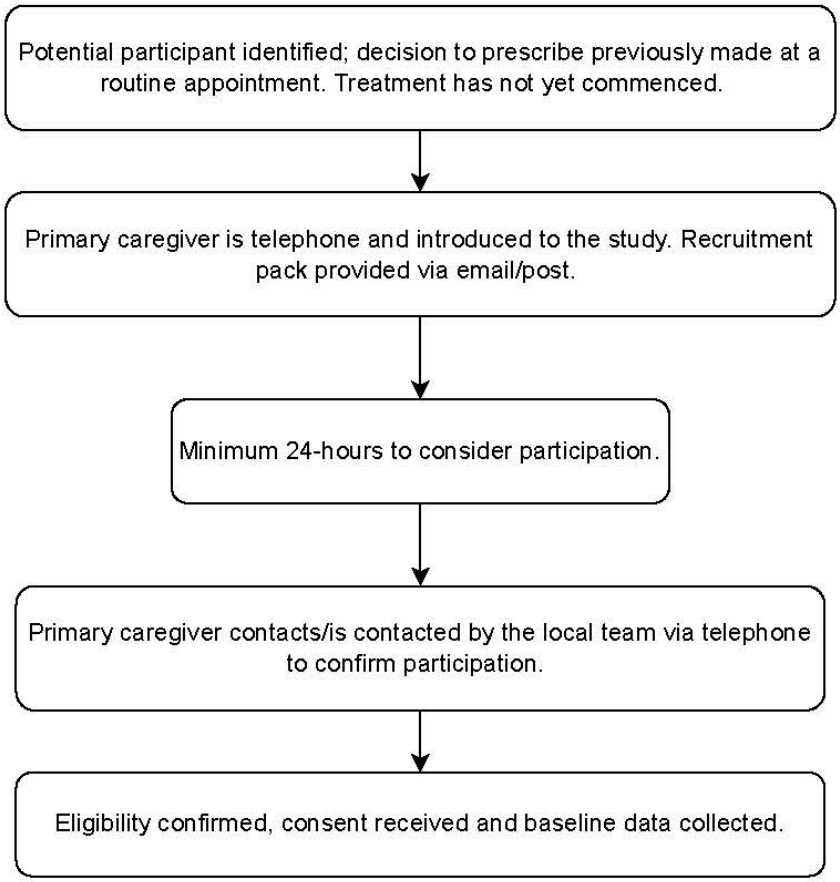
Figure 2. Recruitment flowchart; prospective approach at routine clinic appointment



Retrospective approach via telephone:

In some cases, a potential participant may be identified where the decision to prescribe cannabidiol has already been made at a previous routine appointment, but they have not yet commenced treatment. In these cases, the local study team (who are part of the patient's clinical care team) will contact the primary caregiver via telephone to introduce the study and provide a recruitment pack via email or post. The same process outlined above will be followed after the provision of the recruitment pack to confirm participation and eligibility.

Figure 3. Recruitment flowchart; retrospective telephone approach



In order to comply with the Welsh Language Act 1993, if a patient or their personal consultee were to request the patient-facing documents in Welsh, this would be arranged locally via Swansea Bay University Health Board's internal service.

9.1.3. Recording screening and recruitment information

For potential participants who express an interest in taking part and receive a recruitment pack, a record will be created in REDCap with de-identified data. This will include identification date, participant initials, date the PIS was provided, eligibility screening checklist and basic demographic data (age, sex at birth and ethnicity). This will act as the electronic screening log for the central research team to monitor participant flow and exclusion reasons.

Sites will be provided with a local screening log template, where they can record identifiable information, including the participants name and contact information, to keep track of people who have received recruitment information. This will be held and maintained locally at sites; no directly identifiable information will be entered on the study database.

When the participant receives their follow-up call to confirm eligibility and intention to participate, this will be documented in REDCap. During the call, the participant may be found to be ineligible or uninterested in participating; this should be documented on REDCap.

Data relating to eligibility and screening will be collated within the trial master file (TMF) to ensure reporting is collated and reported in line with the consolidated standards of reporting trials (CONSORT) guidelines.

9.2. Consent

Informed consent must be received from the participant or personal consultee prior to the collection of baseline data. Consent may be received face-to-face at their next clinic visit or via telephone consent. Due to the requirement for consent and baseline data collection to take place prior to commencement of cannabidiol treatment, telephone consent may be received during the follow-up eligibility confirmation telephone call with the local research team.

This study is looking to recruit a complex and vulnerable population of NHS patients. Consenting will, in most circumstances, have to be completed with personal consultees (i.e., relatives/close friends) rather than patients.

The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

Informed consent must be obtained by the site PI, or an authorised delegate, prior to collecting any directly identifiable data or carrying out any study assessments outside of their routine care. Authorised delegates (recorded on the study delegation log) must be suitably trained in the relevant principles of GCP and the requirements of the trial protocol. Doctors, registered nurses, Allied Health Professionals (band 5 or higher) and trained researchers may be authorised to receive consent for this study. Consent should only be received after potential participants have had enough time (minimum of 24-hours) to consider and discuss the study with their clinicians, family or friends. If they agree to take part, written formal consent will be taken from the potential participant by the PI or delegated individual using a study specific informed consent form (ICF).

The PI retains overall responsibility for the conduct of research at their site, this includes receiving informed consent from participants at their site. They must ensure that any person delegated the responsibility to participate in the informed consent process is duly authorised, trained and competent. If delegation of consent is acceptable, then details should be provided in the site delegation log. This will be monitored centrally by PenCTU.

Original versions of completed ICFs should be retained at site in the participant's notes in a secure location and a copy should be provided to the participant for their records. Consent forms **should not** be scanned and uploaded to the electronic Investigator Site File (ISF) hosted on SharePoint. Original consent forms will be monitored by the central study team during remote monitoring sessions. The full process of confirming eligibility and consent should be documented in the participant's medical records.

The participant will be informed they have a right to withdraw from the study, without giving a reason, at any time and without prejudicing their further treatment. Data collected up to the point of withdrawal will still be retained and used in analysis. This data will remain pseudonymised and any intention to utilise such data is outlined in the consent literature.

For adults meeting inclusion criteria to take part but lacking capacity to consent, a personal consultee will be identified to determine whether participation in the study would be in their best interests. In the event that a participant who formerly had capacity lost capacity to consent during the course of the study, their initial consent would not legally endure, and a consultee for the participant would be identified to help determine whether continued participation in the study would be in their best interests, or whether they should be withdrawn from the study.

Researchers will follow a study-specific work instructions depending on whether informed consent is received in-person or via telephone (see Work Instruction 'Eligibility, In-Person Informed Consent and Telephone Informed Consent' for further information) and take responsibility for ensuring that all

participants and/or personal consultees consent voluntarily with full understanding of what is involved in the study.

Individual clauses from the ICF will be read out by the individual receiving consent, to the potential personal consultee/potential participant. The personal consultee/potential participant will respond to each clause in turn, to confirm their understanding and agreement. If consent is received in person, the personal consultee/potential participant will initial next to each clause. If consent is received via the telephone, the person receiving consent will complete a telephone declaration form and initial next to each clause indicating that the personal consultee/potential participant has verbally understood and agreed to each point. The person receiving telephone consent must sign the form to confirm that the personal consultee/potential participant has understood the information sheet and verbally agreed to the consent points. The PI takes responsibility for ensuring that all vulnerable participants are protected and participate voluntarily in an environment free from coercion or undue influence.

9.2.1. Assessing capacity to consent

The clinician should make a judgement about the participant's capacity and whether they are able to provide consent for themselves. Clinicians and members of the local site research team who do not know the patient well, can get an idea about a potential participant's capacity by referring to the participant's medical records and discussing with the participant's usual care team prior to approaching the participant and/or their personal consultee. In order to fully assess capacity, delegates receiving consent should assess whether the participant understands what is being asked of them by agreeing to take part in the study.

The participant is deemed to have capacity if they understand the information relevant to the decision, they can retain the information, they can weigh up the information provided to them and are able to communicate a decision. A way to assess this is often to go through the study with them and ask the participant to relay specific information about the study back to the researcher, in order to confirm their understanding.

In line with the Mental Capacity Act (2005), reasonable adjustments will be made so that potential participants are offered the study information in a way that gives them the best chance of understanding and being able to consent for themselves. Easy read Pictorial Participant Information Sheets and Pictorial consent forms are available to aid discussions with the participant about the study, if appropriate.

If there is any doubt regarding a participant's understanding of the study and what is being asked of them, the researcher should follow the process for receiving consent from a personal consultee.

It is expected that the majority of participant's that meet the eligibility criteria will lack capacity and require a personal consultee. The participant will also require a primary caregiver who is willing to complete caregiver reported outcome measures; this is still a requirement if the participant has capacity to consent for themselves.

9.2.2. Participant has capacity to consent for themselves.

If the investigator receiving consent, deems the participant to have capacity and can consent for themselves, the participant will be asked to complete the pictorial consent form to indicate their permission to take part in the study. If consent is received via telephone, the investigator will complete this, with permission, on the participants behalf. The investigator should ensure that the participant

has capacity to provide consent, has read and understood the participant information sheet, has had enough time to consider taking part in the research, and has had the opportunity to ask any questions they might have. If all the requirements listed above have been met, the investigator can proceed with to receiving consent.

If consent is received in-person, the individual receiving consent should ensure that the participants initial each statement box that they wish to consent to. The participant should provide their full name, provide a wet ink signature and date of consent, if they are able to. If the participant has the capacity to consent but they are unable to write, they should make any mark that they are able to on the consent form. This should be witnessed with the witness printing their full name, providing a wet ink signature, and including the date on the consent form. If consent is received via telephone, the investigator will initial and sign on behalf of the participant after receiving verbal consent for each point.

9.2.3. Participant does not have capacity to consent for themselves.

If the participant does not have the capacity to consent for themselves, the researcher is required to seek advice from a personal consultee on what the wishes and feelings of the person might be and whether they would want to take part if they could decide for themselves. A personal consultee can be defined as somebody whom the person who lacks capacity would trust with important decisions about their welfare. These could include: a close relative or friend, carer (unpaid), an individual with Lasting Power of Attorney or a court-appointed deputy.

Under the Mental Capacity Act (2005), no one gives consent on behalf of a person lacking capacity, therefore the role of the consultee is to give advice to the researcher regarding whether they believe the participant would have wanted to take part if they were able to decide for themselves. If at any point, the participant conveys in any way what could be deemed as not wishing to participate in the study, this should precedent any advice provided by the consultee and the participant's involvement in the study should end.

The individual receiving consent should ensure that the consultee writes their initials in each statement box that they wish to provide advice for. The consultee should print their full name, provide a wet ink signature and date of consent. The researcher should also print their full name, provide a wet ink signature, and include the date of the declaration. If consent is received via telephone, the investigator will initial and sign on behalf of the participant and personal consultee after receiving verbal consent for each point.

9.3. Baseline visit

Once the participant has consented to take part in the study, baseline data will be collected and entered in REDCap. This must be collected prior to the commencement of cannabidiol treatment and can be collected via telephone or in-person with the primary caregiver and use of medical notes. This may take place directly after consent is received. Alternatively, a more convenient time may be arranged with the primary caregiver. Baseline data collection will take approximately 45 minutes.

The following baseline data will be collected:

<u>Demographics</u>

- Age at baseline
- Sex at birth
- Ethnicity

Medical History
- Diagnosis of LGS, DS or TSC
- ID classification (mild/moderate/profound)
- Co-morbidities (including neurodevelopmental conditions, psychiatric diagnoses, and chronic physical health disorders)
- Care setting (living with family/care home/day care centre/assisted living/home care)
- Concomitant medications (anti-seizure and psychotropic)
- Cannabidiol daily dose (mg/kg/day) and estimated start date

Seizure Information
- Seizure type (tonic clonic/tonic/atonic/absence/focal/myoclonic)
- Seizure frequency (estimated average number of monthly seizures over the last 180 days); the primary caregiver can be provided with a seizure diary to help keep track of seizures over the duration of the study.

Clinical and carer-reported outcome measures:
- ABC-2*
- HONOS-ID
- EQ-5D-5L Proxy Version 2*
- Resource use questionnaire*

Demographic and clinical information will be collected via use of the participant's medical notes and discussion with the primary caregiver. The carer-reported outcome measures (denoted with an *) must be completed by the participant's primary caregiver. These will be completed with the support of a member of the local research team on the telephone or in clinic; paper questionnaires will be provided.

Contact information for the primary caregiver be recorded; they will be informed that this contact information will be used when the researcher/clinician calls them to collect the follow-up data 90 days and 180 days post-treatment initiation. This contact information is held locally and is not entered onto the REDCap database.

9.4. *90 day and 180 day* follow-up

The following data will be collected remotely on the telephone with the primary caregiver at 90 days and 180 days post-treatment initiation (+/- 1 week) and entered into REDCap:

- Cannabidiol daily dose (including whether they have stopped treatment)
- Changes to concomitant medications
- Any significant events that have that significantly impacted behaviour over the last 4-weeks

Seizure Information
- Seizure type (tonic clonic/tonic/atonic/absence/focal/myoclonic)
- Seizure frequency (primary caregiver will be asked to report the number of
- seizures experienced over the last 90 days)

Clinical and carer-reported outcome measures:
- ABC-2*
- HONOS-ID
- EQ-5D-5L Proxy Version*
- Resource Use questionnaire*

Clinician reported outcome measures:

- CGI **(180 days only or when the participant has their routine follow-up visit)**
- If the participants have experienced any side effects from cannabidiol **(180 days only or when the participant has their routine follow-up visit)**

The caregiver-reported outcome measures (denoted with an *) must be completed with the participant's primary caregiver; these will be completed on the telephone with the local research team. The primary caregiver will be provided with copies of the questionnaires in the recruitment pack, so they are able to familiarise themselves with the questions prior to the follow-up telephone call. The HONOS-ID will be completed by the researcher, supported by discussion with the primary caregiver. Seizure records and key event records are provided in the recruitment pack for the primary caregiver to keep track of seizures/key events that occurred over the previous 90 days to improve accuracy and efficiency of follow-up data collection.

The follow-up calls will take approximately 45 minutes and should take place with the named primary caregiver.

9.4.1. Payment

Participants will receive a £10 gift voucher at the end of their time on the study.

10. QUALITATIVE COMPONENT – WORK PACKAGE 2

10.1. Background

An embedded qualitative study will explore the experiences and views of individuals, carers and clinicians to understand the impact and acceptability of treatment with cannabidiol for individuals with LGS, DS and TSC. Findings from this will provide insight on the impact of cannabidiol on challenging behaviour, seizures and the quality of life of individuals and their families. Interviews will take place 180 days post-treatment initiation with the participant's primary caregivers and at the end of participant follow-up for clinicians. Interviews will take approximately 60 minutes for the primary caregivers and 30 minutes for the clinicians.

10.2. Qualitative objective

To gain a deeper understanding of participant/primary caregiver/clinician's experience of cannabidiol on challenging behaviours, quality of life and seizures, including treatment acceptability.

10.3. Methods

A semi-structured approach will be used to collect in-depth information from carers and clinicians, whilst also affording sufficient flexibility for interviewees to expand on issues particularly pertinent to their experience. Semi-structured interviews will take place via telephone or online videoconferencing (i.e. Zoom or Teams), depending on the participant's preference, and take approximately 60 minutes. Interviews will follow a structure denoted in the topic guides and cover topic such as:

- Reasons for starting cannabidiol treatment

- Response to cannabidiol treatment
- Prescribing process/practicalities
- Changes in behaviour/quality of life
- Positive and negative impacts of treatment

10.4. Sampling & recruitment

The WP2 cohort will comprise of participants reflecting a diverse range of primary caregiver and WP1 participant's age, gender and ethnicity, and diagnosis of WP1 participant. The sample will consist of primary caregivers of those who participated in WP1 to its endpoint, as well as those who withdrew from WP1 but were still willing to participate in WP2. It is valuable to obtain such data on participants who did not participate in WP1 to its endpoint, as this will give a more holistic perspective with regards to the acceptability of treatment with cannabidiol on behaviour. Clinician interviews will comprise of one clinician from each site who was involved in the study and has experience prescribing cannabidiol to people with LGS, DS or TSC.

10.4.1. Group 1: Primary caregiver interviews

15 primary caregivers (approximately 25% of the WP1 sample) will be recruited using a combination of convenience and purposive sampling approaches to achieve a range of views and experiences based on diversity in age, gender, ethnicity, severity of WP1 participant's ID and study centre.

All primary caregivers of those taking part in WP1 are asked an optional consent point on the declaration form whether they consent to being contacted regarding taking part in the qualitative interviews. A convenience sampling approach will be used initially; primary caregivers who consented to being contacted will be invited to take part in an interview at the end of the participant's time on the study (180 days after treatment commenced). A sampling matrix will then be used to keep track of the demographics of the qualitative participants being recruited (e.g., in terms of caregiver and WP1 participant's age, gender, ethnicity, ID severity and study centre) and purposive sampling will be used to recruit any gaps within the matrix.

Carers who consent to being contacted will be sent a letter and PIS inviting them to participate. The information sheet will inform them that the researcher will contact them in a few days to see if they are still interested in taking part. If they do not wish to be contacted, or know that they are not interested, they can use the contact details for the qualitative research team provided. If it has not been possible to contact the carer after 2 weeks, a reminder invite letter will be sent to them. If the reminder letter is not acted upon, no further contact will be made, and they will be documented as not interested.

When the researcher contacts the carer, they will have the opportunity to ask questions. If they wish to participate, the researcher will then receive consent via the telephone. The researcher will read out each point on the consent form and ask the carer to verbally confirm whether they agree with each statement. A copy of the consent form will be posted to the carer.

After consent has been received, a date and time for the interview will be scheduled via the carers' preferred method of contact (either telephone or videoconferencing). This may take place on the same phone call that consent was received, if the carer wishes to do so. Otherwise, a more convenient date and time will be arranged. Carer interviews will take up to 60 minutes.

10.4.2. Group 2: Clinician interviews

One clinician from each participating site who has been involved in the study and cannabidiol prescribing for LGS, DS or TSC patients will be invited to take part in an interview to discuss their views and opinions of cannabidiol treatment from a clinical perspective. This may include doctors, nurses, pharmacists or any other relevant health care professional. They will be contacted initially via email by the central study team to determine if they are interested in participating, if so, they will be sent the participant information sheet to read and informed that the qualitative researcher will contact them in a few days to see if they wish to participate. If no response is received after two weeks, a reminder email will be sent, at which point no further contact will be made. Invitations will be sent after participant follow-up has concluded at the site.

The researcher will contact clinicians who have confirmed interest via email on the telephone to complete the telephone consent form. A convenient time for the interview will be scheduled (either via telephone or videoconference); this may take place straight after consent is received, if this is convenient for the clinician. Clinician interviews will take approximately 30 minutes.

10.5. Data analysis

Interviews will be recorded, transcribed and subject to thematic analysis according to methodology described by Braun and Clarke[46]. Any personal identifying information will be removed or masked in interview transcripts and reports.

11. ECONOMIC EVALUATION COMPONENT

The objectives of the health economics component of this study are:

- To assess the feasibility of collecting data on health, social care, and wider societal resource use.
- To assess the feasibility of collecting participant-level data on health-related quality of life to inform a future cost per quality-adjusted life-year (QALY) analysis.

We will use a modified version of the Client Service Receipt Inventory (CSRI)[47] to measure resource use with relevant items will be identified from the Database of Instruments for Resource Use Measurement (DIRUM)[48] and recent literature. Primary care givers at baseline and follow-up will complete the resource use questionnaire and the EQ-5D-5L Proxy Version 2[4].

12. PARTICIPANT WITHDRAWAL

Participants will be able to withdraw from the study at any time with no impact on their ongoing care; the entirely voluntary nature of the research study will be emphasised during the consent process. Similarly, for participants lacking capacity to consent to take part in the study, their consultee would be able to withdraw them from the study. Where participants do withdraw from the study, any data collected up until the point of withdrawal will be retained; participants (and consultees where applicable) will be advised of this as part of the study consent process.

The PI may withdraw a participant from the study if it is determined that the participant's health is compromised by remaining in the study. All data collected from withdrawn participants will be included in the study report.

A PI may decide to withdraw a participant from the study or reduce their participation at any time for any reason.

The reason for withdrawal will be clearly stated (wherever possible) and recorded in the CRF. Any participant who withdraws will be asked to provide a reason but will be made aware that they are under no obligation to provide one, and that their withdrawal from the study shall in no way affect their access to ongoing treatment.

If at any point, the participant conveys what could be deemed as not wishing to participate in the study, in any of the follow-ups, this should take precedent over any advice provided by a consultee and the participant's involvement in the study should end.

If the participant discontinues cannabidiol use during the 180-day study period, they will not be required to withdraw and will remain in the study on an intention-to-treat basis.

12.1. End of study

Data collection will end when all 60 participants have been recruited and completed their 180 day follow-up, formally withdrawn from the study, or been lost to follow-up and all qualitative interviews have taken place. Data will be analysed within 6 months of the completion of data collection.

13. STATISTICS AND DATA ANALYSIS

13.1. Target sample size and justification

In total, 60 patient-participants will be recruited over approximately 7 months, and each person will be followed up at 90 and 180 days intervals or to their time of drop out (if it happens within 180 days). A sample size of 52 will allow us to detect an effect size of 0.5 on the ABC-2[1], based on 80% power and 5% significance, allowing for 15% loss to follow-up, we require 60 participants.

WP2: Estimated interviewees would be up to 25 (15 primary caregiver and 10 clinicians).

13.2. Planned recruitment rate

This study will include approximately 10 UK based centres. It is difficult to predict the exact recruitment rate at each site due to the sporadic prescribing of CBD. Recruitment is estimated between 2-6 participants; hence 60 participants should be recruited over approximately 7 months. Recruitment will be monitored closely and additional sites or an extension to the recruitment period will be considered if the study is not meeting planned recruitment rates.

13.3. Statistical analysis plan

The study will be reported in line with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement for observational studies[49]. The Statistical and Health Economic Analysis Plan (SHEAP) will be reviewed and signed off by an independent statistician and will be signed by the SMG prior to database lock.

13.3.1. Summary of baseline data, outcomes and flow of patients

A flowchart detailing the number of patients potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed will be presented. Baseline clinical and demographic characteristics will be described using means (standard deviation), median (inter-quartile range) or number (percentage). Appropriate summary statistics for the proposed primary and secondary outcomes will also be presented at each time-point: mean (standard deviation; SD), median (inter quartile range; IQR) or n (%). For the primary outcome, subscale totals will also be summarised using mean (SD) or median (IQR).

13.3.2. Primary outcome analysis

To examine the change in the proposed primary outcome (ABC-2 Irritability subscale score) from baseline to 90 and 180 day follow-up and its association with cannabidiol dose, we will use a linear mixed effects model, with time (baseline, 90 days and 180 days) alongside baseline score as fixed covariates and recruitment site as the random effect. Associations from the model will be presented alongside 95% confidence intervals (CI*s) and p-values.

13.3.3. Secondary outcome analysis

For the secondary outcomes, linear mixed linear mixed effects models, with time (baseline, 90 days and 180 days) alongside baseline score as fixed covariates and recruitment site as the random effect will be used to investigate if there is a change in other behavioural (HONOS-ID, ABC-2), clinical (CGI (2 separate sub-domains: 1) illness severity, 2) global improvement) and psychological (HONOS-ID, ABC-2) outcomes (Secondary Objective 1).

To explore the association between cannabidiol dose and change in challenging behaviour (Objective 2), cannabidiol dose will be added to time and baseline score as fixed covariates in the linear mixed model in section 13.3.2 (Secondary Objective 2).

The mean frequency (SD) of seizures by type will be summarised at baseline, at 90 days and 180 days post-treatment initiation to determine there are any changes from baseline (Secondary Objective 3). The type of seizures will be summarised using frequency (%) at each time point.

The linear mixed model in section 13.3.2 with ABC-2 as the outcome and group (meeting threshold of challenging behaviour or not) included alongside time and baseline score as fixed covariates and site as a random effect, will be used to investigate if there are differences in changes to challenging behaviour between the two groups from baseline to 180 days post-treatment initiation (Secondary Objective 6).

13.3.4. Subgroup analyses

To explore sub-groups, e.g., to explore changes in challenging behaviour between those who met threshold for moderate to severe challenging behaviour at baseline and those who and do not meet threshold for moderate to severe challenging behaviour - i.e., no challenging behaviour or mild challenging behaviour at baseline, linear mixed effects models will be used, with sub-group, baseline score and recruitment site as fixed covariates.

13.4. Interim analysis and criteria for the premature termination of the trial

There is no planned interim analysis.

13.5. Participant analysis population(s)

Statistical analysis will be undertaken once the final group of participants has completed the final assessment, and the database is locked.

13.6. Procedure(s) to account for missing or spurious data

Reasons for being unable to collect data during an assessment will be recorded on the electronic CRF, where appropriate. CRFs will be assessed for missing data by PenCTU and sites will be regularly chased for missing data. PenCTU will maintain a record of site compliance with CRF completion. If data completion is poor, a monitoring visit may be scheduled (See Section 19 Monitoring, Audit and Inspection).

The CRFs will include mandatory fields; if a form is saved without these fields being completed an automatic flag will be displayed to the user. Where questions may need to be left blank, options such as 'Not applicable' or 'Prefer not to say' will be available, to differentiate these from missing data. Validations will be written into the REDCap database, to raise queries with particular data field, such as flagging if the date of a visit does not correspond to the correct timepoint.

The PenCTU data manager will write a series of R scripts[51] to perform the following data tasks to aid data completeness, including checking overall completeness by field of all CRFs, checking all visits have been recorded in a logical order. The scripts will be run on a regular basis and any concerns will be raised individually with sites.

Outcome-specific published guidance will be used to carry out imputation of missing data. In the absence of such guidance, data will not be imputed. Sensitivities of all treatment effect estimates to missing outcome data will be explored.

14. DATA MANAGEMENT

Data management activities are summarised in this section. Detailed data management activities are described in a separate data management plan (DMP).

14.1. Data collection tools

A REDCap database[50] will be used to collect participant screening and outcome data. It will be a web-based, fully validated system, compliant with MHRA guidance and ALCOA+ (Attributable, Legible, Contemporaneous, Original, Accurate, Complete, Consistent, Enduring, Available) principles. Data will be captured in accordance with the best principles of clinical data management and the relevant standard operating procedures on Clinical Data Management System Specification and Validation. PenCTU will be responsible for the database build and system validation. Inbuilt validation features will be utilised alongside post-entry monitoring, performed using validated R scripts to ensure data quality and completeness.

Data will be hosted externally by ARO on Microsoft Azure datacentres located within the UK (Liverpool, England). ARO are NHS Data Security and Protection Toolkit compliant and hold ISO27001 and Cyber Essentials Plus certifications. Microsoft Azure datacentres are Service Organisation Control (SOC) type 1 and 2 compliant. Data will be stored on hardware dedicated to PenCTU's instance of REDCap. All electronic data are regularly backed up and stored with a full audit trail. The electronic data capture forms and configuration of REDCap will be managed by PenCTU's information systems team. Requisite permissions and training required for data collection at any sites

will be provided by PenCTU. Data Protection Impact Assessments, Data Sharing Agreements will be developed where appropriate.

Audio data from qualitative interviews will be recorded either via Microsoft Teams or Zoom or using an encrypted digital audio recorder. Data collected using both Microsoft Teams and encrypted digital recorders will be stored on Microsoft SharePoint on the University of Plymouth's secure server using the participant's unique study number. All data will be deleted from digital recorders as soon as it is securely transferred. Audio recordings and transcribed data will only be accessible to the designated members of the qualitative evaluation team.

Transcription of audio recordings of interviews or sessions will only be carried out by members of the research team or professional services with confidentiality agreements in place.

14.2. Source Data

Source data will include participants' medical records (e.g., for certain eligibility criteria and medical history), participant/consultee-completed documents (e.g. informed consent forms), worksheets provided by PenCTU and CRFs. In the context of clinical care, investigator site staff must ensure that details of a participant's participation in the study are recorded in the participant's health record. At a minimum, the participant's health record should be updated to include:

• Consent and eligibility for trial

• Dates of all study visits and follow ups

• Completion or discontinuation of trial

Source data should be compliant with ALCOA+ guidance. PenCTU will verify source data and source documents as stipulated in the trial monitoring plan (see Section 15.6 Trial Monitoring).

The participating site should keep a record of all participants and all original signed informed consent forms. Any paper forms completed by site staff or participants should be retained in the ISF.

The research team will ensure that the participant's identity is protected at every stage of their participation in the trial, according to the Caldicott principles. If any patient information needs to be sent to a third party the trial team will adhere to maintaining pseudo-anonymous participant parameters in correspondence.

Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit project-related monitoring, audits and inspections. The sponsor operates a risk-based monitoring and audit program to which this study will be subject. All members of the local research team will have access to participant data during the study. Access will also be permitted to other National Health Service professionals and University staff, who are bound by the same duties of confidentiality; this will be detailed in the participant consent documentation.

14.3. Archiving

Following submission of the end of trial report, the Sponsor will be responsible for archiving the study data and TMF in a secure location for at least ten years after the end of the study. End of study is defined as completion of project closure report or publishing of final articles. PenCTU will prepare the TMF for archiving in accordance with the requirements of the University of Plymouth's Research Data Policy (Research Data Policy (libguides.com)). PenCTU will prepare a copy of the final dataset for

archiving according to the requirements of their SOP, as well as copies of all electronic source data files.

Principal investigators at sites will be responsible for archiving ISFs according to local policy. No study-related records should be destroyed unless or until the Sponsor gives authorisation to do so. Medical records containing source data or other study related information should be labelled, physically or electronically, to ensure retention until the Sponsor gives authorisation to destroy, e.g., "Keep until dd/mm/yyyy" where the date given is ten years after the last participant's data is entered).

15. MONITORING, AUDIT & INSPECTION

16.1 Study Monitoring

In accordance with PenCTU standard operating procedures for risk assessment and monitoring, a specific monitoring plan will be generated by the PenCTU, based on the PenCTU's risk assessment, with input from the SMG. The monitoring plan will be signed off by the CI and Sponsor prior to implementation.

PenCTU will perform ongoing central monitoring, outputs from which will be discussed by the SMG. Central monitoring will include close supervision of participant recruitment rates, attrition rates, data completeness (missing data), data quality (using range and consistency checks), protocol non-compliance, calendar checks (to identify deviations from participants' visit schedules), consent process checks (through collection of completed consent forms) and appropriateness of delegated duties at investigator sites (through collection of site delegation logs).

Central monitoring will be used to identify areas of potential poor performance at individual investigator sites. Poor performance at sites may trigger on-site monitoring visits, hosted by the investigator site PI and relevant members of the PI's team. On-site monitoring (if applicable) will be conducted by university staff according to established PenCTU SOPs.

Identification/recruitment Performance at each site will be closely monitored by the SMG.

16.2 Audit

Independent audits may be conducted by the Study Sponsor, funder, or regulatory bodies. Site PIs, the CI and CTU will permit access to all records required by auditors to fulfil their audit duties.

16. Public and Patient Involvement

A Patient Advisory Group (PAG) consisting of 4-5 parents and carers of people with DS, LGS or TSC has been formed to provide input into the research. PAG members have been sourced through Dravet UK and Cornwall Intellectual Disability Equitable Research (CIDER). The PAG met during study set-up and design to provide input on the acceptability of outcome measures, participant pathway and participant and consultee facing documentation. The PAG will meet every 6-months during the study period to review study progress and provide advice on ways to improve retention and recruitment, if needed. The PAG will have input during dissemination of results and help produce a lay summary of study results and advise on methods to disseminate the results to the wider public.

17. ETHICAL AND REGULATORY CONSIDERATIONS

17.1. Research Ethics Committee (REC) review

Before the study begins recruitment, the CI will obtain approval from the UK Health Research Authority (HRA) and favourable opinion from the Research Ethics Committee (REC) for the trial protocol, informed consent form and other study documentation (e.g., patient information sheet, consultee declaration form).

Substantial amendments will not be implemented before review and acceptance by the REC and HRA, as applicable. NHS Research and Development (R&D) departments have up to 35 days after HRA approval to decide whether they can implement the substantial amendment in practice at sites. It is the sponsor's responsibility to decide whether an amendment is substantial or non-substantial.

The CI will ensure that the study is conducted in full conformity with relevant regulations and with the UK Policy Framework for Health and Social Care Research (2017), which have their basis in the Declaration of Helsinki.

All correspondence with the REC will be retained in the TMF. The CI will notify the REC at the end of the trial, and if the trial is ended prematurely, including the reasons for the premature termination. Within one year after the end of the trial, the CI will submit a final report with the results, including any publications/abstracts to the REC.

17.2. Peer review

The project is funded by Jazz Pharmaceuticals who provided peer review.

17.3. Regulatory Compliance

The study will be conducted in accordance with the current approved protocol, ICH-GCP, relevant regulations, and standard operating procedures. The Research will not commence until all regulatory approvals are in place, NHS confirmation of Capacity and Capability, and Sponsor Green Light are given. The University of Plymouth operate a risk-based audit programme to which this study will be subject.

The study will not commence until a favourable REC opinion and HRA approval have been obtained. Before any site can enrol patients into the study, the CI/PI or designee will ensure that appropriate approvals from participating organisations are in place. For any amendment to the study, the CI or designee, in agreement with the Sponsor, will submit information to the appropriate body for them to issue approval for the amendment. The CI or designee will work with sites (R&D departments at NHS sites as well as the study delivery team) so they can put the necessary arrangements in place to implement the amendment to confirm their support for the study as amended.

17.4. Protocol compliance

Non-compliance with the protocol will be captured on specific non-compliance report forms according to instructions provided by the PenCTU and in accordance with PenCTU standard operating procedures. Protocol non-compliance will be reviewed periodically by the SMG as part of central monitoring, with the aim of identifying and addressing recurrent episodes of non-compliance. Each reported non-compliance is reviewed by the PenCTU trial manager. PenCTU staff must immediately inform the PenCTU quality assurance (QA) Manager if they believe that a serious breach has occurred (see below). Where the trial manager and/or QA manager believes that a non-compliance might

constitute a serious breach, the trial manager should ensure that a completed non-compliance report form is provided to the Sponsor immediately.

17.5. Notification of Serious Breaches to GCP and/or the protocol

A “serious breach” is a breach which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the participants of the trial; or
(b) the scientific value of the trial

Where a non-compliance meets the above criteria, PenCTU will immediately notify the CI and Sponsor. The Sponsor (or delegate) will email a serious breach report to the REC and to the HRA (using the breaches.nrec@nhs.net email address) within seven days of becoming aware of the event.

17.6. Data protection and patient confidentiality

All investigators and participating site staff must comply with the requirements of the UK Data Protection Act 2018 and the UK General Data Protection Regulation (GDPR) with regards to the collection, storage, processing and disclosure of personal information and will uphold the Act and regulation’s core principles.

Data will be collected and retained in accordance with the UK Data Protection Act 2018 and GDPR. The trial Sponsor is the Data Controller for the trial data. PenCTU is a Data Processor, centrally managing trial data generated at investigator sites. The University of Plymouth is the data custodian since data are stored on databases managed by the University of Plymouth.

Investigator site staff will ensure that the participants’ anonymity is maintained through protective and secure handling and storage of patient information in accordance with ethics approval.

Any paper-based data collection tools (e.g., worksheets and questionnaires) for capturing source data will remain at investigator sites. Investigator site staff will enter participant data into purpose designed data capture systems. Access to the system for all users (including PenCTU staff) is *via* a secure password-protected web-interface, with two-factor authentication. Each participant will be allocated a unique system-generated study number which will be related to site and recruitment number e.g., 01001. Participants will be identified in all trial-related documentation by their study number. Data collected and analysed during the trial will be pseudonymised by the use of this unique identifier. A record of trial participants’ names and contact details and assigned trial numbers will be stored securely in a locked room at the trial site and is the responsibility of the site PI.

17.7. Financial and other competing interests

At the time of protocol writing, the CI and PIs have no competing interests, financial or otherwise that may influence the design, management or reporting of the results for this study.

17.8. Indemnity

This is a University of Plymouth sponsored study. The University has in force a Public Liability Policy (see Zurich Municipal Insurance Policy), which is renewed annually on a rolling basis.

17.9. Amendments

If changes to the study are required, these must be discussed with the Sponsor, who is responsible for deciding if an amendment is required and if it should be deemed substantial or non-substantial.

Substantial amendments will be submitted to the relevant regulatory bodies (REC and HRA) for review and approval. The amendments will only be implemented after approval from the HRA, once they have received a favourable opinion from REC. Non-substantial amendments submitted to the HRA for their approval/ acknowledgements will not be implemented until all relevant approvals are in place.

Amended documents will be allocated a new sequential version number. Once approved by the REC, the version will supersede any previous versions.

17.10. Post trial care

This is an observational study with no intervention or change to usual care. Participants will continue to receive their usual care after the study is completed.

17.11. Access to the final study dataset

During the study, the PenCTU data team will have access to the study dataset. Other members of PenCTU and the wider study team will have restricted access to pseudonymised trial data. Access to the dataset will be granted to the Sponsor and host institution on request, to permit trial-related monitoring, audits, and inspections. Access will be overseen by the PenCTU Data Manager and Trial Manager. Access to the final dataset, and any interim datasets required, will be provided to the trial statisticians for analysis.

After the trial has been reported, the deidentified individual participant data that underlie the results will be available on request from the CI and Sponsor, along with supplementary files as required (e.g., data dictionaries, analysis code, etc.). Data will be shared with (or access to the data will be provided to) requesters whose proposed use of the data has been approved by the CI and Sponsor, under an appropriate data sharing agreement. It will not be possible to identify participants personally from any information shared.

18. DISSEMINIATION POLICY

18.1. Dissemination policy

The data arising from the study will be owned by the Sponsor. On completion of the study, the data will be analysed and tabulated, and a Final Report prepared. This report will be submitted to the Sponsor and Funder and will be accessed on request by contacting PenCTU. Participating investigators will not have rights to publish any of the study data without the permission of the CI and Sponsor.

The study will be reported in a manuscript that will be submitted to a peer-reviewed medical journal as open access. The trial will be reported in accordance with relevant Consort Guidelines. All publications arising from this trial will acknowledge the Funder and a copy of all manuscripts will be provided to the Funder for review at the time of submission to a journal. However, the Funder does not have the right to revise any submission prior to publication. The trial protocol will also be submitted for open access publication to a peer-reviewed journal. A lay summary of the trial results will be produced and published on the CANABID-LD PenCTU / University of Plymouth website. During the informed

consent process, trial participants and/or their personal consultees will be given the option to receive a notification of the publishing of the final report via email instead of accessing via the website. An anonymised participant level dataset will be produced and held within PenCTU.

The results of this trial will be submitted to peer-reviewed journals for publication as soon as data analysis is completed. Participants will not be identified in any publications. PPI representatives involved in the trial will support the dissemination of the information into the public domain and to the participants involved in the trial, in an appropriate manner. The findings will be presented at relevant national and international conferences. Findings will also be presented at relevant ID organisations, including the Learning Disability National Professional Senate, The Challenging Behaviour Foundation, Speakup Self Advocacy, and Mencap. Findings may be disseminated and publicised through links with organisations with a large social media presence.

Social media will be used to disseminate updates throughout the study's progress. This may include (but is not limited to): when a participating site receives greenlight to begin recruitment, when participating sites have met their recruitment targets, and to share links to related publications. Patient identifiers will not be shared. 'X' (formerly Twitter) will be the primary platform for this mode of communication, and updates will be shared from the PenCTU's profile (@PenCTU).

Upon completion of the trial, an End of Trial report will be generated and submitted to REC within 12 months. As the funder for the trial, Jazz Pharmaceuticals will also be provided with a report of the trial, per their requirements.

18.2. Authorship eligibility guidelines and any intended use of professional writers

Authorship of all manuscripts relating to this study will be determined according to the International Committee of Medical Journal Editors criteria. All members of the SMG who have contributed to study design, management, analysis, and interpretation will be granted authorship of the Final Study Report. The CI will retain lead author status on the Final Study Report.

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