Clinical Protocol

Children's Health Queensland Hospital and Health Service

EPIDIOLEX® CAS: A Compassionate Access Scheme (CAS) of an investigational Purified Cannabidiol Oral Solution (Epidiolex®) in paediatric patients with severe refractory epilepsy

Protocol Number: CAN-1

Protocol Version 2.0, 8 February 2017

(Based on Protocol Version 2, 2 August 2016 received from the Sydney Children's Hospital Network and updated for use in the Queensland CAS with permission.)

Revision Chronology:

Date of change	Summary of changes
08/02/2017	General updates throughout document

CONFIDENTIAL

CONTENTS

PROTOCOL SYNOPSIS

Title	EPIDIOLEX® CAS: A Compassionate Access Scheme (CAS) of an investigational Purified Cannabidiol Oral Solution (Epidiolex®) in paediatric patients with severe refractory epilepsy
Objectives	The objective is to delineate a protocol for the provision and safety monitoring of a compassionate access scheme. CAN-1 is not a clinical trial and therefore no clinical research questions are defined.
Design	A compassionate access scheme to provide an investigational product to a group of children with severe epilepsy.
Outcomes	Safety monitoring of adverse events and limited efficacy data
Study Duration	Until Epidiolex® is TGA registered in Australia or until no longer available
Interventions	Safety monitoring including regular scheduled clinical review and blood monitoring of adverse events
Number Of Participants	30 patient doses at any given point in time
Population	Children (2 to18 years of age) with intractable epilepsy not suitable for inclusion in a standard clinical trial. Because some patients are expected to discontinue use (e.g. condition worsens), the total number of patients to be treated under this CAS is unknown.

GLOSSARY OF ABBREVIATIONS

Abbreviation	Term
AE	Adverse Event
AED	Anti-epilepsy drug
AP	Authorised Prescriber
CAS	Compassionate Access Scheme
CBD	Cannabidiol
CHQHHS	Children's Health Queensland Hospital and Health Service
HREC	Human Research Ethics Committee
MoU	Memorandum of Understanding
PISCF	Patient Information Sheet Consent Form
PO	CHQHHS Clinical Cannabis Project Office

1. ADMINISTRATIVE INFORMATION

1.1. Sponsor

Study Sponsor	Children's Health Queensland Hospital and Health Service
Contact name	Dr Geoff Wallace, Director Neurosciences Department
Address	501 Stanley Street, South Brisbane, QLD, 4101

1.2. Expected duration

Until Epidiolex® is TGA registered in Australia or until no longer available.

1.3. Contributorship

Name	Summary of Contribution
[redacted]	Primary Author
[redacted]	Author

2. INTRODUCTION

2.1. Background and rationale

Epidiolex® is expected to become the first pharmaceutical-grade (e.g.: GMP manufactured) cannabis product made available in Australia for the treatment of refractory paediatric epilepsy. Due to the age and co-morbid health issues of this patient population, pharmaceutical-grade rather than uncontrolled "street" or "food-grade" products are necessary to ensure and provide the necessary consistency and strength.

Though currently an unapproved product, both locally and internationally, Epidiolex® is currently undergoing Phase 3 trials in the treatment of Lennox-Gastaut, Dravet Syndromes and Tuberous Sclerosis syndromes around the world. These trials are expected to be completed in 2016, with NDA submission to follow soon after. In addition, there is an emerging body of both pre-clinical and clinical safety data; the latter predominantly from Expanded Access Programmes and open-labelled studies.

There has not been any randomised placebo controlled clinical trials performed to date that involve giving Epidiolex® to children under 2 year of age. One open-labelled interventional

trial enrolling 214 participants from age 1 to 65 years with severe epilepsy have received CBD oral solution (Epidiolex®), however, this has not been within a formal clinical study (there was no placebo or 'dummy' treatment). On average, monthly seizure frequency was reduced by approximately a third (36%) in this group (Devinsky et al, 2015).[1]

The supply of Epidiolex® for a series of clinical activities was negotiated between the Queensland Government and the manufacturer, GW Pharmaceuticals. These activities were formalised in a Memorandum of Understanding (MoU); one of these being a Compassionate Access Scheme (CAS) enabling access to Epidiolex® for up to 30 patients at any one time. This treatment option is provided to children who suffer from severe epilepsy and are unable to participate in clinical trials.

GW Pharmaceuticals intends to provide ongoing supply of Epidiolex® in accordance with this protocol and related agreements until such time that the Australian Therapeutic Goods Administration (TGA) approves a marketing authorisation application for the product, (e.g. Epidiolex® is placed on the Australian Register of Therapeutic Goods) or until the product is no longer available.

2.2. Aim(s)

Primary Aim

1) To prescribe Epidiolex® as an anticonvulsant for a group of 30 eligible children (2 to18 years) at any one time with severe refractory epilepsy.

Secondary Aim

2) To provide paediatric neurologists with the experience of prescribing and managing Epidiolex®.

3. OBJECTIVES

CAN-1 is not a clinical trial and therefore no clinical research questions are defined.

The objective is to delineate a protocol for the provision and safety monitoring of a compassionate access scheme. The scope of data collected is the same as in other GW Pharmaceuticals Epidiolex® Expanded Access Programs around the world. A secondary purpose of the data collection is to allow evaluation of the safety data in an Australian population.

[1] Devinsky, O, et al. 2015. 'Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial', *The Lancet Neurology*, vol. 15, no. 3, pp. 270-278.

4. DESIGN

4.1 Type

CAN-1 is a Compassionate Access Scheme designed to provide access to Epidiolex® to a maximum of 30 eligible paediatric patients (at any one time).

Epidiolex® will be prescribed by physicians endorsed by the TGA under the Authorised Prescriber scheme. Paediatric neurologists with an appointment at any QLD Public Health Organisation are invited by the CHQHHS Clinical Cannabis Project Office (PO) to submit an application to participate in CAN-1. The PO will assist the clinician where they meet the criteria prescribed in this protocol to obtain Authorised Prescriber status via the required application to their institutional HREC and then to the TGA.

Due to the limited supply of Epidiolex® at any given time, approval of an AP does not necessarily guarantee the inclusion of their patients in the CAS, but rather enables them to make application to the PO for consideration of eligibility. Further information concerning inclusion on the CAS is provided at Section 5.2.1 below.

Application to the PO will be made after the AP/Paediatric Neurologist contacts the patient and obtains verbal consent to release certain health information to the PO. This de-identified information, linked to the patient's file via unique identifier, will be used by the PO to rank the patient and determine suitability for inclusion in the CAS. Consent will be noted in the patient's file.

If the PO approves a request, the AP will be notified at which time they would schedule a screening visit with patient/parent. During this visit, the AP will review the Patient Information Sheet and Informed Consent Form (PISCF) with the patient/parent and address any questions. If the patient/parent voluntarily consents, the patient's eligibility will be reviewed, and if confirmed eligible, would be provided an initial prescription for up to 3 months of Epidiolex®. A site based coordinator will be scheduled to facilitate during this enrolment process.

Upon review of a successfully completed informed consent form, the PO will provide the appropriate hospital pharmacy with the patient's unique identifier or authorization code, DOB and AP name. This information will also be present on the script. The pharmacy will only dispense the product once the unique identifier, DOB, and informed consent have been confirmed by the PO.

PO personnel will be available to Authorised Prescribers to assist in recruitment, screening, baseline and monthly telephone review and quarterly clinical visits. As well, the Project Office will be available to provide educational and logistical support to the APs so long as the CAS is in effect.

4.2 Sites

- Lady Cilento Children's Hospital

4.3 Education of Authorised Prescribers

All APs will be required to attend an educational session facilitated by the PO ahead of prescribing Epidiolex®. This education session will cover:

- The responsibilities and obligations of the AP
- The recruitment process, including key eligibility criteria and the informed consent procedure.
- Mandatory safety reporting
- Patient monitoring, data collection and reporting.

Attendance will be recorded in a training log.

5. PARTICIPANTS AND RECRUITMENT

5.1 Number of Participants

A maximum of thirty (30) patients may access this product at any given time. With replacements possible, the total sample size is unknown.

5.2 Eligibility Criteria

Participants will be assessed initially by the Authorised Prescriber for eligibility using a set of predetermined objective criteria as defined in Section 5.2.1 below. Where the patient meets the inclusion criteria, and does not meet the exclusion criteria, their suitability to receive product is based on their ranking against all other applicants based on the total number of non-elective, epilepsy-related hospital admissions in 2016. A second tier of ranking based on younger patients having higher priority may be required.

5.2.1 Inclusion Criteria

Potential patients for inclusion on the CAS must meet ALL of the following:

• Have a clinical diagnosis of severe, intractable childhood epilepsy.
• Be 2 to18 years of age at the time of consent.
• Experience seizures at least daily for the past six months.
• Have had at least one non-elective epilepsy related hospital admission during 2016. This does not include elective admissions such as epilepsy related investigations or initiation of the ketogenic diet.
• Failure of a clinical trial of at least five anti-convulsant drugs, including one trial of a

combination of two drugs. Vagal nerve stimulation, epilepsy surgery, deep brain stimulation, or ketogenic diet are considered equivalent to a trial of an anti-convulsant drug for the purpose of this inclusion criteria.

• Attempted and failed[2] an appropriate anticonvulsant where specifically indicated for genetic epilepsy syndromes (e.g. Stiripentol in Dravet syndrome, Vigabatrin for TSC, etc.)

• The dominant seizure type being uncountable, i.e. not suitable for a typical randomized clinical anti-convulsant trial; for example, atypical absence, non-convulsive status, multiple tonic seizure cluster, large number of daily seizures

• Being administered between 1 and 4 baseline anti-epileptic drugs at stable doses for a minimum of 4 weeks prior to enrolment. Vagus nerve stimulator (VNS) and ketogenic diet do not count toward this limit.

• Verbal consent to have certain health information used in determining patient suitability to participate in the CAS.

• Written informed consent obtained from the patient or the patient's parent/guardian.

• Parental/guardian compliance to CAS monitoring requirements including regular blood testing and safety data collection and storage.

5.2.2 Exclusion criteria

Patients who meet any of the following criteria are not eligible for participation:

• Pre-existing abnormalities of complete blood count, electrolytes, coagulation, hepatic function or enzymes that are considered clinically significant as judged by the Authorised Prescriber (e.g. WBC < 4, Platelets < 60000, ANC < 1.5, ALT or AST > 2 times upper limit of normal)

• Clinically significant ECG abnormalities (e.g. QTc > 460 msec, PR > 0.2 sec, QRS > 0.1 sec)

• Have a terminal illness, with life expectancy not longer than 3 months.

• Use of any cannabis-related product in the month prior to consent

• Female subjects who are pregnant will be excluded. Cannabidiol is contraindicated in pregnancy. If a female subject is able to become pregnant, she will require a negative serum pregnancy test before entry into the scheme. Female subjects will be informed not to become pregnant while taking cannabidiol. Female subjects must inform the investigator and consult an obstetrician or maternal-fetal specialist if they become pregnant during the study.

• Known allergy to CBD or any cannabinoid or any component of Epidiolex®.

5.3 Identification of potential participants

To identify potential participants, the neurologist will review their patient records and, where they believe the patient meets eligibility criteria, contact the patient and seek verbal consent to provide DOB and number of 2016 hospitalisations to the PO for the purposes of

[2] "failed to respond" is defined as either partial or full failed response to anticonvulsant medication

prescreening. Where obtained, consent will be documented in the patient's medical record.

The initial recruitment of patients will be staged over six months and will be ongoing with 30 patients being eligible at any one time.

A registry of eligible patients will be established and held by the PO and used to determine which patients are invited for a screening visit and which remain on the waiting list. This process is ongoing, in that additional, eligible patients can be notified to the PO at any time.

5.4 Consent

Consent will involve a two-step process. Initially, verbal consent will be obtained prior to forwarding DOB and number of hospital admissions to the PO. (See Section 5.3). Consent will be recorded in the patient file.

Patients who are objectively deemed suitable for inclusion in the CAS, will be invited for a screening visit. At this meeting and before any CAS procedures are conducted, patients will be provided with a Patient Information Sheet and asked to provide their consent for screening as well as, if deemed eligible, for the purpose of ongoing monitoring and data collection activities. (PISCF, Appendix 1).

Given the age and the severe medical condition of patients, a parent or legal guardian will be required to provide written consent on their behalf. The AP will countersign the consent form acknowledging the information that has been discussed. The patient will be given a copy of the PISCF to retain and a copy kept of the patient's medical records.

5.5 Dispensing process

The Epidiolex® product will be dispensed only by pharmacies within QH facilities, including:

- Lady Cilento Children's Hospital

Dosing Guidelines may be reviewed with the patient and caregiver by the hospital pharmacy (Appendix 2).

The PO will provide the appropriate pharmacy the list of unique identifiers, corresponding DOBs and name of the Authorised Prescriber for each patient enrolled in the CAS. The pharmacies will crosscheck this information with that provided on the prescription. Only if the information matches may the product be dispensed.

Hospital pharmacies will dispense the prescription directly to the patient, the patient's parent or guardian, or authorised recipient. The product may not be couriered to a local pharmacy for dispensing.

6. INTERVENTION

6.1 Product Information

Trade name: Epidiolex®

6.1.1 Route of administration and dosage

Route of administration:

Epidiolex® oral solution 100 mg/ml will be administered orally or via peg tube.

Dose / titration schedule:

Initiation of treatment will begin with 5 mg/kg/day CBD given in two divided doses. The dose will be increased by 5 mg/kg/day at a minimum of every seven days up to a maximum dose of 25 mg/kg/day given in two divided doses with the aim of arriving at an optimal dose with regards to safety and tolerability.

Doses of concomitant antiepileptic drugs may be altered and recorded during this study if necessary.

6.1.2 Dose modification

The Authorised Prescriber has the discretion to modify the dose within the parameters of the schedule above. This means if there is efficacy demonstrated the dose does not need to be increased. Conversely if side effects emerge such as drowsiness, reducing either Epidiolex® or concomitant medications is acceptable as per the Authorised Prescriber's usual practice.

Doses greater than the recommended 25mg/kg/day are not to be used. Any further escalation

in dose would require a protocol amendment following agreement between GW Pharmaceuticals and CHQHHS.

6.1.3 Preparation and administration of study drug

The patient or parent/guardian, via plastic syringe, administers Epidiolex® orally (see Appendix 2) or via peg tubing (see Appendix 7). The AP and/or Pharmacist may assist in selecting the appropriate size syringe for giving the patient's dose regime, if needed.

Syringes can be used more than once but care should be taken that the syringe is completely dry prior to placing it into the bottle. Moisture may cause the solution to turn cloudy.

The product shelf life is 18 months. The expiry date is provided on the label. Once opened the product may be used for no more than 28 days, after which any remaining amount must be discarded.

Do not store product above 30°C. Do not refrigerate or freeze. Keep away from heat and direct sunlight.

See Appendix 2 for Dosing Instructions.

6.1.4 Dispensing and product accountability

At the inception of the CAS, the PO will review the expected demand and ensure adequate stock is available at each participating hospital pharmacy. Product is ordered (from the depot) by Head of Hospital Pharmacy or delegate. The depot keeps a delegations log of persons authorised to place an order.

The pharmacy will receive from the project office the names of all Authorised Prescribers as well as eligible patient's DOB and identifier. In order to dispense the product, the pharmacist must review & confirm the script, which will include the AP's name, patient's DOB and associated identifier.

The Pharmacy will maintain accurate records of the date and amount of product received from the depot, and what has been dispensed. The PO is authorised to request an Epidiolex® stock reconciliation from the pharmacy at any time.

Patients are asked to return the product to the pharmacy where the product was dispensed if any drug is remaining after 28 days of opening bottle, where it will be disposed.

6.1.5 Excluded medications and treatments

The participant is not eligible if a cannabinoid has been used in the month prior to consent. There are no other excluded medications.

Patients are advised not to take any cannabis-related products in conjunction with Epidiolex® as this may create a risk of inappropriate and uncontrolled dosing of cannabinoids. No more than 4 anticonvulsant medications in total are allowed to be concurrently prescribed as per the eligibility criteria.

In vitro, CBD is an inducer and inhibitor of selected liver enzymes CYP450 and UGT. Whether in vivo there is a clinical consequence of this is still under investigation. It is advised that careful titration of CBD be undertaken in those patients taking concomitant medications metabolised by these liver enzymes. Ongoing phase 3 studies are addressing this question directly.

7. CAS VISITS AND PROCEDURES

Once enrolled, participants are required to comply with monitoring requirements that take place both on a routine schedule and during unscheduled visits.

If under uncontrolled circumstances the participant is unable to perform a physical visit to the institution to complete a procedure outlined in the protocol (e.g. blood test), the institution can request a waiver and upon approval by the PO have the procedures completed at a local site. This does not mean that Epidiolex® can be dispensed at the local site. Epidiolex® can only be dispensed by an approved AP pharmacy and only by a pharmacist delegated to dispense Epidiolex®.

The following data will be collected during monitoring:

- Seizure types
- Seizure Intensity or duration (week 4 onwards):
- “Increased” (I) or “Decreased” (D) or No change (N)
- Body Weight
- Seizure Types
- Number of:
    - Days Rescue Medication was Used (in last 28 days)
    - Episodes of Status Epilepticus (SE) in the last 28 days, both convulsive and non-convulsive
    - Emergency Room (ER) visits in the last 28 days
    - Hospitalisations in the last 28 days
- Epidiolex® and Concomitant AEDs:
    - Dose
    - Plasma level (AED only)
- Biochemistry and Full Blood Count (FBC)
    - Na+
    - K+

- Cl-
- HCO3
- BUN
- Creatinine
- RBC
- HCT
- HGB
- MCV
- MHC
- MCHC
- WBC and differential
- Platelets

- Liver Function Tests (LFT)
  - AST
  - ALT
  - Albumin
  - Total bilirubin
  - Gamma-glutamyl transferase (GGT)
  - Alkaline phosphatase (AP)
  - INR

For any clinically significant (> 3 x ULN) elevation of ALT or AST in patients being treated with Epidiolex®, the following laboratory measures, at minimum, should be assessed within 72 hours: repeat ALT/AST, total bilirubin, alkaline phosphatase, and GGT.

All CAS participants with elevated LFTs should be followed until all abnormalities return to the baseline state as assessed by the AP with AST/ALT < 3X ULN. Please refer to section 7.8.1 for LFT abnormality criteria as a reason for withdrawal from the study.

- 24 hour Video EEG
- Serum Pregnancy Test (in all females of reproductive age)
- ECG
- Global Impression of Change (measured by patient/parent, and separately physician)
- Adverse Events
  - Diagnosis, syndrome, signs, symptoms
  - Severity
  - Plausible relationship to CAS medication
  - Action taken with CAS medication
  - Other action taken (if any)
  - Outcome
  - Serious adverse event (if yes, then reason for seriousness)
  - Start and Stop date

- Duration if <24hrs
- Epidiolex® dose

7.1 Monitoring Schedule

Data will be collected at Screening, Baseline, Monthly Phone follow up, Quarterly visits, Withdrawal visit, Unscheduled visits, Participant withdrawal and at CAS closure and the detailed below. See Appendix 3 for a complete Monitoring Schedule.

7.2 Screening

The purpose of the screening visit is to determine patient eligibility. Completing the Participant Informed Consent process is required before initiating screening activities with the patient.

- Obtain and document consent from potential participant.
- Review medical history to determine eligibility based on inclusion/exclusion criteria.
- Review medications history to determine eligibility based on inclusion/exclusion criteria.
- Perform serum pregnancy test in females of reproductive age.
- Perform blood investigations to ensure meets eligibility criteria.

7.3 Baseline

Relevant information collected during the patient consent process and screening may be used in baseline monitoring, provided the patient completes all processes in the same visit. Female patients of child-bearing age will be subject to a serum pregnancy test. Patients who are pregnant will be excluded.

7.4 Monthly Phone Follow-up

Monitoring activities may be conducted via phone at 4 weeks and 8 weeks after the baseline, or quarterly in-person visits. A study coordinator will make the calls and record the relevant information. Section 9, Data Management, describes the recording and management requirements for this information.

7.5 Quarterly visit

The AP will schedule quarterly visits with the patients and invite the project office staff to participate. The first visit will be 3 months (+/- 2 week window) from baseline.

7.6 Withdrawal visit

A patient may withdraw at any time. In this case the patient will be assessed for FBC, EUC, LFT, AED plasma levels, and ECG. Reason for withdrawal will be recorded. CBD is recommended to be tapered at 10%/day until completely off of drug.

7.7 Unscheduled visit

The AP is required to notify the project office if there is an unscheduled visit. Details of the reason for the visit, any adverse events, and blood tests would need to be documented and forwarded to the project office. If the visit is due to an Adverse Event or a Serious Adverse Event, then all procedures described in Section 8, Adverse Events and Risks, will be followed.

At a minimum, weight & height, FBC, EUC, LFT, AED plasma levels will be measured and recorded.

7.8 Participant Withdrawal

7.8.1 Reasons for withdrawal

Patients are free to withdraw from the study at any time upon their request or the request of their legally acceptable representative. Withdrawing from the study will not affect their access to standard treatment or their relationship with the hospital and affiliated health care professionals.

The patient must be withdrawn from the CAS if any of the following events occur:

• The patient experiences an Adverse Event or Serious Adverse Event which in the opinion of the AP would compromise the continued safe participation of the patient in the CAS
• Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria
• The patient becomes pregnant, as evidenced via a positive pregnancy test
• The patient is unwilling or unable to continue, or the parent/legal representative is unwilling or unable to allow the patient to continue
• The AP decides that withdrawal is in the patient's best interests
• ALT or AST >8xULN
• ALT or AST >5xULN for more than 2 weeks
• ALT or AST >3xULN and (TBL >2xULN or INR >1.5)
• ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

All patients with elevated LFTs should be followed until all abnormalities return to the baseline state as assessed by the investigator with AST/ALT < 3X ULN.

The Authorised Prescriber may withdraw a patient from the CAS if the patient:

• Does not fulfil the monitoring requirements
• Shows an increase, or no measureable improvement, in seizure frequency and/or severity as assessed by the AP.

The Authorised Prescriber will also withdraw all participants if the CAS is terminated either

due to Epidiolex® being registered by the TGA, or in the event GW Pharmaceuticals ceases to supply product.

7.8.2 Handling of withdrawals and losses to follow-up

Suggested dosing schedule for withdrawal:

Although there is limited information, abrupt withdrawal of CBD has not been associated with any withdrawal-type symptoms. Because information is limited it is suggested that the dose be reduced by 10% each day until ceased. If a severe serious adverse event (SAE) occurs then the dose may need to be stopped immediately. Abrupt termination of CBD is not recommended, as there is a potential for status epilepticus or a marked deterioration in seizures. This is not a specific reported problem with CBD but a general principle that applies to anticonvulsant management.

When a patient withdraws from the CAS, they will need to complete their final monitoring, as per Section 7.7

7.8.3 Replacements

The AP will notify the PO of any withdrawals. The PO will determine the next patient in-line to be invited to participate, and contact their AP.

7.9 CAS Closure

The PO will notify the APs of any known or upcoming changes to the supply of Epidiolex®, including the submission of a registration application by GW Pharmaceuticals to the TGA. Patients participating in the CAS will be notified by their AP of expected CAS closure timeframes.

8. ADVERSE EVENTS AND RISKS

8.1 Definitions

Adverse Events

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Surgical procedures are not AEs; the reason for the surgical procedure is the AE. Elective

hospitalisations for pre-existing conditions are not considered as SAEs.

Adverse drug reaction (ADR)

For unapproved medicines: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions.

The phrase 'responses to a medicinal product' means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information

(e.g., Investigator's Brochure for an unapproved investigational product or Product information/Package Insert/Summary of Product Characteristics for an approved product)

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

• Results in death;
• Is life-threatening*;
• Requires in-patient hospitalisation or prolongation of existing hospitalisation;
• Results in persistent or significant disability/incapacity; or
• Is a congenital anomaly/birth defect
• Is medically significant**.

*Note: the term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Medical and scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations. Important medical events may not be immediately life threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias, prolonged status epilepticus events or the development of drug dependency.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is any SAE that is both suspected to be related to the investigational product and is unexpected (i.e. not consistent with applicable product information - the Development Core Safety Information section of the Investigator Brochure).

8.2 Assessment and documentation of adverse events

For the purposes of the CAS the Authorised Prescriber is responsible for the recording of all Adverse Events, regardless of their relationship to study drug, with the following exceptions:

• Conditions that are present at screening and do not deteriorate will not be considered adverse events.

• Abnormal laboratory values will not be considered adverse events unless deemed clinically significant by the investigator and documented as such.

AEs will be reviewed for each patient at their scheduled visit and during unscheduled visits including phone calls from patients/parents and relevant health professionals. During the visit the AP or Study Coordinator will collect the following information from the patient:

The description of each AE will include:

• A description of the AE (Diagnosis of Syndrome only [if known] or signs/symptoms);
• The date started, stopped, as well as duration if <24hrs;
• Epidiolex® total Daily Dose at Time of Event;
• Outcome (recovered, recovered with sequelae, continuing, death);
• Severity (mild, moderate or severe);
• Plausible relationship to medication (Yes/No);
• Any action taken, (e.g. treatment, follow-up tests);
• Is it an SAE? If yes, reason.

Where required information is unavailable during the visit, a follow-up will be made by the AP as soon as practicable to complete the AE record.

If the AE is determined to be an SAE, then the AP will inform the relevant parties as per Table 8.4 Serious Adverse Event Reporting including within the specified timeframes and reporting formats.

The AP or study coordinator will record all AEs in WebSpirit in real-time, or transcribed from hardcopy (see Appendix 3) on a monthly basis, as described in Section 9.1.2. If transcribed from hardcopy, then the hardcopy source documentation is kept in the patient's file.

An AP according to the definition in section 8.1 will assess the seriousness of an AE.

For ongoing fluctuations in the severity of an AE, the most severe assessment should be documented. AEs characterised as intermittent will be documented for each episode. All AEs will be followed to adequate resolution, where possible.

Causality assessment is required for all AEs and SAEs. Causality assessment must only be

assigned by the AP. All cases judged as having a reasonable suspected causal relationship to the Epidiolex® must be reported as such. The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

The following question which must be answered by the Physician for all AEs is used to capture the reasonable causal relationship of an event to the Epidiolex®:

"In your opinion is there a plausible relationship to the Epidiolex®?" The answer is "***yes***" or "***no***".

Where a pre-treatment event worsens in severity following the first dose of Epidiolex® a new event record should be entered into the records.

For all AEs and especially SAEs, it is important that the AP assesses not only the possible role of Epidiolex®, but also competing etiological factors as the underlying cause (which may include medical history, worsening of underlying condition / lack of efficacy, social or concomitant medication factors.

8.3 Eliciting adverse event information

Adverse events will be recorded from the time the patient signs the informed consent form until 30 days after the last dose of study medication. At every visit patients (or parents, legal guardians) will be asked "How have you (s/he) felt since your (their) last visit?" in order to elicit any medically related changes in their well-being. They will also be asked if they have been hospitalised, had any accidents, used any new medication or changed concomitant medication regimens. In addition, AEs will be documented from physical examination findings, clinically significant lab results or other documents that are relevant to patient safety.

8.4 Serious adverse event reporting

The AP is responsible for the reporting of SAEs according to the timelines and reporting requirements below, however, the PO will facilitate reporting once notified.

The AP will make an initial report within the specified timeframes, based on "first awareness" of the SAE, and follow-up as additional information becomes available until the SAE investigation is complete. All SAE submissions are signed/endorsed by the AP even where submitted by a delegate.

AP SAE Timelines and Reporting Requirements

Entity	Initial report within	Report format	Comment
Project Office	Immediately	(hardcopy) GW SAE Australia Form Appendix 4a	As per TGA, CHQHSS is "sponsor". As such CHQHSS reports fatal or life-threatening ADRs (SUSARS) to TGA on "ADRAC Blue Card" (Appendix 5) within 7 calendar days. Follow-up within 8 additional days. For all other serious and unexpected ADRs, (SUSARS) full report no later than 15 calendar days of first knowledge.
GW Pharmaceuticals	24 hours	(hardcopy) GW SAE Australia Form	Project office to facilitate, Requires AP's signature
HREC	72 hours	(online) CHQHHS-SAE form Appendix 4b	Project office to facilitate

Principal investigators at LCCH are responsible for expedited reporting of SUSARs that occur at their site to CHQHHS HREC and CHQHHS Research Governance Office. Expected suspected SAEs should be reported as soon as possible to the CHQHHS Research Governance Office.

The Chief Investigator will, on a six monthly basis, provide CHQHHS HREC an EU format report listing all SUSARs, Australian and International, for Epidiolex® and include any investigator and sponsor comment as to whether any actions are planned for the CAS.

8.5 Other required Adverse Event Reporting (non-SAE)

In addition to the SAE reporting described in Section 8.4, the AP is required to report the following safety information.

Type	Entity	Frequency/Timing	Report format	Comments
Any Adverse Drug Reaction	TGA	As promptly as possible, to reach TGA within 15 days	ADRAC blue card	PO to facilitate
Any AEs	GW Pharmaceuticals	Monthly	GW Pharmaceuticals supplied AE Tabulation	Project office to facilitate

Sponsor AE Reporting Requirements to Regulatory Authorities

Adverse events reporting, including suspected serious unexpected adverse reactions will be carried out in accordance with applicable local and government regulations.

9. DATA MANAGEMENT

9.1 Data Collection

The APs are responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. All source data will be dated and initialed by the AP prior to submission to the PO. The PO will maintain adequate records of participants, including routine monitoring data and source documentation.

9.1.1 Source Data

Table 9.1: Summary of Source and Secondary Data

Type	template	Source data format	Stored in Hospital CAS file (hardcopy)	Recorded in Excel spreadsheet	Time points	Comments
Informed consent	CAN-1: PISCF	hardcopy	yes	tick-box to verify completion	recruitment	
Lab results	n/a	PowerChart	yes	yes	Screening, monthly, quarterly, unscheduled	
Script	CAN-1: Script template	hardcopy	yes	yes	Initial, as needed	
AEs	CAN-1: AE report	Hardcopy	yes	yes	Monthly, as needed	
SAEs	GW SAE- Australia Form	Hardcopy	yes	yes	As needed	
	CHQHHS-HREC	On-line	yes	Only date of submission		
	ADRAC “blue card”	Hardcopy	yes	Only date of submission		
non-lab data	GW Pharmaceuticals monthly monitoring form	hardcopy	No (TBC)	yes	Screening, monthly, quarterly, unscheduled	

9.1.2 Data Capture and Storage

Data will be captured at the following time points:

- Recruitment
- Screening
- Baseline
- Monthly (phone) visit
- Scheduled quarterly visit
- Unscheduled visit
- AE/SAE
- Termination/Withdrawal/Closure

Patient data will be captured in paper (hardcopy) and electronic formats, as outlined in Table 9.1.

Hardcopy CAS Patient Files

Hardcopy hospital-based CAS patient files will store identified information such as the Patient Informed Consent. Access will be restricted to the local hospital study staff as indicated in the signature log and delegations log. Records are maintained in a restricted access area, under lock and key.

All hardcopy records are to be reviewed, date and initialed by the AP.

Electronic data

The dataset will be held on a password protected computer and password protected file. Participant information will be held separate to the main file and coded re-identifiable data will be held in separate Password protected file. The system is password protected with access levels (e.g. read only) assigned by the user. Participants' identifiable data will not be stored on the database. The database will house data collected including safety related (e.g. AE and SAE) and routine monitoring (e.g. lab results).

Local hospital based project office staff will enter data into the database. Where applicable, data will only be entered once the trial coordinator has reviewed and dated / initialed the hardcopy record. Data entry accuracy will be verified by a second authorised user who will make any needed corrections in real-time. Upon completion of verification, the hardcopy record is dated, initialed and marked "QC checked".

9.2 Record Retention

Note that data must be kept for at least 15 years after the completion of a clinical trial, or until the 25th birthday of the youngest participant, whichever is later, in accordance with the

requirements of the Therapeutic Goods Administration and Health Privacy Principals.

10. CAS OVERSIGHT

10.1 Governance structure

The Queensland Government via a Memorandum of Understanding with GW Pharmaceuticals (GW) has established the conduct of this CAS. Representatives from Queensland Health and GW Pharmaceuticals via an Advisory Committee provide oversight of the activities in the MoU, including this CAS.

The CHQHHS Neurodevelopmental Steering Committee will provide oversight on the progress of the CAS.

The Project Office will provide logistical support to the Authorised Prescribers, and updates to the Steering Committee and QLD/GW Pharmaceuticals Advisory Committee.

GW Pharmaceuticals will review safety data on the frequency established in Section 8, Adverse Events, as well as on a monthly basis during routine reporting.

10.2 Quality Control and Quality Assurance

In the first instance, local hospital Project Office Staff will ensure compliance to protocol requirements for patients under the AP's care. This will include completeness and accuracy of all documentation, hardcopy and electronic. (See Section 9 for further information.) Reviews of patient hardcopy files will be conducted on a monthly basis. Any issues will be taken directly to the AP. If unresolved, the Project Office manager will be notified.

The Project Office manager ensures that any issues raised are addressed in a timely manner. Issue resolution may involve additional training, contacting various internal/external stakeholders, or recommending protocol revisions.

Training of local hospital project staff and APs will be documented in a central log held by the PO. Training will include kick-off meetings and registries for acknowledgement of receipt of key documents (e.g.: investigator's brochure, protocol)

11. ETHICS AND DISSEMINATION

Approval of Authorised Prescribers will be made according to the TGA Guidance, Authorised Prescribers. CHQHHS-HREC is the central Ethics Committee for all Authorised Prescribers under the CAS. In the first instance, the Project Office will make a single submission on behalf of all Authorised Prescribers. Qualifying Authorised Prescribers are paediatric neurologists with an appointment at a Queensland public hospital.

Upon approval by CHQHHS-HREC, a subsequent submission will be made to the TGA. Initiation of this CAS will occur upon written approval from the TGA.

11.1 Modifications to the protocol

The CAS will be conducted in compliance with the current version of the protocol. Any change to the protocol document or PISCF that affects the CAS design (including maximum dose/kg), patient safety, or may affect a participants willingness to continue participation in the CAS is considered an amendment, and therefore will be written and filed as an amendment to this protocol and/or informed consent form. All such amendments will be submitted to the HREC and GW Pharmaceuticals, for approval prior to becoming effective.

11.2 Protocol Deviations

All protocol deviations must be recorded in the patient record (source document) and must be reported to the Project Office. The PO will assess protocol deviations for significance. Those deviations deemed to have a potential impact on the integrity of the CAS, patient safety or the ethical acceptability of the trial will be reported to the HREC, TGA and/or GW Pharmaceuticals (depending on the issue) in a timely manner. Where deviations to the protocol identify issues for protocol review, the protocol will be amended as per Section 11.2.

11.3 Confidentiality

Participant confidentiality is strictly held in trust by the participating APs, Project Office staff, their delegates, and the sponsoring institution. This confidentiality applies to the clinical information relating to participating participants.

All parties will ensure protection of participant personal data will not include participant names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. Participant names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by the PO in order to de identify the trial participant. In case of data transfer, the PO will maintain high standards of confidentiality and protection of participant personal data.

The CAS protocol, documentation, data and all other information generated will be held in strict confidence. No information concerning the CAS or data will be released to any unauthorised third party, without prior written approval of CHQHHS HREC and GW Pharmaceuticals.

Authorised representatives of the sponsoring institution may inspect all documents and records maintained by the AP, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the CAS participants. The participating hospitals will permit access to such records.

All laboratory data, reports, evaluation forms and other records that leave the site will be identified only by the unique identifier to maintain participant confidentiality.

Clinical information will not be released without written permission of the participant, except as necessary for monitoring by HREC or regulatory agencies.

11.4 Participant Reimbursement

No payments or stipends will be provided to the patient or parent. Epidiolex® will, however, be provided free of charge.

11.5 Financial Disclosure and Conflicts of Interest

None

11.6 Dissemination and translation plan

The safety and clinical data from the CAS may be presented at local, national or international clinical meetings or form the basis for submission of a scientific manuscript for publication to a peer-reviewed journal.

The primary responsibility for publication of the results of the CAS will fall with the PO.

12. APPENDICES

Appendix 1: Patient information Sheet/Informed Consent

Appendix 2: Instructions for Administration of Epidiolex®

Appendix 3: CAS Monitoring Schedule

Appendix 4a: GW SAE Form

Appendix 4b: CHQHHS SAE form

Appendix 5: TGA Blue Card: Suspected Adverse Reaction

Appendix 6: CAS Patient Withdrawal Form

Appendix 7: Administration of Epidiolex® vis Tube Feeding