**STUDY PROTOCOL**

**Valentius Observational Study (VOS):**

**Observation of Safety and Health-related Outcomes in Patients**

**Undergoing Medicinal Cannabis Therapy**

**INVESTIGATOR-INITIATED STUDY**

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**Study Number: 2024-05-0611**

**Document: VOS Study Protocol**

**Version Number: 2.0**

**Status: Tracked**

**Release Date: 01 July 2024**

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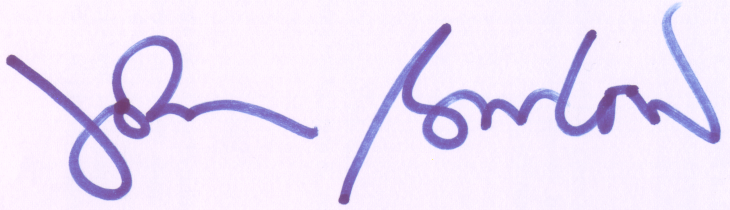
# Project Acknowledgement

By signing this Protocol, the Investigator acknowledges and agrees:

The Protocol contains all necessary details for conducting the project. The Investigator will conduct this study as detailed herein, in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements and will make every reasonable effort to complete the study within the time designated.

This document contains information that is privileged or confidential. As such, it will not be disclosed unless specific prior permission is granted in writing by the Investigators or such disclosure is required by federal or other laws or regulations. Persons to whom any of this information is to be disclosed must first be informed that the information is confidential. These restrictions on disclosure will apply equally to all future information supplied, which is indicated as privileged or confidential.

The Investigators will have access to any source documents from which Case Report Form information may have been generated. The Case Report Forms and other data pertinent to this study are the sole property of the Investigators (SCH Research), who may utilise the data in various ways, such as for submission to government or regulatory authorities or in publication of the results of the study.

****

**Signed:** Dr John W. Barlow, BSc, MSc, PhD

Principal Investigator

**Date:** 1 July 2024

# List of Abbreviations

|  |  |
| --- | --- |
| **Abbreviation** | **Definition** |
| **AE** | Adverse event |
| **APS** | Authorised Prescriber Scheme |
| **BPI** | Brief Pain Inventory |
| **CBD** | Cannabidiol |
| **CRF** | Case Report Form |
| **GCP** | Good Clinical Practice |
| **HREC** | Human Research Ethics Committee |
| **ICH** | International Conference on Harmonisation |
| **MS** | Multiple sclerosis |
| **MCID** | Minimum Clinically Important Difference |
| **NHMRC** | National Health and Medical Research Council |
| **PGIC** | Patient Global Impression Change |
| **PICF** | Participant Information Sheet and Consent Form |
| **PROMIS** | Patient-Reported Outcomes Measurement Information System |
| **PTSD** | Post-traumatic stress disorder |
| **SAS** | Special Access Scheme |
| **TGA** | Therapeutic Goods Administration |
| **THC** | Δ**-**9 Tetrahydrocannabinol |
| **TSQM** | Treatment Satisfaction Questionnaire Medication |
| **VOS** | Valentius Observational Study |
|  |  |

# Study Contacts

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**Site Location**

|  |  |
| --- | --- |
| **Clinic** | **Location** |
| **\*Valentius Clinic** | Level 5, 2 Barrack St Sydney 2000 |

# 

\*Note that all project direction, administration and data analysis will be conducted at the Valentius Clinic, Barrack Street, Sydney.

Patient data will be collected via telehealth consultations and stored securely in Valentus medical software as described in this protocol.

# Funding

This study is funded by SCH Research with commercial support in the form of data research grants from licensed medicinal cannabis product suppliers and manufacturers. These include but are not limited to:

Singe Estate Pty Ltd

Suite 7, 36 Morley Ave Rosebery,

Sydney NSW, 2018

Precision Pharmaceuticals Pty Ltd

7/30 Raubers Rd.

Banyo QLD 4011

# Protocol Summary

|  |  |
| --- | --- |
| **Title:** | Valentius Observational Study (VOS): Observation of safety and health-related outcomes in patients undergoing medicinal cannabis therapy |
| **Design** | Open-label, prospective observational cohort study |
| **Objectives:** | To monitor a range of self-reported outcome and experience measures in patients treated with medicinal cannabis for any medical condition that has had an inadequate response to conventional treatment approaches. |
| **Investigational Drug:** | Any medicinal cannabis product of defined formulation that is available to be prescribed through the TGA access schemes (SAS-B or APS) or via compounding prescription in Australia. |
| **Population:** | Approximately 3000 patients undergoing medicinal cannabis therapy within Valentius Clinic. Adults, aged 18 years and older |
| **Number of Sites:** | One site located at level 5, 2 Barrack St Sydney 2000 |
| **Study Duration:** | The entire study is expected to last 3 years |
| **Subject Participation Duration:** | It will take 12 months (including follow-up) to conduct the study for each participant |
| **Sponsor:** | SCH Research Pty Ltd |
| **Registration (ANZCTR):** | To be advised |

# 1. Purpose of Study

Treatment with medicinal cannabis remains controversial and healthcare providers and consumers need more information concerning both the positive and negative effects of medicinal cannabis products to better guide treatment decisions. This study will monitor a number of safety and health-related measures in patients undergoing medicinal cannabis treatment at Valentius that have been collected as routine standard of care. Analysing this information will give us a better understanding of the role of medicinal cannabis in treating conditions that have proven to be refractory to conventional medical therapy and will help shape future clinical trials. These conditions include, but are not limited to intractable pain, epilepsy, depression, anxiety, multiple sclerosis, fibromyalgia, endometriosis, cachexia and post-traumatic stress disorder (PTSD). This study brings together our previous ethically approved studies of medicinal cannabis including other observational trials of pain, epilepsy, cachexia, fibromyalgia, endometriosis, PTSD and other anxiety disorders.

# 2. Background Information

Medicinal cannabis products are being used at a growing rate for the treatment of palliative care, epilepsy,

chemotherapy-induced nausea and vomiting (CINV), multiple sclerosis (MS) chronic pain conditions [1] and

cachectic conditions such as cancer-related anorexia-cachexia syndrome [2]. When administered in accordance with medical advice, there has been some evidence to support their safety and efficacy as a last-line therapeutic option for these conditions.

Data used to determine the efficacy and safety of medical cannabis describe the product and its dose in terms of two key active components, cannabidiol (CBD) and Δ-9 tetrahydrocannabinol (THC). THC is a psychoactive drug with a range of clinical consequences such as increased appetite, analgesia and sedation, while CBD is a non-intoxicating cannabinoid that has been reported to display antioxidant, anxiolytic, anticonvulsant and potential anti-inflammatory effects [3].

In Australia, a single medicinal cannabis product, Sativex® (1:1 CBD and THC) has obtained ARTG approval (registration). Sativex® is approved for the treatment of symptoms in patients with moderate to severe spasticity due to MS. Currently a second product, Epidiolex (>98% CBD) is under review for ARTG approval for the treatment of Dravet syndrome and Lennox-Gastaut syndrome.

The evidence regarding the safety and efficacy of medicinal cannabis is still emerging and many authorities concede that further evidence is required [5-9]. Whilst the highest level of evidence can be obtained from randomised-controlled trials, these projects can be expensive, logistically difficult to establish and not always able to predict adverse events in real-world settings. Observational studies can help evaluate their effects in broader populations and provide valuable information for the design of future clinical trials. A recent open-label observational study of 40 patients with paediatric epilepsy treated with CBD under the Authorised Prescriber scheme (APS), was recently published and provides the first experience of this approach to treatment in Australia [10].

Recent reviews have reported promising results of cannabinoid therapy for anxiety, depression, PTSD and other neuropsychiatric disorders. [9, 11, 12] as well as inflammatory conditions, cancer, addiction and epilepsy [13].

It has been postulated that these wide-ranging effects of cannabinoids arise from their actions on the endocannabinoid system, a ubiquitous modulatory neurotransmitter system that functions differently to the classical neurotransmitter systems. This may explain, at least in part, why patients tolerate cannabinoid therapies relatively well and why the number of indications being managed with cannabinoids is so broad, given the broad, diverse nature of the endocannabinoid system involvement.

**2.1 Medicinal Cannabis**

**Cannabinoids**

Cannabinoids are derived from the plant *Cannabis Sativa* L. Medicinal cannabis products may be botanically derived from cannabis or hemp plant material or may be synthetically manufactured. Purified CBD or THC containing products have residual contaminants (including terpenes or other minor cannabinoids) whereas synthetically manufactured cannabinoids such as dronabinol (THC) or synthetic CBD are structurally identical but do not contain the contaminants associated with botanically derived cannabinoids. These are not to be confused with “synthetic cannabinoids”, which are novel chemical entities which are designed by modifying the molecular structure of the compound, primarily for recreational purposes, to intensify the potency at the cannabinoid receptors (CB1 receptors) that are responsible for the intoxicating effects of THC.

**Formulations and preparations**

Preparations of purified cannabinoids primarily contain CBD or THC or a combination of CBD and THC in approximately equal quantities. For example, Sativex® (nabiximols), is a botanical extract that includes the following cannabinoids: THC, CBD, cannabinol, cannabigerol, cannabichromene, cannabidiolic acid, tetrahydrocannabinolic acid, tetrahydrocannabivarin, and cannabidivarin, where THC and CBD are in equal proportions and comprise not less than 90 percent of the total cannabinoid content.

Sativex® is administered as an oromucosal spray but more commonly, cannabinoids are delivered drop-wise as a CO2-extracted oil from hemp or cannabis plants, as hemp oil mixed with sunflower, MCT or sesame oil packaged as an oral oil, in a gelatine capsule at a specific cannabinoid concentration, as dried cannabis leaf and/or flower or as gels or patches as appropriate for the condition being treated.

**Safety and tolerability of medicinal cannabis products**

There is no specific or recommended dose of cannabinoids. Treatment with Sativex commences with one spray per day (2.7 mg THC: 2.5mg CBD) titrating to a maximum of 12 sprays per day (maximum 32.4 mg THC/30 mg CBD daily). Daily doses of other THC preparations vary between 3 mg and 40 mg [25]. Importantly, there have been no recorded deaths directly attributable to acute toxicity of cannabis in humans, even among cannabis smokers ingesting up to 820 mg/day. In mammals the median lethal dose of THC has been estimated to be >800 mg/kg while CBD appears to be generally of very low toxicity [25].

Reports from clinical experience with CBD products show that it is generally regarded as having low toxicity with acute oral doses of up to 6000 mg and repeated doses of 1500 mg/day being well-tolerated in humans [4,18]. Further, studies in patients with hepatic impairment showed no significant toxicity with oral CBD up to 200 mg/day [19].

The study proposed here aims to analyse clinical information from patients treated with medicinal cannabis. The dose and formulation of the therapy will be chosen by the treating medical practitioner according to the degree and severity of each patient’s medical condition. Self-reported changes in these conditions will be used by the medical practitioner to adjust cannabinoid therapy appropriately. Large-scale analysis of the reports will help to determine the therapeutic efficacy of specific cannabinoid formulations, informing larger randomised controlled trials and ultimately potentially leading to development of more effective therapies for intractable disease.

**2.2 Accessing treatment**

1. Patients seeking treatment with medicinal cannabis are referred to Valentius by their local doctor. Once a referral is received, patient demographic details and contact information are collected to be able to contact the patient to book them in for a telehealth appointment with the Valentius doctor. These details, along with their referral and patient history are stored in Medirecords under a newly created patient ID.
2. Prior to their first appointment at Valentius, patients are sent a confirmation email which details their appointment information and provides a link to the online Patient Information Sheet and Consent Form that outlines the Valentius Observational Study (VOS) study and requirements but also includes their medical consent for treatment at Valentius (link to consent form [here](https://docs.google.com/document/d/12yQAncA0Effd_nEiHxt43ClMoE5cLfal/edit)). Patients are able to consent to medical treatment at Valentius independent of participation in the VOS research study. Patients are instructed to read the PICF before their first appointment, consult with their referring doctor, friends or family if they wish, and only after they are happy to consent, sign the form online. If the patient has any questions about the consent form, they are advised to defer signing it until the appointment, allowing for any questions or concerns to be addressed by the Valentius doctor.

At the first appointment the Valentius doctor outlines the administrative protocol involved in accessing medicinal cannabis and responds to any questions or concerns the patient might have. If the patient’s concerns are satisfied, the patient signs the PICF using the online form. If a patient is not able to complete the consent online they will be requested to complete it in a hard copy format that will be scanned into their file, or in the event it is a telehealth appointment then patient’s will be asked to mail it to Valentius for them to file. Record of the signed PICF is electronically stored in the participant’s Medirecords medical file. Any hard copies are filed in a secure location in Valentius premises.

1. The Valentius doctor conducts a clinical assessment and discusses the options available for treatment of the patient’s condition with medicinal cannabis. If appropriate, the doctor either prepares an application to the TGA (SAS-B application) citing details of the patient’s condition, proposed treatment and with relevant supporting clinical documentation (e.g. specialist letters, results of investigations), or if they are an Authorised Prescriber, may write a prescription for a specific product at the same visit. For SAS-B applications, Valentius staff submit the TGA application and await the outcome (usually <1 week).

For SAS-B relevant participants: On notification from the TGA, a Valentius staff member contacts the patient and informs them of the outcome. For those patients approved for medical cannabis treatment, a follow up appointment is made. Once the patient has received their prescription, they are emailed the instructions on how to complete an online baseline assessment of health status (including [PROMIS-29](https://drive.google.com/file/d/16o2aoT5dmRhYnj2LvTVkGlolUGAPBvJV/view?usp=drive_link) form ). Patients are requested to read these instructions prior to their next medical appointment with a Valentius doctor.

# 3. Study Objective

**3.1 Primary Objective:**

To examine the effect of cannabis formulations in patients with intractable chronic disease of any cause and who have had an inadequate response to standard treatment approaches, as measured by improvement in health-related Quality of Life domains.

**3.2 Primary outcome measures:**

Change from Baseline in **PROMIS-29 domain T scores** [Timeframe: Baseline, 1, , 3, 6, 9 and 12 months post-enrolment]

* + - Change from baseline on depression scores;
    - Change from baseline on anxiety scores;
    - Change from baseline on physical function scores;
    - Change from baseline on pain interference scores;
    - Change from baseline on fatigue scores;
    - Change from baseline on sleep disturbance scores;
    - Change from baseline on ability to participate in social roles and activities scores;
    - Change from baseline on pain intensity raw scores.

Patient-Reported Outcomes Measurement Information System (PROMIS-29) will be used by patients to measure self-reported physical, mental and social health and wellbeing. It has been tested and exhibits validity evidence (e.g., expected associations, discrimination among known groups) in a wide range of populations [9]. It is a generic health-related quality of life survey that assesses each of the seven PROMIS domains with four questions. The questions are ranked on a 5-point Likert Scale and converted to T-scores for analysis and reporting. There is also one 11-point rating scale for pain intensity. Pain impact scores will also be calculated and analysed (according to the NIH task force outline, ref. 16) to determine the change in pain impact on patien’s’ quality of life.

In the case where specialist follow up is indicated by patient responses to the PROMIS-29 questionnaire, the medical practitioner will give patients the appropriate referral for specialist treatment. Opioid and other medication use will be determined from the patient’s clinical record as collected by medical practitioners during clinical reviews. Changes to other medications will be self-reported by patients in the progress questionnaire.

Reference population scores have been calculated for each domain such that a score of 50 represents the mean of the reference group. A score of 60 means that the person is one standard deviation above the reference population (standard deviation = 10). High scores represent more of the domain being measured. Thus, on symptom-oriented domains of PROMIS-29 (anxiety, depression, fatigue, pain interference, and sleep disturbance), higher scores represent worse symptomatology. In the function-oriented domains (physical functioning and social role) higher scores represent better functioning. For example, a high sleep disturbance score indicates high levels of sleep disturbance; a high physical functioning score indicates better physical function.

Previous studies indicate a conservative value for the minimum clinically important difference (MCID, effect size) is 0.2 SD of the PROMIS domain score (approx. 2 points). Specifically, MCID’s have been reported for various PROMIS instrument domains that will be referenced to determine if a patient has a meaningful improvement, lack of change or worsening in PROMIS domains. These MCIDs are as follows:

Pain Intensity (MCID = 2.0) [17]

Pain Interference (MCID = 2.0) [17]

Physical Function (MCID = 1.9) [17, 20]

Anxiety (MCID = 2.3) [22]

Depression (MCID = 3.0) [22]

Fatigue (MCID = 2.5) [21]

Impact score – pain (MCID = 3.0) [17]

Social functioning (MCID = 2.0 as default given there is no published MCID value in literature)

Sleep disturbance (MCID = 2.0 as default given there is no published MCID value in literature)

# 4. Data Collection Timetable

Clinical information and outcome measures are collected in accordance with the timetable in Table 1.

**Table 1: Study Data Collection Schedule**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Time (Months)** | Base line | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** |
| Informed consent (PICF) completed and patient enrolled into study | X |  |  |  |  |  |  |  |  |  |  |  |  |
| Prescription of cannabinoid medicine | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Promis29 questionnaire | X |  |  | X |  |  | X |  |  | X |  |  | X |

Patients are advised to attend Valentius on this schedule for optimal management of their medicinal cannabis therapy. Given the observational nature of this study however, we recognise that data collection schedules may vary for reasons beyond our control and it is foreseeable that missing data may occur.

To maximise data collection, Valentius staff will contact patients via sms prior to each visit to remind them to complete the Promis29 measure. Valentius staff will follow up with patients no more than three times within a one-month period. Patients who do not complete the questionnaire following the third attempt will be recorded as missing data.

# 5. Selection of Volunteers/Participants

**5.1 Sample size & Power**

Approximately 3000 participants (total) will be examined:

* + - * One study group measuring continuous endpoints (means).
      * For the PROMIS-29 outcome measures, the population mean for the T-score is 50 (SD=10)
      * Literature states a conservative clinically important difference/effect size for PROMIS-29 measures is a T-score difference of 0.2 SD, approximately 2 points.
      * A study population of 3000 participants, with a mean T-score of 52 or 48, with type I error set at alpha =5% suggests this study will have 93% power after correction for multiple testing.
      * When accounting for a conservative 30% loss in participant numbers (remaining n=2100) the study will still have > 90% power.

We recognise observational study data capture incurs reduced compliance compared to a structured interventional study and have accounted for this reduced compliance in our power analysis (i.e. 30% loss in participant numbers).

**5.2 Inclusion Criteria**

Selection criteria for the study are:

1. Aged 18 years or over,
2. Seeking or in pre-treatment stages, or currently receiving medicinal cannabis therapy within Valentius.
3. Approved for medicinal cannabis treatment through one of the legal access pathways including SAS-B or Authorised Prescriber Scheme.

## 

**5.3 Exclusion Criteria**

1. Any severe cognitive, intellectual disability, medical or psychiatric condition that impairs the participant’s ability to provide informed consent and understand study procedures.

2. Those who have been identified as meeting the criteria for a cannabis use disorder (per DSM-5 or ICD-10 criteria.)

**5.4 Withdrawal Criteria**

Patients may withdraw from their treatment at any time without prejudice. Withdrawal may be complete (i.e. from further study procedures and any follow up), or partial (e.g. from study procedures but allowing the possibility of further follow up). All communication surrounding the withdrawal will be noted in the patient’s records and where withdrawal is complete, no further data will be collected for that patient. Data up to the time of withdrawal can be included in the study if it is anonymised.

Patients may also be discontinued from observation at the discretion of the Investigator for lack of adherence to treatment or visit schedules or because of a severe adverse event. The Investigator may also withdraw subjects who violate the study plan, or to protect the subject for reasons of safety or for administrative reasons. It will be documented whether or not each participant completes the full course of treatment. Any adverse events that occur after the subject completes or withdraws from treatment will also be documented in the patient record.

# 6. Methodology

This is an open-label, prospective observational cohort study, examining the effect of cannabinoids in patients with intractable disease of any cause, who have had an inadequate response to standard treatment and are undergoing medicinal cannabis treatment within Valentius. A range of patient-reported outcome and experience measures will be monitored at regular intervals over a 12-month treatment period. The data being collected is part of the standard of care for individuals attending Valentius. This study allows for analysis of this data for research purposes.

Patient reported outcome and experience measures for approximately 3000 participants will be collected using a website, and scheduled to occur at study enrolment (Baseline), and then at approximately monthly intervals for a 12 month period following their enrolment in the study. The questionnaires take between 5−20 minutes to complete each time. The study findings will be communicated as grouped data, with no identifying participant information.

This study is observational in nature, not an interventional clinical trial conducted under CTN or CTX conditions and therefore, all treatment decisions (regarding medication choice, dosage, and medication costs), are determined by the treating medical practitioner.

Consenting to medicinal cannabis treatment within Valentius also allows the Investigators to extract specific information from patient medical records such as demographics (e.g. age, gender, employment), condition (diagnosis for which medical cannabis is used) and treatment (e.g. side effects reported, dosage information, changes to concomitant medications). The clinic doctor may make changes to the cannabis formulation, the dosage and the frequency and duration of administration at any time according to the efficacy of treatment. The results from patient-completed questionnaires may assist in this evaluation and course of treatment.

All study data is confidential and only available to the treatment team and study investigators. No identifying details regarding patient identity will be reported or disclosed to others.

**6.1 Patient Informed Consent**

Participation in the study is under conditions of written informed consent and is not a requirement for accessing medicinal cannabis treatment at Valentius. Patients of Valentius will have access to medicinal cannabis treatment under Special Access Scheme or Authorised Prescriber Scheme conditions irrespective of participation in the study. Participation in the study will not affect current or future treatment options, nor will it affect the relationship with any of the doctors or Valentius staff.

Patients that agree to the items outlined in the PICF note that questionnaires are sent to them as part of their standard of care at Valentius. It is the responsibility of patients to complete these questionnaires voluntarily, however it is noted in the PICF that these questionnaires may be used by their treating doctor to evaluate how patients are progressing with their treatment.

Participants that consent to participate in the research study agree that this consent allows their (de-identified) clinical data to be evaluated by the ACR team for research purposes. Patients who do not consent to the optional research study are not disadvantaged in any way in terms of the care from their treating doctor and their care will not be affected in any way.

In consenting to the study, patients will permit trial-related monitoring, audits, ethics review, and regulatory inspection that require access to source data/documents. Informed consent shall be sought in order for relevant de-identified data to be extracted from patients’ clinical records. Specifically, this includes

* demographic information (age, gender, employment/pensioner/DVA Card Holder, ATSI Status, postcode)
* details regarding clinical diagnoses (e.g. PTSD, chronic pain, depression, anxiety)
* details regarding medicinal cannabis treatment plan;
* details regarding patient’s concomitant medications;
* adverse events (AEs) associated with medicinal cannabis treatment.

# 7. Safety Monitoring & Reporting

Adverse event data, as a measure of participant safety is collected by medical practitioners during clinical reviews. Valentius collects clinical data as part of the **routine course of treatment** and evaluation of this data within the study is not a formal assessment of medicinal cannabis. The TGA requires all prescribing medical practitioners to monitor and collect adverse event information. This information will be collected during clinical reviews over 12 months.

The following framework is used for collecting AE information:

* At regular clinical reviews, any side effects or other concerns are identified and assessed by the medical practitioner and documented on the AE Log maintained by the treating medical practitioner for each patient.
* The AE Log will be formally reviewed by treating medical practitioners at each clinical visit attended by the patient. In addition, patients will be asked to report any side effects they have experienced regularly via the patient reported questionnaires administered at each visit.
* Data from these reviews will be extracted from the clinical information system and uploaded to Medirecords by Valentius staff.
* An adverse event is defined as any untoward event that may inconvenience a study participant and may or may not be related to the treatment received within the framework of the study [15]. This includes the onset of new illness and the exacerbation of pre-existing conditions. AEs are assessed as to the severity, likelihood of relation to drug and outcome, as defined in Table 2.

**Table 2: Definitions for Adverse Event Reporting**

|  |  |
| --- | --- |
| **Severity of event** | |
| Mild (Grade 1) | Awareness of sign, symptom or event, but easily tolerated |
| Moderate (Grade 2) | Discomfort enough to cause interference with usual activity and may warrant intervention |
| Severe (Grade 3) | Incapacitating with inability to do usual activities or significantly affects clinical status, and warrants intervention |
| Life-threatening or disabling (Grade 4) | Life-threatening consequences; urgent intervention indicated. |
| Death (Grade 5) | Death related to adverse event. |
| **Likelihood of relation to drug** | |
| Unlikely related | No temporal association or the cause of the event has been identified, or the drug cannot be implicated |
| Possibly related | Temporal association but other aetiologies are likely to be the cause. However, involvement of the drug cannot be excluded |
| Probably related | Temporal association, other aetiologies are possible but unlikely |
| **Outcome** | |
| Resolved | AE has resolved |
| Ongoing | AE is ongoing |

# 8. Statistical Methods

**8.1 Statistical Analyses**

Data will be analysed using SPSS (v25.0, IBM Analytics). Descriptive statistics will be produced with summary data regarding participant demographics, treatment and patient-reported assessments. Continuous variables with normal distribution will be presented as means with standard deviation; non-normal distribution will be presented as medians with an interquartile range (IQR). Categorical variables will be presented as counts and percent of the total.

The study will use t-test for the analysis of the continuous variables with normal distribution, and non-parametric Wilcoxon test used whenever parametric assumptions are not satisfied. Longitudinal outcome data overtime (i.e., changes from baseline) will be analysed using repeated measures analysis (e.g. ANOVAs or ANCOVAs to correct for any confounding variables).

Multivariate Logistic regression will be used to analyse factors associated with treatment outcomes and Bonferroni-corrected to adjust for multiple testing.

If necessary, analyses will be performed throughout the treatment period in order to seek approval from the TGA to continue treatment beyond the initial approval period (which may vary depending on the approved application submitted by the treating clinician).

# 9. Data Management

**9.1 Medical Records and Trial Source Data**

All original (source) patient data will be stored in the Medirecords practice management software.

Each patient has their own individual record in practice management software and includes the following:

* demographic information including the patient’s date of birth, gender, cultural background
* all clinical information relating to the patient–Patient Identifier, indication, medication, adverse events, clinical notes
* Promis29 survey data

For study participants, data can be extracted from Medirecords to a CSV file format for analysis in SPSS.

Patients will complete the questionnaires within the Medirecrods online platform from a link that is either emailed or sent via SMS (depending on the preference they have told the clinic) to each patient by Valentius taff. For those individuals unable to complete the questionnaires online (e.g. no internet access), patients will have the option to complete questionnaires over the phone with assistance from a member of the ACR research team. Data will be transferred from the Medirecords to SPSS for analysis.

**9.3 Data Security, Retention and Back up**

All study data will be stored securely using the Medirecords cloud platform. Medierods cloud platform runs within the geographical confines of the Commonwealth of Australia, on the Microsoft Azure platform. Medirecords uses encryption protocols to protect data at rest and in transit. Patient data is protected using username and password combined with 2 factor authentication. Data backup aad retention is automatic within the Medirecords system. Patient files will be accessed only by the treating medical practitioners, administrative staff and the Study Manager.

All reports will be prepared such that no individual patient can be identified.  Data that are published will be retained for at least five years from the date of publication and fifteen years from the end of a clinical study. At the end of this period all hard copy data will be securely shredded. Electronic data will be expunged from the file.

# 10. Human Research Ethics Committee (HREC) Approval

The protocol and the informed consent document will be reviewed and approved by the appropriate HREC. The reviewing Human Research Ethics Committee for this study is Bellberry Limited.

# 11. Ethical Conduct of the Study

This study will be conducted in accordance with the protocol, the Declaration of Helsinki and subsequent amendments, the ICH GCP Guidelines, and in compliance with applicable regulatory requirements.

# 12. Protocol Deviations

No deviations from or changes to the protocol will be implemented without documented approval from the HREC of an amendment, except where necessary to eliminate an immediate hazard(s) to study participants or when the change(s) involves only logistical or administrative aspects of the study. Any deviations from the protocol which were implemented to eliminate an immediate hazard and the proposed amendment, if appropriate, will be submitted to the HREC for review and approval as soon as practicable.

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