
ASSESSING HEALTH-RELATED QUALITY OF LIFE IN PATIENTS ACCESSING MEDICINAL CANNABIS

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Doctor of Philosophy

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STATEMENT OF ORIGINALITY

This is to certify that to the best of my knowledge; the content of this thesis is my own work.

This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

.....

Margaret-Ann Tait

Date: 12 December 2025

ABSTRACT

There is growing interest worldwide in using medicinal cannabis (MC) to manage symptoms and side-effects of chronic health conditions when conventional therapies fail. Although many countries allow MC, barriers to accessing prescriptions persist due to historical legal restrictions on cannabis use and the subsequent delay in developing a therapy-focused evidence-base. A patient-centred approach to healthcare requires patient-reported outcome (PRO) evidence. Health-related quality of life (HRQL) is a widely assessed and important outcome for patients with chronic conditions. This mixed methods thesis contains a series of studies aimed to contribute to the evidence-base by assessing HRQL and the experiences of patients prescribed MC. A literature review explored how HRQL is assessed in this cohort, along with a meta-analysis of findings from the past decade. Following a published protocol, a nation-wide prospective study quantitatively assessed short-, and long-term HRQL and other PROs in patients newly prescribed MC. Finally, patients were interviewed and their experiences after being prescribed MC long-term explored using qualitative methods.

The findings from this research demonstrated that patients with chronic health conditions prescribed MC had significant and clinically meaningful improvements in HRQL and reduced their dependence on conventional medicines. Despite the potential benefits from MC, conflicting regulations and barriers to accessing MC persist and should be addressed with an evidence-informed patient-centred care approach.

Incorporating MC evidence into clinical guidelines, policy, and education, can potentially reduce the economic burden and patient suffering caused by chronic conditions and problematic conventional treatments, while also reducing the risk of harm from self-

medicating. Future research looking at the economic impact of prescribing MC for chronic health conditions is recommended.

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AUTHOR ATTRIBUTION STATEMENT

This thesis contains five published manuscripts (four published and one under review). I made a substantial contribution to the design of all the studies included in this thesis; obtaining ethics approvals; recruitment and data collection, curation, and analyses; drafting manuscripts and revisions following peer review. Detailed authorship attribution statements are also provided at the beginning of each relevant chapter.

Chapter 2 of this thesis has been published as '*Health-related quality of life in patients receiving medicinal cannabis: Systematic review and meta-analysis of primary research findings 2015 – 2025*'. I designed the study and literature search, extracted data (74%) with Louise Acret, analysed the data, and wrote the drafts of the manuscript.

Chapter 3 of this thesis has been published as '*The QUEST initiative – Quality of life Evaluation Study Assessing Health Related Quality of Life in patients receiving Medicinal Cannabis: Protocol for a longitudinal observational study*'. I co-designed the study with Claudia Rutherford, Daniel SJ Costa, Rachel Campbell, Richard Norman, and Stephan Schug, and I wrote the drafts of the manuscript.

Chapter 4 of this thesis has been published as '*Health-related quality of life in patients accessing medicinal cannabis in Australia: The QUEST Initiative results of a 3-month follow-up observational study*'. I co-designed the study with Claudia Rutherford and Leon Warne, collected and analysed the data, and wrote the drafts of the manuscript.

Chapter 5 of this thesis has been published as '*Improvements in health-related quality of life are maintained long-term in patients prescribed medicinal cannabis in Australia: The QUEST Initiative 12-month follow-up observational study*'. I co-designed the study with Claudia

Rutherford and Leon Warne, collected and analysed the data, and wrote the drafts of the manuscript.

Chapter 6 of this thesis has been published as *‘Experiences of patients prescribed medicinal cannabis in Australia long-term: A qualitative interview study’*. I designed the study and collected the data, analysed the data (75%) with Rachel Campbell, and wrote the drafts of the manuscript.

No content produced by generative AI tools has been used in the preparation of this thesis.

In addition to the authorship attribution statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Margaret-Ann Tait

12 December 2025

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Claudia Rutherford

12 December 2025

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LIST OF ACRONYMS AND ABBREVIATIONS

AHPRA	Australian Health Practitioner Regulation Agency
AIHW	Australian Institute of Health and Welfare
CBD	Cannabidiol
DASS-21	Depression Anxiety and Stress Scale - 21 item Short Form
EORTC	European Organisation for Research & Treatment of Cancer
EQ-5D	5-item measure of health outcome developed by the EuroQol group
FDA	US Food and Drug Association
HRQL	Health-Related Quality of Life
ISOQOL	International Society for Quality of Life Research
LGP	Little Green Pharma Pty Ltd
MC	Medicinal Cannabis
MCID	Minimal clinically important difference
MS	Multiple sclerosis
NRS	Numeric Rating Scale
PRO	Patient-Reported Outcome
PROM	Patient-Reported Outcome Measure (questionnaire)
PROMIS	Patient-Reported Outcomes Measurement Information System
QoL	Quality of Life
RCT	Randomised controlled trial
REDCap	Research Electronic Data Capture software
SD	Standard deviation
SEM	Standard error of the mean
SPSS	Statistical Package for the Social Sciences
TGA	Australian Therapeutic Goods Administration
THC	Delta-9-tetrahydrocannabinol
VAS	Visual Analogue Scale
WHO	World Health Organisation

PEER-REVIEWED PUBLICATIONS INCLUDED IN THIS THESIS

Chapter 2:

Tait M, Acret L, Costa DSJ, Campbell R, White K, Rutherford C. Health-related quality of life in patients receiving medicinal cannabis: Systematic review and meta-analysis of primary research findings 2015 – 2025, *Quality of Life Research*, 2026; 35:56. doi:10.1007/s11136-026-04170-7 (5-year Journal Impact Factor: 4.1)

Chapter 3:

Tait M, Costa DSJ, Campbell R, Norman R, Schug S, Rutherford C. The QUEST initiative – QQuality of life Evaluation Study Assessing Health Related Quality of Life in patients receiving Medicinal Cannabis: Protocol for a longitudinal observational study, *JMIR Research Protocols*, 2021; 10(11):e32327. doi:10.2196/32327 (5-year Journal Impact Factor: 1.5)

Chapter 4:

Tait M, Costa D, Campbell R, Norman R, Warne LN, Stephan Schug, Rutherford C. Health-related quality of life in patients accessing medicinal cannabis in Australia: The QUEST Initiative results of a 3-month follow-up observational study, *PLOS One*, 2023; 18(9):e0290549. doi:10.1371/journal.pone.0290549 (5-year Journal Impact Factor: 3.2)

Chapter 5:

Tait M, Costa D, Warne LN, Norman R, Campbell R, Stephan Schug, Rutherford C. Improvements in health-related quality of life are maintained long-term in patients

prescribed medicinal cannabis in Australia: The QUEST Initiative 12-month follow-up observational study, *PLOS One*, 2025; 20(4):e0320756.

doi:10.1371/journal.pone.0320756. (5-year Journal Impact Factor: 3.2)

Chapter 6:

Tait M, Rutherford C , White K, Costa DSJ, Campbell R. Experiences of patients prescribed medicinal cannabis in Australia long-term: A qualitative interview study, *The Australian Journal of Primary Health*, UNDER REVIEW 2025. (5-year Journal Impact Factor: 3.8)

CONFERENCE AND SYMPOSIUM PRESENTATIONS

1. **Tait M**, Costa DSJ, Campbell R, Rutherford C, Prescribed cannabinoids associated with greater patient-reported improvements in sleep, The 10th Annual PROMIS International Conference, Cologne, Germany, 17-18 October 2024. [Oral presentation]
2. **Tait M**, Costa DSJ, Campbell R, Rutherford C. The association of cannabinoid combinations with patient-reported pain improvements in patients with chronic pain prescribed medicinal cannabis, The 31st Annual Scientific Meeting of the International Society for Quality of Life Research (ISOQOL), Cologne, Germany, 13-16 October 2024. *Quality of Life Research*, 2024; 33 (Suppl 1):1010. [Poster presentation] **Best Student Poster Presentation.**
3. **Tait M**, Costa DSJ, Campbell R, Rutherford C, Assessing pain outcomes over 12-months in patients with chronic pain prescribed medicinal cannabis in Australia, The 9th Annual PROMIS International Conference, Banff, Canada, 22-24 October 2023. [Oral presentation]
4. **Tait M**, Costa DSJ, Campbell R, Rutherford C, Assessing health-related quality of Life in patients accessing medicinal cannabis in Australia: Results of the QUEST Initiative 12-month follow-up, The 30th Annual Scientific Meeting of the International Society for Quality of Life Research (ISOQOL), Calgary, Canada, 20 October 2023. *Quality of Life Research* 2023; 32(Suppl 2): S51-S52. [Oral presentation] **Best Student Oral Presentation Finalist.**
5. **Tait M**, Costa DSJ, White K, Campbell R, Rutherford C, Quality of life and Pain outcomes for cancer patients prescribed medical cannabis: the QUEST initiative 12-

month results, NSW Cancer Conference, Sydney, 18-19 September 2023. [Oral presentation]

6. **Tait M**, Costa DSJ, Campbell R, Rutherford C, CANCER-16: Change in quality of life and pain outcomes for cancer patients accessing prescribed medical cannabis: the QUEST Initiative 3-month results. The Multinational Association of Supportive Care in Cancer (MASCC) Annual Meeting, Nara, Japan, 22 June 2023. *Supportive Care in Cancer* 2023; 31(Suppl 1): S399 (S23-S24). [e-Poster presentation]
7. **Tait M**, Costa DSJ, Campbell R, Rutherford C, Assessing Health-Related Quality of Life in patients accessing medicinal cannabis in Australia: Results of the QUEST Initiative 3-month follow-up. The International Society for Quality of Life Research (ISOQOL) Annual Scientific Meeting, Prague, Czechia, 21 October 2022. *Quality of Life Research* 2022; 31(Suppl 2): S147-S148. [e-Poster presentation]

PUBLIC MEDIA AND PRESS

1. **News Release:** Medicinal cannabis is linked to long-term benefits in health-related quality of life (2025) EurekAlert! 2 April. This was further disseminated via 27 news stories by 26 outlets globally (Altmetric:9/05/2025). Available at: <https://www.eurekalert.org/news-releases/1078757>

2. **Editorial: Tait M.** Patient-reported pain improvements with different cannabinoid combinations for patients with chronic pain prescribed medicinal cannabis. QualityTALK: ISOQOL Newsletter, 24 February 2025 Available at: <https://www.isoqol.org/patient-reported-pain-improvements-with-different-cannabinoid-combinations-for-patients-with-chronic-pain-prescribed-medicinal-cannabis/>

3. **Editorial: Tait M.** The QUEST Initiative: Assessing patient-reported outcomes in patients with chronic conditions prescribed medicinal cannabis in Australia. QualityTALK: ISOQOL Newsletter, 17 October 2023 Available at: <https://www.isoqol.org/the-quest-initiative-assessing-patient-reported-outcomes-in-patients-with-chronic-conditions-prescribed-medicinal-cannabis-in-australia/>

4. **Radio Interview:** Nightlife with Suzanne Hill, Sunday Science: Medicinal cannabis, the Irish Famine and platypus (2023) ABC Radio National, 10 September. Available at: <https://www.abc.net.au/listen/programs/nightlife/nightlife/102809478>

5. **Written Interview:** PainRelief.com Interview with: **Margaret-Ann Tait**, Study Assesses Quality of Life After Cannabis Prescribed for Chronic Pain and Other Health Symptoms (2023) Pain Relief at PainRelief.com, 13 September. Available at:

<https://painrelief.com/chronic-pain/study-assesses-quality-of-life-after-cannabis-prescribed-for-chronic-pain-and-other-health-symptoms/>

6. **News Release:** Medical cannabis use in Australian patients with chronic health issues linked to significant improvements in overall health-related quality of life and fatigue levels (2023) EurekAlert! 6 September. This was further disseminated via 38 news stories by 34 outlets globally (Altmetric:13/03/2024). Available at:

<https://www.eurekalert.org/news-releases/1000177>

ETHICAL CLEARANCE

All the empirical research included in this thesis has been conducted in accordance with relevant Human Research Ethics Committee (HREC) approvals.

The studies described in chapters 3-6 were approved by the University of Sydney HREC (approval number **2020/589**). Copies of authorisation letters are attached in Appendix 3.

Ethical approval was not required for other chapters.

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Sydney Cancer Partners, The International Society for Quality of Life Research, PROMIS Health Organisation, and the Faculty of Medicine and Health, University of Sydney, provided further travel support funding to disseminate PhD findings at conferences nationally and internationally.

PART A

HOW AND WHY IS HEALTH-RELATED
QUALITY OF LIFE ASSESSED IN PATIENTS
USING MEDICINAL CANNABIS

CHAPTER 1

PART A. HOW AND WHY IS HRQL ASSESSED IN PATIENTS USING MC

CHAPTER 1: INTRODUCTION AND CONTEXT TO THE RESEARCH

CHAPTER OVERVIEW

Following government regulatory changes in 2016, doctors in Australia began prescribing medicinal cannabis (MC) to patients with chronic health conditions to manage symptoms not responding to conventional therapies. Previously, most countries had criminalised cannabis use and research was primarily focused on negative consequences of illicit cannabis use, with very few studies considering medicinal potential, and even fewer assessing individual perceptions of the benefits and harms of MC therapy. Due to these limitations, little was known about the expected impact of prescribing MC on patient wellbeing, or health-related quality of life (HRQL). This chapter describes the complexity, prevalence, and impact of chronic health conditions and importance of HRQL and other patient-reported outcomes (PROs) in health research and for the clinical management of patients with chronic conditions. The introduction of MC as therapy is explored as well as the need for assessing PROs and HRQL using validated measures in this patient group. The chapter concludes with the thesis research aims and an outline of how the thesis chapters are structured to address these aims.

CHRONIC HEALTH CONDITIONS

The US Centers for Disease Control and Prevention (CDC) defines chronic diseases as 'conditions that last 1 year or more and require ongoing medical attention or limit activities of daily living or both'.¹ Half of the Australian population suffer from a chronic health

condition, and 80% of Australians have long-term health conditions that last at least 6 months.² The most common types of chronic conditions are mental and behavioral, such as anxiety, depression, and attention deficit disorders, followed by back problems, arthritis, asthma, diabetes, cardiovascular disease, osteoporosis, Chronic Obstructive Pulmonary Disease (COPD), and cancer.² Common long term conditions in Australia include anxiety, depression, migraines, endometriosis, as well as hay fever, allergies, and impaired vision and hearing.² The first lines of response are typically medical or psychological interventions, removing environmental or workplace hazards that may be contributing to the health condition, and managing lifestyle risks, such as smoking, exercise, diet, alcohol, and sun exposure. Some mental health conditions may be managed effectively through psychological therapy and counseling. When these methods alone are insufficient, patients are typically prescribed medications. Usually, the primary objective of medical interventions and medications is to treat the underlying disease or illness and reduce the risk of progression or recurrence. However, chronic conditions are complex and often co-occur, with one chronic condition often developing due to the presence of another.³ People who have co-occurring health conditions typically experience more severe medical, social, and emotional problems compared with those having only one condition.⁴ For example, nearly half of people with chronic pain in Australia also suffer anxiety or depression,⁵ and having a sleep disorder significantly increases your risk of anxiety, depression, cardiovascular disease, and stroke.³ Even when an underlying disease or illness is managed successfully, as one adjusts to new ways of living in changed bodies, the symptoms of disease, side effects of their treatments, or the secondary conditions they precipitate, may persist well beyond the acute stages of disease-treatment. In these cases, adjuvant or complementary therapy is

required for ongoing symptom management. For many chronic conditions, including chronic pain, anxiety and depression, symptom management may be the primary aim of therapy.

PREVALENCE AND BURDEN OF CHRONIC CONDITIONS

Of the 49.9% of Australians with chronic health conditions, an estimated 3.4 million have anxiety disorders, 1.9 million have sleep disorders, and 3.24 million are living with chronic pain, half of whom have a resulting disability or restricted ability to perform activities of daily living and selfcare.⁵

Unlike other chronic conditions, pain is considered chronic when it persists for longer than three months, and can be chronic secondary pain, initiated as a symptom of an underlying disease or injury, or chronic primary pain, a disease in its own right.⁶ Chronic pain is a widespread health issue with economic consequences. More than two thirds of Australians living with chronic pain are of working age and 40% of people who take early retirement were forced to due to chronic pain issues.⁵ The estimated social and economic cost of chronic pain was \$139.3 billion Australian dollars (AUD) in 2018. This included loss of wellbeing due to disability and premature death (AUD\$66.1 billion), and a significant financial cost (AUD\$73.2 billion), with productivity losses alone estimated at (AUD\$48.3 billion).⁵

The prevalence and impact of chronic pain and other chronic conditions are comparable in other Western countries. In the UK, an estimated 35% of adults experience some level of chronic pain, and more than 10% report moderate to severely limiting chronic pain.⁷

According to the CDC, 60% of Americans have at least one chronic disease;^{1,8} and a national study found that in 2020, 46% of adults had chronic pain, and 36% of them experienced

chronic pain that limited life or work activities on most days or every day.⁹ The economic cost of chronic pain grew from USD\$560 billion in 2011,¹⁰ to USD\$725 billion in 2022.¹¹ The various categories and types of chronic pain are discussed further in chapter 3.

Back pain, anxiety, and depression are the top three leading causes of disability in Australia.¹² Anxiety is the most common mental health condition worldwide effecting 359 million people of all ages, roughly 4.7% of the global population.¹³ In Australia, 17% of people aged over 16 years experienced anxiety disorders in 2022 and 8% had an affective disorder (e.g. depression).¹⁴ Compared with the general population, people with depression have a 40% to 60% greater risk of premature death due to neglected physical health issues and suicide.¹⁵ The estimated economic costs due to disability and reduced life expectancy for those living with mental illness in Australia is AUD\$122 billion per year, with productivity loss, informal care, and health services costing a further AUD\$70 billion.¹⁶

Often, pain, anxiety, depression, and insomnia co-occur as evidence suggests these disorders share common brain structures, neural pathways, and underlying neurobiological processes.¹⁷ Sleep disorders and sleep deprivation exacerbate and contribute to the development of anxiety disorders.¹⁸

An estimated 1.9 million Australians suffer from sleep disorders,¹⁹ with social and economic costs around AUD\$51 billion.³ This is mostly loss of wellbeing due to disability and premature death (AUD\$36.6 billion), but a substantial amount (AUD\$14.4 billion) was financial cost due to reduced productivity and increased healthcare use, with productivity losses alone estimated at AUD\$11 billion.³

CONVENTIONAL TREATMENTS

The World Health Organisation (WHO) recommendations for treating pain follow a three-stepped approach starting with non-opioid analgesics, then weak opioids, and finally stronger opioids, supplemented with adjuvant drugs at each step depending on the pain type. For most people, low- and moderate-level pain events are generally managed with easily accessible, over the counter, non-opioid medications such as paracetamol for headaches, and aspirin or ibuprofen for inflammatory pain. For more persistent or severe pain, patients typically consult with health practitioners for stronger prescription medications, often opioids. Between 2016 and 2017, 5.7 million oxycodone prescriptions were dispensed in Australia to treat pain, followed by codeine (3.7 million prescriptions) and tramadol (2.7 million prescriptions).²⁰ Today, approximately 12.5 million opioid prescriptions are dispensed annually for pain (not counting prescriptions to treat opioid dependence) to 2.9 million patients, roughly 10.7% of the Australian population.²¹

A 2020 systematic review of randomised controlled trials (RCTs) found that in patients with chronic pain, opioids were not superior to nonopioid therapies, but were associated with greater risks of short-term harms.²² Every day in Australia, opioids cause 150 hospitalisations, 14 emergency department presentations, and three deaths, with prescription opioids responsible for twice as many hospitalisations compared with illicit heroin.²⁰ An editorial in the *Journal of Pain Research* published in July 2025, pleaded with clinicians globally to acknowledge the influence pharmaceutical companies' biased research and misleading messages have had over their prescribing practices and to redirect their attention to patient-centred, independent, and transparent scientific evidence to inform decision-making.²³ Concerned by the increasing reports of harm caused by opioid

prescribing in Australia and globally, the Australian Government introduced tighter restrictions for accessing opioid medications in 2020, leaving some patients with inadequate pain management, and increased risk of developing mental health issues.²⁴

Currently, one in five Australians suffer chronic mental health issues, including anxiety and depression.² More than 11.9 million prescriptions for antidepressants, specifically selective serotonin reuptake inhibitors (SSRIs), were dispensed in 2023,²⁵ and approximately 7 million benzodiazepine (e.g. Valium) prescriptions are dispensed annually to treat anxiety and insomnia. Antidepressants, benzodiazepines and other prescribed sedative-hypnotics accounted for 7.2% of all drug-related hospitalizations in 2023, with 600 deaths directly related to benzodiazepines.²¹ As with strong opioids, some benzodiazepines are listed in Australia as Schedule 8 medicines: highly controlled prescription-only drugs with evidence of high potential for misuse and risk of addiction. Australia's national classification of drugs follows a scheduling system with higher schedules signifying greater restrictions due to risk of abuse, addiction, or poison (schedule 10 drugs are completely prohibited). Most second line drugs for treating symptoms of chronic conditions fall under Schedule 4: prescription only medicines, including many benzodiazepines, SSRIs, and barbiturates for epilepsy, anxiety, and insomnia.

When conventional medications fail, patients continue to suffer the symptoms of their condition with impaired functioning that negatively impacts their HRQL. Patients, often feeling distraught and frustrated, may turn to alternative, or unproven, therapies or self-medicate with unregulated or illicit drugs.²⁶ The most used illicit drug world-wide is Cannabis.²⁷

MEDICINAL CANNABIS AS THERAPY

Cannabis is a genus of flowering plants that contains 120 phytocannabinoids.²⁸

Cannabinoids are substances that interact with cannabinoid receptors (CB1 and CB2), part of the endocannabinoid system vital for harmonising physiological and cognitive processes in mammals.²⁹ They include endocannabinoids, which are naturally occurring cannabinoids found in the human brain and bodily organs important for regulating mood, appetite, energy, memory, and pain;³⁰ or synthetic cannabinoids, compounds chemically created in a laboratory to mimic the effects of cannabinoids or to activate or suppress cannabinoid receptors; and phytocannabinoids, the cannabinoids extracted from the cannabis plant. Although cannabis had been used as medicine since 2600 BC,³¹ the plant's cannabinoid compounds were not identified until the 1940s.³² Analgesic properties were discovered in what is currently considered the two most important phytocannabinoids, cannabidiol (CBD) and Δ^9 -tetrahydrocannabinol (THC), potentially positing MC as adjunctive treatment for the symptomatic relief of chronic pain.³³ However, its pharmaceutical viability waned because, unlike its competitors, aspirin and morphine, cannabinoids are not water soluble and could not be standardised and administered via popular drug delivery systems.³⁴ The US Marijuana Tax Act of 1937 effectively stalled much of the scientific and medical investigation into cannabis, and in 1951 the WHO added cannabis to its list of narcotics, citing its potential for abuse while discounting any medicinal value.³⁴ By 1961, the United Nations had classified cannabis as a narcotic drug in the same category as heroin and sought international agreement on total prohibition with penalties for cultivation or use regardless of purpose.³⁵

In response to user activism and calls from the community to review the science behind cannabis drug laws,³⁴ a number of countries, amid growing concerns around the misuse and adverse events associated with opioids,³⁶ introduced legislation to allow the use of cannabis for scientific and medicinal purposes, including Australia in 2016. The past few decades have seen a resurgence in cannabis research,³⁴ particularly since discovering the endocannabinoid system in the mid-1990s,³² and its important role in most bodily functions.³⁰ Evidence from RCTs and observational studies indicated MC may reduce chronic pain,^{37,38} cancer pain,³⁹ neuropathic pain,^{40,41} chemotherapy-induced nausea,⁴² spasticity in Multiple Sclerosis,^{38,43,44} and epileptic seizures.^{45,46} Findings from observational studies further suggested MC may alleviate depression,^{47,48} anxiety,^{47,49} improve sleep,^{50,51} and reduce opioid prescription numbers.⁵² In 2017, the Australian Therapeutic Goods Administration (TGA) conducted a systematic review of studies evaluating MC for pain, multiple sclerosis, epilepsy and palliative care. They found overall moderate evidence from RCTs supporting the use of MC for reducing chronic non-cancer pain and Multiple Sclerosis-related pain,⁵³ but insufficient evidence for reducing epileptic seizures,⁵⁴ muscle spasticity,⁵⁵ and symptoms experienced by patients in palliative care.⁵⁶ Similarly, a recent systematic review of RCTs evaluating MC for mental health issues found no high-quality evidence that MC effectively treats anxiety, PTSD, or depression.⁵⁷ Considering observational studies cannot provide evidence of efficacy, and the overall findings from RCTs are inconsistent, the evidence has not been strong enough for the TGA to approve cannabis as a medicine.

PRESCRIBING MC IN AUSTRALIA

As a legally permitted, but unapproved therapy in Australia, MC prescriptions can only be obtained in one of two ways: from a prescribing health practitioner who receives approval

via a Special Access Scheme (SAS) Category B application for each patient, or from a medical practitioner who is an Authorised Prescriber. A prescribing health practitioner is a person who is registered or licenced to practice including, but not limited to, medical doctors, dentists, nurses, pharmacists, and psychologists.⁵⁸ The TGA currently approves SAS B applications from health practitioners who provide a clinical justification for prescribing MC where conventional therapies have failed. However, the process of submitting applications and waiting for TGA approval for each patient takes time and resources. On the other hand, Authorised Prescribers have TGA approval to prescribe MC for a particular condition without requiring further approvals for individual patients. Any medical practitioner (doctor) can apply to be an Authorised Prescriber. Typically, applications also require approval from an ethics committee or endorsement from a specialist college, however, this requirement was removed in 2021 if prescribing products that were listed in the TGA's Established History of Use list (now covering CBD dominant and CBD:THC balanced products administered orally as liquid, capsule, or spray solution).⁵⁹ There are no TGA-imposed restrictions on the types of health conditions that can be treated with MC.

Since Australia legalized cannabis for medicinal use in 2016, the TGA has received over 457,795 SAS B applications to prescribe MC to patients with chronic pain, 253,225 applications for anxiety, 91,356 for sleep disorders, and 19,128 for post-traumatic stress disorder, from 6,789 medical practitioners.⁶⁰ In addition, an estimate of more than 200,000 patients are currently receiving MC prescriptions from 3,474 Authorised Prescribers.⁶¹

Clinical practice guidelines support trialling MC for pain relief, after first- and second-line therapies fail, due to patients' placing high value on small improvements, and willingness to accept small to modest risks of adverse effects.^{62,63} In Australia, MC is typically prescribed as

either flower (dried herb inhaled using a medical vaporiser), sprays taken under the tongue, ingestible oil-filled capsules and wafers, or oils and liquids administered directly under the tongue. Oils and liquids are the most common prescribed form of MC (48%), followed by flower (34%). Adverse effects, such as intoxication, usually occur due to high levels of THC. Adverse effects from most MC products taken at therapeutic levels are relatively rare and usually mild. This is because dosing regimens for MC are tailored to individual needs by starting at low-doses and, under clinician supervision, slowly titrating up until a therapeutic dose is achieved without unwanted side-effects.⁶⁴ Unlike illicit cannabis and MC flower, which usually contains high concentrations of THC, pharmaceutical MC formulations such as MC oil allow for greater control over dosage levels and typically contain a proportion of the non-intoxicating component, CBD. There is evidence suggesting CBD attaches to the CB1 receptor responsible for intoxication causing the receptor site where THC binds to change shape, thus reducing THC binding and less activation of the CB1 receptor.⁶⁵ However, in 2023, an RCT of healthy adults orally administered cannabinoids found that combining a large dose of CBD (640mg) with THC (20 mg) increased adverse effects and intoxication compared with THC (20 mg) alone.⁶⁶ When properly titrated for therapeutic benefit, large doses of either THC or CBD may be avoidable, particularly considering THC doses above 5mg have been associated with poorer mental health outcomes.⁶⁷ Continuing research into appropriate dosing, cannabinoid-cannabinoid and cannabinoid-drug interactions will help inform future guidance for prescribing to further minimize risks of adverse effects.

Identified barriers for patients accessing MC in Australia include a lack of clinician education about the endocannabinoid system, MC products available, and how to prescribe them; limited information for patients and clinicians on how to access MC; complex access

pathways and state-specific regulatory hurdles; the financial burden on patients paying for unsubsidised MC products (over AUD\$100 per 100ml) and expensive visits to specialist cannabis clinics not covered by Medicare; driving laws that criminalise drivers, whether impaired or not, if any trace amount of THC is detected during a random roadside drug test; and competition with the illicit drug market because patients, without clinician guidance and monitoring, self-medicate with more affordable and accessible cannabis products.⁶⁸ A recent national survey found that between 2022 and 2023, only 22% of people accessing cannabis for medicinal purposes always did so via a prescription.²⁷

The ability for doctors to manage and monitor cannabis therapy may improve patient outcomes particularly as doctors do not always know when patients are self-medicating with MC,⁶⁹ and how that may interact with other therapies.⁷⁰

PATIENT-REPORTED OUTCOMES (PRO) AND HEALTH-RELATED QUALITY OF LIFE

PROs are important clinical trial and treatment outcomes. Historically, evaluation of treatment efficacy in clinical trials was limited to physical indicators of disease reduction (e.g. imaging or pathology results), and disease-free survival. While these are very important endpoints, they do not consider treatment side-effects, the quality of life after treatment, or the ongoing burden from chronic diseases. As more treatment options with similar survival outcomes became available, treatment side-effects and quality of life became more important considerations when evaluating treatment success. This is because reducing side-effects improves treatment adherence and real world efficacy.⁷¹ However, some symptoms and treatment effects are only apparent to the person experiencing them. While clinicians may accurately assess observable behaviours, such as nausea and vomiting, studies have

shown that somatic side-effects, such as pain and fatigue, are consistently rated as significantly less severe by clinicians when compared with patient-reported self-assessments.^{72,73}

A PRO is a health-related outcome reported by patients, or more specifically:

“a measurement of any aspect of a patient’s health status that comes directly from the patient, without interpretation of the patient’s responses by a clinician or research associate.”⁷⁴

The term PRO describes the source of the outcome rather than any specific aspect of health. Therefore, when collecting PROs, it is important to be explicit about the outcome of interest. For example, a clinician or researcher may be interested in symptoms of a particular disease, side-effects of a treatment, or an aspect of functioning after treatment (e.g. physical, role, social, or sexual). Another outcome of interest is health-related quality of life. Quality of life, in general, may be influenced by any number of factors external to the healthcare context. However, in health settings, quality of life centres on the impact of disease and/or treatment and using the term *health-related quality of life* (HRQL) makes this explicit.

In clinical studies, a widely accepted definition of HRQL is:

“a multidimensional construct encompassing perceptions of the impacts – positive and negative - of a disease or its treatment on physical, emotional, social, and cognitive functions, as well as somatic discomfort and other symptoms.”⁷⁵

For effective patient-centred care, the quality of patients’ lives is an important consideration

when making treatment decisions as many treatments come with both a benefit (relieving symptoms) and possibility of harm (side-effects).⁷⁶ The need for standardised methods for measuring PROs was identified in the early 1970s as a way of assessing the somatic side-effects of radiotherapy and chemotherapy, particularly pain, in cancer clinical trials.⁷⁶ This prompted the development of new methods for measuring HRQL using validated measures during the 1980s. This led to the inclusion of HRQL as an endpoint in cancer clinical trials, and the US Food and Drug Administration (FDA) adopting HRQL as one of the “key efficacy parameters” in cancer clinical trials.⁷⁷ By the mid-1990s, the American Society of Clinical Oncology treatment guidelines included HRQL as one of the three key endpoints for cancer clinical trials alongside tumour response and survival.⁷⁸ Today, PROs are key outcomes when evaluating the efficacy of most interventions, and are particularly important endpoints when assessing patients with chronic conditions where disease-free survival is less relevant and the primary aim is to palliate symptoms.⁷⁹ When PRO evidence is used to support the efficacy of products, the FDA requires investigators to be specific about the outcome assessed and the context or situation.⁷⁴ While a number of PROs have been discussed in this chapter, such as pain, anxiety, and depression, the central outcome of interest in this thesis is HRQL, in the context of patients with chronic health conditions prescribed MC.

As indicated above, PROs and HRQL are captured and quantified using validated and reliable standardised PRO measures (PROMs) to allow comparisons between groups, or within groups and individuals, over time. Generic PROMs are designed to measure a range of constructs applicable across diseases and healthy populations, useful for broad comparisons of the relative impact of healthcare across disease types. Whereas condition-specific PROMs are tailored for specific diseases or conditions and are more responsive to subtle changes in

those conditions.

PRO MEASURES

To ensure PROs reliably assess outcomes regarded as important to patients and worded in a way that is meaningful and understandable by patients, guidelines have been established to support the development of standardised PROMs.⁷⁴ This involves psychometrically testing PROM properties (reliability, validity, and responsiveness) with patients in clinical settings to ensure it is sensitive to changes in that outcome.⁷⁴ This rigorous process usually results in a multi-item PROM.

HRQL PROMs are designed to assess the multiple dimensions of HRQL encompassed by its definition. This helps to ensure all patients consider the same aspects of HRQL in their response. Presenting a single item of global HRQL (e.g. “How would you rate your overall quality of life during the past week?”)⁸⁰ following a PROM that comprehensively assesses the multiple dimensions of HRQL likewise primes patients to respond with the same consideration of multidimensionality. However, if we were to use a single item alone and simply ask patients to rate their overall HRQL, the respondent is left with greater ambiguity to interpret the meaning of the item.⁸¹ This would potentially lead to unreliable responses that are challenging for clinicians and researchers to interpret, both at an individual and group level.

To aid in the design and selection of PROMs appropriate for evaluating interventions, the International Society for Quality of Life Research (ISOQOL) recommends the following minimum standards:⁸² 1) A PROM should have documentation defining the concept(s) being evaluated (e.g. HRQL) and who it is intended to be administered to (e.g. cancer patients); 2) Reliability at or above 0.70 (e.g. test-retest reliability showing consistent responses within a

short time period when change is not expected); 3) Evidence of validity - content validity (PROM items are relevant and cover a concept comprehensively), construct validity (PROM scales correlate as expected with other similar and dissimilar PROMs), responsiveness (ability to measure expected change in the outcome over time); 4) Interpretability (documentation on what high and low scores mean); 5) PROM translation (evidence of methods used if the PROM was translated into another language); and 6) Patient and investigator burden (justification for the number of items, frequency of data collection, and literacy demand). Following these minimum standards, researchers can select appropriate PROMs relevant to their research focus, patient group, and intervention evaluated. For example, evaluating HRQL in patients receiving an intervention for chronic back pain would require a PROM with items that capture the impact of back pain on HRQL (discomfort, functioning, and emotional) administered before intervention, when an intervention is expected to work, and when HRQL may be impacted by possible side-effects of the intervention. If patients have a variety of chronic conditions, more generic HRQL PROMs may be used (e.g. RAND SF-36)⁸³, or HRQL PROMs commonly used for cost-utility analyses where health economics is the research focus (e.g. EuroQoL EQ-5D).⁸⁴

HRQL may be interpreted as a single outcome, such as global HRQL, or a set of PRO items covering a number of HRQL domains, depending on the clinical context. Unfortunately, many MC studies use PROMs with limited validity in the conditions assessed,⁴⁷ or have not been validated to assess the outcome of interest. Considering the variety of conditions treated and the diversity of condition-specific PROMs assessed in patients receiving MC, this thesis focuses on HRQL assessment because it provides an overall evaluation using a PRO that is equally important across all chronic conditions. Therefore, comprehensive

assessment of HRQL in patients prescribed currently available MC products is needed to enable clinically relevant evaluation and provide ongoing evidence for decision making both in practice and at a policy level.

RESEARCH AIMS

Health practitioners and researchers need to be able to monitor all treatment outcomes.

HRQL is a widely assessed and important outcome in patients with chronic conditions. Real-world HRQL data from MC patients is needed to develop the current scientific evidence base to inform regulation and policy-making.⁸⁵

The overarching aim of this research is to describe and evaluate HRQL in patients prescribed MC and explore the experiences of patients accessing MC in Australia.

Specific aims for each stage of the research are outlined within each chapter.

RESEARCH STRUCTURE

This thesis, using mixed methods to evaluate HRQL in patients accessing MC, consists of seven chapters, including an Introduction, five published manuscripts (Chapters 2 to 6), and a Discussion with Conclusions (Figure 1).

CHAPTER		KEY MESSAGES
Literature Review	1 Introduction and context of research	- Chronic health issues place significant burden on individuals and the community - MC research increased after discovering the endocannabinoid system in the 1990s - HRQL is an important outcome for people with chronic conditions
	2 How is HRQL assessed & reported in MC studies? <i>Systematic Review & meta-analysis</i>	- Meta-analysis finds moderate short-, and long-term HRQL improvements in patients receiving non-synthetic MC - MC studies rarely define HRQL in context - impacting PROM selection and conclusions - Most used outcome measure is EQ-5D-5L
Quantitative Evaluation	3 Protocol with statistical analysis plan	- Published protocols with analysis plans prevent outcome reporting bias - MCID evaluation is important when large studies potentially detect trivial differences as statistically significant
	4 Short-term HRQL and other PROs with MC <i>Multi-site 3-month pre-post study</i>	2327 participants across Australia - Participants reported significant, clinically-meaningful improvements in HRQL, fatigue, and insomnia - Anxiety, depression, and pain conditions improved over 3-months
	5 Long-term HRQL and group differences with MC <i>Multi-site 12-month pre-post study</i>	2353 participants across Australia - PRO improvements at 3-months were maintained up to 12-months - Greater improvements associated with different CBD:THC ratios and types of health condition
Qualitative Interviews	6 Exploration of patient experience <i>Qualitative interviewing</i>	15 participants across Australia - MC often prescribed to replace opioids and failed conventional medicines - Secondary improvements seen in mental health, productivity, and relationships - GP stance and driving laws seen as barriers
	7 Discussion and conclusions	- Evidence suggests people with chronic health conditions have improved HRQL and symptom management after receiving MC - A review of policy and processes is recommended for timely access to MC to improve patient HRQL

Figure 1. Structural outline of thesis chapters and key messages

Chapter 1 describes the need for collecting HRQL and other PROs using valid methods of measurement in research and in the clinical management of patients with chronic conditions. The emergence of MC as therapy for this patient population is described in its historical and political context. To explore how HRQL is defined and measured in patients treated with MC therapy, **Chapter 2** presents a systematic review of primary research over the past 10 years reporting HRQL in patients receiving MC, including a meta-analysis and narrative summary of study findings.

Chapter 3 presents the protocol for conducting a longitudinal study to assess HRQL in patients prescribed MC in Australia with a statistical analysis plan for analysing outcomes and interpreting the clinical relevance of findings. The longitudinal study is analysed at two timepoints reflecting short-term and long-term results. The overall short-term outcomes across the cohort after 3 months of MC therapy were analysed using linear mixed models and presented in **Chapter 4**. **Chapter 5** reports the follow-up linear mixed models analysis at 12-months to determine whether changes observed at 3-months were maintained long-term. Group differences in change scores are also explored for different health conditions and cannabinoid compositions of MC therapy.

To gain a deeper understanding of patients' lived experience of being prescribed MC in Australia, a phenomenological constructivist approach was used to conduct qualitative interviews with a subset of participants from the longitudinal study described in chapters 4 and 5. As reported in **Chapter 6**, these interviews were thematically analysed through an hermeneutic lens to provide insight into patients' experiences of accessing prescribed MC, and what the outcomes of therapy meant to them.

A discussion of the key findings and clinical implications of this thesis is presented in **Chapter 7**, along with areas for future research and policy recommendations concerning patients with chronic conditions prescribed MC.

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CHAPTER 2

CHAPTER 2: SYSTEMATIC LITERATURE REVIEW AND META-ANALYSIS

CHAPTER OVERVIEW

To understand how HRQL is assessed in patients using MC, and evaluate current evidence and research quality, Chapter 2 presents a systematic review of primary research over the past decade reporting HRQL in patients accessing MC, including a narrative summary and meta-analysis of study findings. This Systematic Review was prospectively registered on the Prospero platform on 27 Feb 2022 (ID: CRD42022306778). Supplementary material referenced in the publication can be found in Appendix 1, along with the PRISMA checklist.

PUBLICATION DETAILS

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AUTHORSHIP ATTRIBUTION STATEMENT

The co-authors confirm the contribution of Margaret-Ann Tait as the primary author, in compliance with the international Committee of Medical Journal Editors (ICMJE) authorship criteria, for the following manuscript:

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Margaret-Ann Tait made the following contributions:

- Conception and design of the research
- Designed the data extraction instrument
- Systematic literature search
- Title and abstract screening
- Full-text screening
- Data extraction
- Data synthesis
- Meta-analyses
- Drafting and revising the paper
- Responding to reviewer comments
- Coordinating the submission of the paper for publication

CR, RC, RN, and DC contributed to the study concept and design. LA contributed to screening and data extraction. All authors contributed towards interpretation of data and reviewed and provided critical feedback on the final manuscript.

As the primary supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

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ABSTRACT

PURPOSE

The global burden of chronic health conditions is significant. Medicinal cannabis (MC) is a legalised treatment option for patients with chronic health conditions in some countries. Health-related quality of life (HRQL) is an important patient-reported outcome across all chronic health conditions. We aimed to determine how studies of MC therapy justify, measure, and report HRQL, and assess the current evidence for HRQL following MC treatment.

METHODS

Systematic review searching OVID Medline, AMED, Web of Science, Scopus, Embase, Cinahl, and PsycINFO from Jan 2015 to Apr 2025. Studies using validated HRQL measures pre-, and post-MC treatment for any chronic health condition were included. Screening and data extraction were performed independently by two reviewers. Completeness of HRQL reporting was evaluated. Meta-analyses for short-term (2-weeks to 3-months), medium-term (>3 to <12-months), and long-term (≥ 12 -months) HRQL outcomes were conducted, with Risk of Bias (RoB) assessed in randomised control trials (RCTs).

RESULTS

Of 16,674 retrieved citations, 64 studies were retained for analysis: 12 RCTs; 38 cohort studies; 13 case series; 1 non-randomised experimental study. Thirty-nine studies (61%) provided justification for assessing HRQL and five (8%) provided HRQL definitions. Studies used generic ($n=52$, 81%) or condition-specific ($n=12$, 19%) HRQL measures, with EQ-5D-5L most commonly used. Meta-analyses: RCTs showed small short-term HRQL improvements ($d=0.30$, $p=0.03$), with some concerns or low RoB. For observational studies, HRQL improved

in all follow-up periods ($d=0.43$ to 0.74 ; all $p<0.001$). HRQL improvement varied between, and within, different health conditions.

CONCLUSION

This systematic review and meta-analyses of studies published between 2015-2025 found that few studies provided HRQL definitions, and a third of studies did not explain why they measured HRQL. To ensure appropriate measures are used for this important treatment outcome, future studies should define HRQL and justify the HRQL assessment in the context of research objectives. Overall, improvements in HRQL were observed across studies of patients using MC.

PLAIN ENGLISH SUMMARY

Medicinal cannabis (MC) is a treatment option for patients in countries where prescribing MC is legal. Health-related Quality of Life (HRQL) can mean different things to different people but remains an important treatment outcome for all patients, regardless of their specific health condition. HRQL varies depending on the context and measurement tool (questionnaire) used. We aimed to find out 1) how HRQL assessment is justified, defined and measured in MC research, and 2) if HRQL improves in patients prescribed MC. We looked at studies published over the past decade that reported HRQL in patients before and after MC treatment. Most studies (81%) used generic HRQL questionnaires (e.g., EuroQol Group: EQ-5D) and others used condition-specific questionnaires (e.g. Multiple Sclerosis Quality of Life: MSQoL-52). Overall, HRQL improved in patients using MC. However, only a few studies provided HRQL definitions, and a third of studies didn't explain why they measured HRQL. This information is needed to ensure HRQL is measured and interpreted appropriately in future studies.

INTRODUCTION

Globally, chronic health conditions place a significant burden on individuals, health systems, and society more broadly, with chronic pain being the leading cause of disability worldwide.¹ The identification of cannabinoids, cannabidiol (CBD) and Δ^9 -tetrahydrocannabinol (THC), as analgesics in 1940 ignited interest in using a cannabis-based medicine as adjunctive treatment for the symptomatic relief of chronic pain.² However, most United Nations countries criminalised the consumption of cannabis in the 1960's,³ consequently limiting research in this area. The past few decades have seen a resurgence of research on cannabis therapy, particularly after the discovery of the endocannabinoid system in the 1990's and its important role in regulating mood and emotional responses.⁴ Medicinal Cannabis (MC) began to be posited as a potential alternative to opioids associated with increasing incidence of adverse events,⁵ including hospitalization and death from overdose.⁶ To enable MC research and build an evidence base for its therapeutic efficacy,⁷ many countries have since revised their policies and introduced legislation to allow the use of cannabis for research and medicinal purposes, starting with Canada in 2001,⁸ and most recently, Ukraine in 2024.⁹

PATIENT-REPORTED OUTCOMES AND THE IMPORTANCE OF HEALTH-RELATED QUALITY OF LIFE

A patient-reported outcome (PRO) is any report coming directly from patients, without interpretation by physicians or others, about how the patient feels in relation to their health condition and its therapy.¹⁰ PROs are particularly important endpoints to include in clinical studies of patients with chronic conditions where the primary aim is to palliate symptoms.¹¹ A validated PRO measure (PROM) is a standardised questionnaire that allows comparisons

between treatment groups, and within groups and individuals over time. PROMs can measure symptom burden, aspects of functioning, and health-related quality of life (HRQL). In this review, HRQL is defined as a *“multidimensional construct encompassing perceptions of the impacts – positive and negative - of a disease or its treatment on physical, emotional, social, and cognitive functions, as well as somatic discomfort and other symptoms”*.¹² There are other definitions of HRQL, for example, *“the value assigned to the duration of survival as modified by the impairment, functional states, perception and social opportunities that are influenced by disease, injury, treatment, or policy.”*¹³ Optimal HRQL is universally valued as an important outcome across all health conditions, making it an important endpoint in clinical research. Considering the various ways of conceptualising HRQL, definitions will depend on the research context. It is important for researchers to be aware that HRQL is often defined, measured, and reported in different ways, and to be explicit about the specific meaning and context of HRQL in their studies.¹⁴ Having a clear definition helps inform the selection of appropriate HRQL measures and improve scientific rigor. This is particularly important considering HRQL results can differ within the same group of patients depending on the PROM used to measure HRQL.¹⁴

PREVIOUS HRQL EVIDENCE FOR MC

Two systematic reviews of HRQL in patients treated with MC have been published covering studies from inception to April 2015: Goldenberg et al 2017,¹⁵ and Whiting et al 2015.¹⁶ Between them, they looked at 14 conditions including chemotherapy-induced nausea and vomiting, chronic pain, multiple sclerosis spasticity, depression, inflammatory bowel disease, anxiety, and sleep disorder. Goldenberg et al found small HRQL improvements in patients with pain, multiple sclerosis, and inflammatory bowel disease.¹⁵ Moderate-quality

evidence supported MC for treating chronic pain and spasticity, but only low-quality evidence for chemotherapy-induced nausea and vomiting, appetite, sleep disorders, and Tourette syndrome.¹⁶ In meta-analyses, overall effect sizes (Cohen's d) were small and non-significant: 0.05 for HRQL¹⁵ compared with controls, and 0.35 for HRQL¹⁵ in pre- and post-therapy observational studies. However, analyses included all available data without categorising results by follow-up period. For example, HRQL assessed two weeks after MC therapy was combined with studies reporting HRQL following many months of therapy.¹⁵ Notably, half of studies included within both reviews used synthetic cannabinoids rather than cannabinoids extracted from the cannabis plant (presumably due to historical legal and access restrictions). Since then, more countries have supported MC research and production, and non-synthetic MC formulations, and methods of administration have been further refined. Furthermore, access to MC often relies on the judgement and clinical justification of a prescribing doctor, which may cover a wider range of health conditions than previously reviewed.

OBJECTIVES AND RESEARCH AIMS

This review analysed all new evidence since 2015 assessing patients' HRQL before and after receiving MC treatment. The research aims were to: 1) determine how HRQL was defined in studies of patients being prescribed MC, and identify which PROMs were used for HRQL assessment and the rationale for choosing them; 2) assess the quality and completeness of HRQL reporting in MC research; and 3) through meta-analyses, determine any short-, medium-, and long-term HRQL improvements in patients receiving MC.

METHODS

LITERATURE SEARCHES

This systematic review was prospectively registered with PROSPERO (CRD42022306778)¹⁷ and followed guidelines from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).¹⁸ Bibliographic databases were searched (OVID MEDLINE, Web of Science, PsycINFO, EMBASE, AMED - Allied and Complimentary Medicine, Scopus, and Cinahl) for studies published since 1 January 2015 until 8 April 2025 using MeSH terms “medical marijuana” or “Cannabis” and “quality of life” or “patient-reported outcome measures”. See Online Resource 1 for example of search strategy used for OVID MEDLINE. Electronic searches were supplemented by a search of reference lists of eligible studies.

INCLUSION CRITERIA

Two reviewers screened studies independently. Randomised and non-randomised controlled trials and longitudinal observational studies with pre-treatment baseline, including cohort studies and case series were included. Only studies of adults (over 18 years) with any diagnosed health condition using MC (prescribed or approved by a medical practitioner) for symptom management, using validated generic or disease-specific multi-item PROMs to assess HRQL at baseline (before therapy) and follow-up (greater than 2-weeks) were included. MC was defined as a non-synthetic pharmaceutical cannabinoid product. Cannabinoid products may constitute one or more of any cannabinoid, including the major cannabinoids; delta-9-tetrahydrocannabinol (THC), and cannabidiol (CBD), and/or minor cannabinoids, for example, cannabichromene (CBC), cannabidivarin (CBDV), cannabichromevarin (CBCV), cannabigerol monomethyl ether (CBGM), cannabinol (CBN),

cannabitol (CBT), tetrahydrocannabitol (THCB), and tetrahydrocannabiorcol (THCC), and many more. Randomised and non-randomised clinical trial comparators included usual care, placebo or no treatment. Observational cohort and case series did not require a control group.

Studies with children and adolescents under 18 years, adults unable to self-report (i.e. assessments by proxy), cross-sectional studies, healthy participants, studies looking at synthetic cannabinoids, and studies not assessing HRQL with validated PROMs were excluded.

Published studies were limited to English language, full text (not conference abstracts), and primary research (not reviews, systematic reviews, meta-analyses, or commentary).

OUTCOMES

Results for overall HRQL were extracted according to predefined time periods: short-term (2 weeks to 3-months), medium term (between 3-months and 12-months), and long-term (12-months or longer), following Cochrane guidelines for systematic reviews in back pain,¹⁹ and time periods reported in similar reviews of chronic health interventions.^{20,21} As patient treatment typically involves a titration period, acute HRQL assessments (within 2 weeks of commencing treatment) were excluded.²² Changes of patient-reported HRQL from baseline to last available follow-up within the predefined time periods were extracted.

DATA EXTRACTION

Standardised data extraction forms developed on the Covidence platform²³ were piloted on a small sample of papers (n=5) and adapted as necessary. To minimise bias and errors, data

extraction involved two independent reviewers. Disagreements were resolved through discussion until consensus was reached or referred to a third reviewer where necessary.

The following information was extracted from included studies: First author; year of publication; country; study design; aim; sample size; health condition(s); MC treatment type; comparison group; HRQL definitions; justification for measuring HRQL; HRQL PROM; assessment timepoints; HRQL results (means; medians; standard deviations; IQR; effect sizes; confidence intervals; statistical tests; odds ratios); and study limitations.

QUALITY ASSESSMENT

The completeness of reporting for included studies was scored formally by two reviewers independently following criteria outlined in the STROBE Checklist for reporting observational studies,²⁴ and CONSORT-PRO checklist for reporting PROs in randomised controlled trials (RCT),²⁵ using data extraction templates managed on the Covidence platform.²³ Existing tools for completeness of reporting quantitative clinical study designs inadequately address key issues for PRO assessment. Therefore, this review assessed the completeness of PRO reporting, specifically. The quality of completeness assessment data extraction template combined CONSORT and STROBE items of similar content and integrated the 14 CONSORT-PRO extension items. To standardise scores across both RCTs and observational studies, items that were RCT-specific were replaced with corresponding STROBE items for observational studies (e.g. CONSORT items 20-22 regarding discussion topics, were replaced with STROBE items 19-21). As typically done with the CONSORT and STROBE checklists, total reporting completeness scores using the revised PRO reporting checklist were calculated as a percentage of total possible score. The final revised PRO reporting checklist of 18 items and criteria are included in Online Resource 2. Additionally,

Risk of Bias (RoB) was assessed separately for RCTs included in the meta-analysis using the revised Cochrane Tool; RoB 2, designed specifically for RCTs and for assisting the interpretation of meta-analyses.²⁶

PRO reporting completeness and RoB 2 was scored by two reviewers independently. Each criterion was scored, and inter-assessor consistency cross-checked with discrepancies discussed until consensus reached.

ANALYSIS

A narrative summary included study characteristics, i.e., study design and aims, population size, geographical location, year, baseline population characteristics, HRQL definition, justification for assessment and PROMs used. Where data was not reported in a format suitable for pooling (e.g. missing measures of variability) or datasets unavailable, study findings were synthesised using descriptive text and tables. Meta-analyses were run separately for studies reporting between group differences and within group differences and for different follow-up time periods (short-, medium-, and long-term). Where multiple studies were conducted on the same participants, analyses for each follow-up time period included data from one report only, selected by highest participant number. A random-effects model with effect size assumed to have a distribution within the population was used to estimate summary measures of effect. Medians and IQR were converted to means and SD using R package (estmeansd).²⁷ For within group analyses, estimates of standard deviation of difference scores and standard error of effect sizes assumed a correlation between repeated measures of $r=0.5$.²⁸ In studies reporting HRQL from multiple PROMs and/or scales, results from one total or utility score were used where possible, chosen as the most comparable with those reported by other included studies. When multiple domain

scores were reported instead of a single HRQL score, previously established domain correlations were used when calculating overall effect size of study (e.g. $r=0.62$ for SF-36 physical and mental composite scores).²⁹ To reduce possible bias from erroneous data, we crossed-checked all statistical information available for determining study effect sizes, including t tests and reported p-values, and where relevant, chose the most conservative estimation for inclusion in meta-analyses. Effect size (Cohen's d) and variation of effect size were calculated in Microsoft Excel spreadsheets, and meta-analyses conducted with IBM SPSS Statistics 28.0 program. As a sensitivity analysis, meta-analyses with high heterogeneity ($\tau^2>0.1$) were re-run without outliers (Cohen's $d>1.5$) and reported separately.

RESULTS

The search yielded 16,674 studies minus duplications. Title, abstract and full text screening resulted in 64 studies of 43,847 patient participants included in our analysis. Results from the search are summarized in the PRISMA diagram (Figure 1). Most studies were observational cohort studies ($n=38$, 59.4%), with the remaining being case series ($n=13$, 20.3%), RCTs using parallel ($n=9$, 14.1%) or crossover ($n=3$, 4.7%) designs, and one non-randomised experimental study (1.5%). An overview of included studies is provided in Online Resource 3. The number of studies conducted in each country is represented in Figure 2 alongside a map of countries and regions where MC is legal. Apart from south African regions and Sri Lanka, the distribution of studies was largely representative of countries where MC is legal. A third of included studies were conducted in the United Kingdom ($n=22$, 34%), with 19 collecting data through the United Kingdom Medical Cannabis Registry. The health conditions of participant groups studied included Chronic Pain

(n=12),^{6,30-40} Multiple Sclerosis (n=8),⁴¹⁻⁴⁸ Cancer (n=5),⁴⁹⁻⁵³ Anxiety disorder (n=4),⁵⁴⁻⁵⁷
 Inflammatory Bowel Disease (includes Crohn's disease and Ulcerative colitis) (n=4),⁵⁸⁻⁶¹
 Epilepsy (n=3),⁶²⁻⁶⁴ Fibromyalgia (n=3),⁶⁵⁻⁶⁷ Arthritis (n=2),^{68,69} Sleep disorder (n=2),^{70,71}
 Chronic neuropathic pain (n=2),⁷² HIV (n=2),^{72,73} Post Traumatic Stress Disorder (n=1),⁷⁴
 Primary Headache Disorder (n=1),⁷⁵ Hypertension (n=1),⁷⁶ or any condition eligible for MC
 (n=16).⁷⁷⁻⁹¹ Online Resource 4 lists health conditions of all participants treated with MC in
 this review (including studies recruiting patients with any condition eligible for MC).

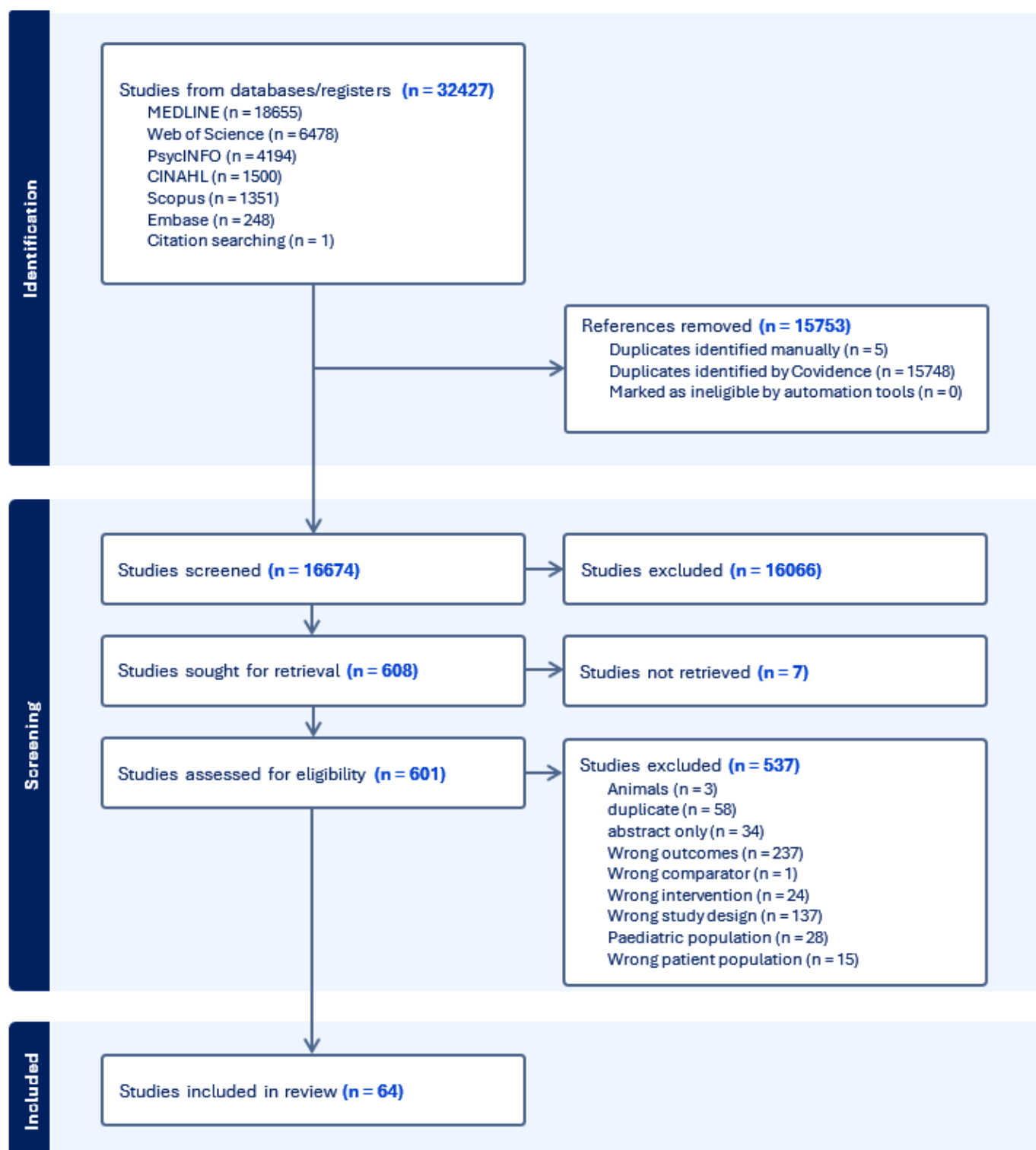


Figure 1. PRISMA flow diagram of studies through the review process

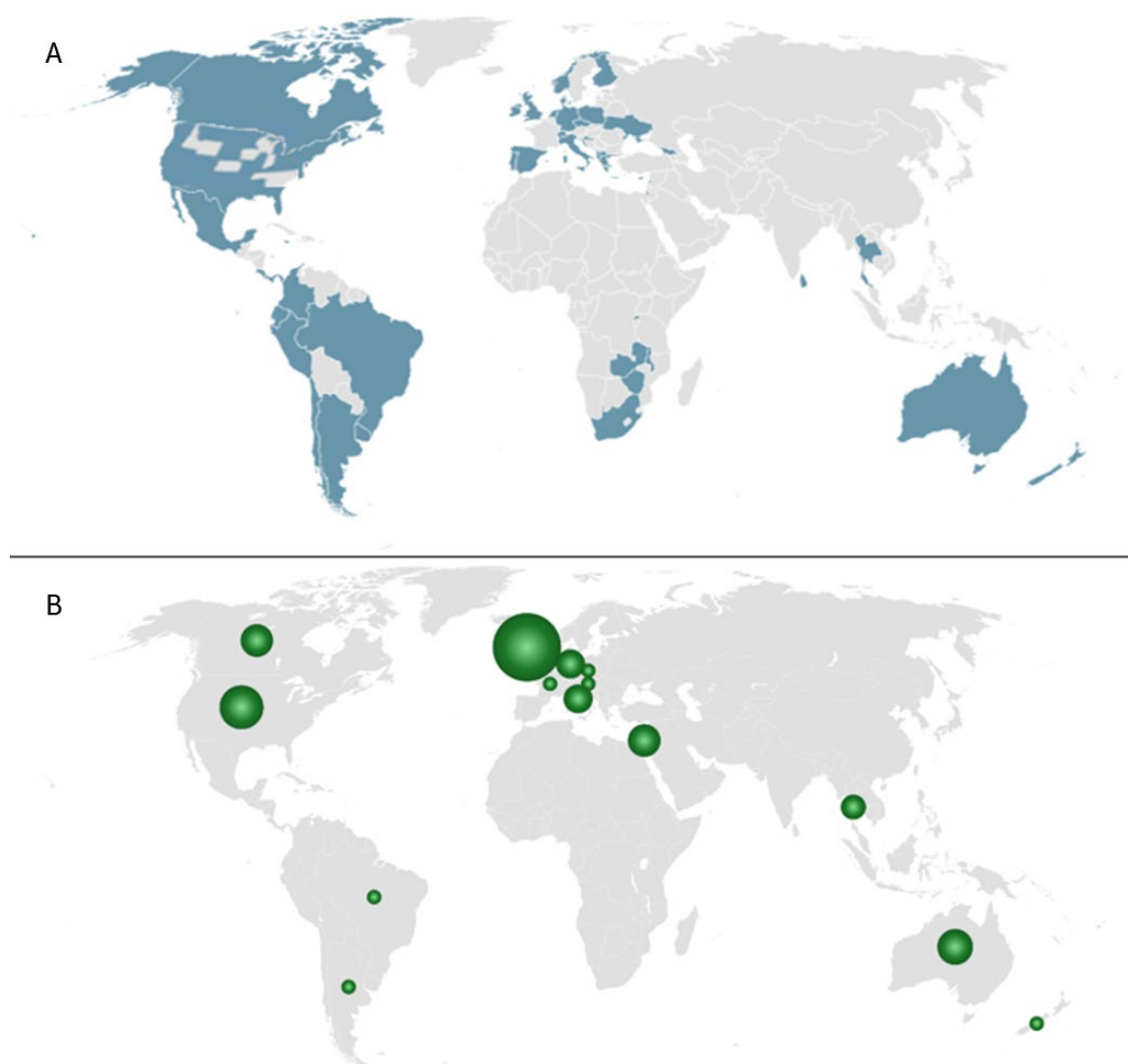


Figure 2. A) Countries and regions where MC is legal and **B)** Bubble plot distribution of studies assessing HRQL in MC patients globally.

HOW HRQL IS DEFINED, JUSTIFIED AND EVALUATED

Although 51 of the 64 studies (80%) mentioned HRQL (or quality of life) in the title or abstract, and 34 (53%) reported HRQL as their primary outcome, only five (8%) studies provided a definition of HRQL (table 1).^{38,76,80,83,85} References for HRQL definitions were provided by four of the five studies and sourced from Osoba et al.¹² and the US Centres for

Disease Control and Prevention.⁹² A reason or justification for including HRQL as an endpoint was provided in 39 (61%) studies. PROMs used to assess HRQL and the methods for reporting HRQL varied across studies. Most studies (n=51; 80%) provided references for PROMs (table 1). Of the 52 (81%) studies using generic HRQL PROMS, the most frequently used was the EuroQol Group EQ-5D-5L,⁹³ (n=31, 48%) or earlier version EQ-5D-3L (n=1, 1.5%), reporting five domain scores and a single utility index (n=24, 37%), score from the visual analogue scale presented at the end of the PROM (n=5, 8%), or five domain scores only (n=2, 3%). Another frequently used generic PROM was the RAND SF-36⁹⁴ (n=14, 22%) or shorter version, SF-12 (n=2, 3%), typically reporting two composite summary scores, physical and psychological (n=6, 9%), 8 domain scores (n=7, 11%), or a total score (n=2, 3%)(table 1). Twelve studies (19%) used condition-specific HRQL PROMs; most frequently, the Multiple Sclerosis Quality of Life,⁹⁵ (MSQoL-54; n=3, 5%); and variants of the Quality of Life in Epilepsy scale,⁹⁶ QOLIE-89, QOLIE-31P, and QOLIE-10 (n=3) (table 1). One study utilised four PROMs covering pain, sleep, and mood and collectively referred to them as measuring HRQL⁴⁰. Table 1 displays characteristics of all included studies and a summary of significant or clinically important PRO findings.

Table 1. Study characteristics, HRQL reporting, and summary of findings of included studies.

Author, Year [ref]	Health Condition	MC composition	Total N (% male)	Mean Age (SD or range)	Follow-up [Recruitment dates]	Study Design	HRQL assessment justified?	HRQL definition? [citation?]	HRQL PROM(s) [citation?]	Summary of HRQL findings
Aiewtrakoon et al., 2024 [71]	Insomnia	CBD	45 (33)	45.96 (11.7)	2-w [Sep 2021 - Apr 2023]	RCT crossover	no	no	EQ-5D-5L [no]	Improved HRQL compared with placebo at 2-weeks (index score).
Arkell et al., 2023 [77]	Any condition	THC:CBD	3148 (46.4)	55.9 (18.7)	20-m [Dec 2018 - May 2022]	Case series	yes	no	SF-36 [yes]	Improved HRQL at 12-months (across all 8 domains).
Aungsumart et al., 2021 [46]	Multiple Sclerosis spasticity	THC:CBD	7 (42.8)	41.3 (1.8)	12-w [Nov 2019 - Jun 2020]	Cohort study	yes	no	EQ-5D-5L [no]	No change in HRQL at 12-weeks (index score).
[‡] Bapir et al., 2023 [34]	Chronic Pain	CBD/THC/ THC:CBD	1254 (54.1)	45.7 (14.4)	3-m 6-m [Dec 2021 - Jan 2022]	Cohort study	yes	no	EQ-5D-5L [yes]	Improved HRQL at 3- and 6-months (index score).
Barre et al., 2024 [73]	HIV	CBD	79 (69.6)	55.97 (12.8)	12-w [May 2022 - Oct 2022]	RCT parallel	yes	no	SF-36 [yes]	No change in HRQL compared with placebo at 12-weeks (physical and mental composite summary scores). Of 8 domains, only physical functioning improved.
Bar-Sela et al., 2019 [50]	Cancer	THC:CBD	34 (41)	63 (nr)	3-m ['2 years']	Non-randomised experimental	no	no	QLQ-30 [yes]	No change in HRQL at 3- months (global QoL). Improved insomnia and appetite (QLQ-C30 domains).
Brett et al., 2024 [62]	Epilepsy	CBD	17 (50)	34.6 (18 - 64)	2.5-m 5-m [Aug 2017 - Jun 2019]	Cohort study	yes	no	QOLIE-31P [yes]	Improved HRQL at 5-months (total score).
Capano et al., 2020 [40]	Chronic Pain	CBD	97 (32)	56.2 (39 - 70)	8-w [Sep 2018 - Dec 2018]	Cohort study	no	no	PHQ-4, PDI, PSQI, PEG [no]	Improved HRQL at 8-weeks (sleep and pain PROMs only). No improvement in PHQ-4 or PDI.
Chaves et al., 2020 [67]	Fibromyalgia	THC	18 (0)	51.9 (nr)	8-w [Sep 2019 - Nov 2019]	RCT parallel	yes	no	FIQ [yes]	Improved HRQL compared with placebo at 8-weeks (total score).
[‡] Datta et al., 2025 [33]	Chronic Pain	CBD/THC/ THC:CBD	1139 (54)	47 (14.1)	3-m 6-m 12-m [Dec 2019 - Jan 2023]	Cohort study	yes	no	EQ-5D-5L [yes]	Improved HRQL at 3-, 6- and 12-months (index score).

Author, Year [ref]	Health Condition	MC composition	Total N (% male)	Mean Age (SD or range)	Follow-up [Recruitment dates]	Study Design	HRQL assessment justified?	HRQL definition? [citation?]	HRQL PROM(s) [citation?]	Summary of HRQL findings
[‡] Dickinson et al., 2025 [30]	Chronic Pain (Hypermobility-associated)	THC:CBD	161 (19.3)	37.42 (10.5)	3-m 6-m 18-m [Dec 2019 - Dec 2023]	Case series	no	no	EQ-5D-5L [yes]	Improved HRQL at 3-, 6- and 18-months (index score).
Dujic et al., 2024 [76]	Hypertension	CBD	64 (57.8)	54.4 (8.9)	5-w [Dec 2021 - Apr 2022]	RCT crossover	yes	yes [no]	SF-36 [yes]	No change in HRQL compared with placebo at 5-weeks (VAS presented after SF-36). Of 8 domains, only fatigue and psychological well-being improved.
Eibach et al., 2021 [72]	HIV-Associated Neuropathic Pain	CBDV	32 (97)	50.31 (9)	3-w [Jan 2017 - Jan 2019]	RCT crossover	yes	no	SF-36 [yes]	No change in HRQL compared with placebo at 3-weeks (across all 8 domains).
[†] Ergisi et al., 2023 [78]	Any condition	THC:CBD	312 (55.1)	44.8 (15.4)	3-m 6-m [Dec 2019 - nr]	Case series	yes	no	EQ-5D-5L [no]	Improved HRQL at 3- and 6-months (index score).
[†] Erridge et al., 2021 [79]	Any condition	THC:CBD	129 (51.2)	46.23 (14.5)	3-m [Dec 2019 - nr]	Case series	yes	no	EQ-5D-5L [yes]	Improved HRQL at 3-months (VAS).
[‡] Francis et al., 2024 [68]	Inflammatory Arthritis-associated Chronic Pain	THC:CBD	82 (50)	47.61 (14.3)	3-m 6-m 12-m [Dec 2019 - Jan 2023]	Case series	no	no	EQ-5D-5L [yes]	Improved HRQL at 3-, 6- and 12-months (index score).
[‡] Francis et al., 2024b [69]	Osteoarthritis-related Chronic Pain	THC:CBD	77 (52)	60.04 (14.3)	3-m 6-m 12-m [Dec 2019 - Jan 2022]	Case series	yes	no	EQ-5D-5L [yes]	Improved HRQL at 3- and 6-months (index score).
Gaston et al., 2019 [64]	Epilepsy	CBD	53 (50.9)	nr	12-m [nr]	Cohort study	yes	no	QOLIE-89 [yes]	Improved HRQL at 12-months (total score).
Gruber et al., 2016 [91]	Any condition	THC:CBD	11 (55)	48.91 (15.1)	3-m [nr]	Cohort study	no	no	SF-36 [yes]	Improved HRQL at 3-months (fatigue domain only).
Gruber et al., 2021 [39]	Chronic Pain	THC:CBD	37 (44)	54.87 (14.0)	3-m 6-m [nr]	Cohort study	yes	no	SF-36 [yes]	Improved HRQL at 3- and 6-months (fatigue, pain and general health domains only).

Author, Year [ref]	Health Condition	MC composition	Total N (% male)	Mean Age (SD or range)	Follow-up [Recruitment dates]	Study Design	HRQL assessment justified?	HRQL definition? [citation?]	HRQL PROM(s) [citation?]	Summary of HRQL findings
Gulbransen et al., 2020 [90]	Any condition	CBD	397 (46.1)	51.48 (19.1)	3-w [Dec 2017 - Dec 2018]	Cohort study	no	no	EQ-5D-5L [yes]	Improved HRQL at 3-weeks (VAS).
Gupta et al., 2024 [58]	Inflammatory Bowel Disease	THC:CBD	116 (81)	39 (9.1)	3-m 6-m 18-m [Dec 2019 - Dec 2023]	Case series	yes	no	EQ-5D-5L [yes]	Improved HRQL at 3-, 6- and 18-months (index score).
Hardy et al., 2023 [52]	Advanced Cancer	CBD	144 (52.8)	64.6 (12.8)	28-days [Feb 2019 - Nov 2021]	RCT parallel	no	no	QLQ-C15 [yes]	No change in HRQL compared with placebo at 28-days (global QoL).
Haroutounian et al., 2016 [6]	Chronic Pain	THC:CBD	206 (61.7)	51.2 (15.4)	6-m [Jun 2010 - Jan 2013]	Cohort study	no	no	S-TOPS [yes]	Improved HRQL at 6-months (all except physical disability domains).
Haupts et al., 2016 [48]	Multiple Sclerosis spasticity	THC:CBD	241 (42)	49.1	3-m [nr]	RCT parallel	yes	no	EQ-5D-5L SF-36 [no]	No change in HRQL compared with placebo at 3-months (EQ-5D index score and across SF-36 domains).
Haupts et al., 2024 [42]	Multiple Sclerosis spasticity	THC:CBD	54 (39)	51.4 (11.1)	12-w [Dec 2021 - Jan 2023]	Cohort study	no	no	MFHW [yes]	No change in HRQL at 12-weeks (total score).
Hershkovich et al., 2023 [66]	Fibromyalgia	THC:CBD	30 (0)	46 (5)	1-month [nr]	Cohort study	yes	no	WHOQOL-BREF [yes]	Improved HRQL at 1-month (pain, sleep, physical, and psychological domains only).
Irving et al., 2018 [61]	Inflammatory Bowel Disease (Ulcerative colitis)	CBD	60 (79)	43.77 (13.9)	10-w [nr]	RCT parallel	no	no	IBDQ [no]	Improved HRQL compared with placebo at 10-weeks (total score).
[‡] Kawka et al., 2021 [32]	Chronic Pain	THC:CBD	110 (49.1)	52.1 (15.4)	3-m 6-m [Dec 2019 - nr]	Case series	yes	no	EQ-5D-5L [yes]	Improved HRQL at 3-months (index score).
Kelley et al., 2024 [81]	Any condition	THC:CBD	103 (39.8)	nr (18 - 65+)	30-days [nr]	Cohort study	yes	no	SF-36 [no]	Improved HRQL at 30-days (across all domains).
Lamonarca et al., 2024 [63]	Epilepsy	CBD	44 (34)	35 (10)	3-m 6-m [nr]	Cohort study	yes	no	QOLIE-10 [yes]	Improved HRQL at 3- and 6-months (total score).

Author, Year [ref]	Health Condition	MC composition	Total N (% male)	Mean Age (SD or range)	Follow-up [Recruitment dates]	Study Design	HRQL assessment justified?	HRQL definition? [citation?]	HRQL PROM(s) [citation?]	Summary of HRQL findings
Lent et al., 2024 [83]	Any condition	THC:CBD	438 (33.6)	46.4 (15.6)	3-m [Sep 2020 - Jun 2023]	Cohort study	yes	yes [yes]	SF-36 [yes]	Improved HRQL at 3-months (across all domains).
# Li et al., 2024 [54]	Generalised Anxiety Disorder	THC:CBD	120 (61.7)	39.38 (12.48)	3-m 6-m 12-m [Dec 2019 - nr]	Case series	no	no	EQ-5D-5L [yes]	Improved HRQL at 3-, 6- and 12-months (index score).
Lucas et al., 2021 [89]	Any condition	CBD/THC/ THC:CBD	1145 (42.4)	51.2 (15.4)	3-m 6-m [nr]	Cohort study	no	no	WHOQOL-BREF [yes]	Improved HRQL at 3- and 6-months (across all 4 domains).
Lynskey et al., 2024 [82]	Any condition	THC:CBD	198 (47)	72.2	3-m [Aug 2020 - Apr 2023]	Cohort study	yes	no	EQ-5D-5L [yes]	Improved HRQL at 3-months (index score).
Markova et al., 2019 [47]	Multiple Sclerosis spasticity	THC:CBD	191 (29.8)	51.3 (10.2)	12-w [nr]	RCT parallel	yes	no	SF-36 [no]	No change in HRQL compared with placebo at 12-weeks (general health domain).
Meng et al., 2021 [88]	Chronic Pain	THC:CBD	757 (38.3)	nr (18 - 65+)	3-m 6-m 12-m [Sep 2015 - Jul 2018]	Cohort study	yes	no	EQ-5D-3L [yes]	Improved HRQL at 3-, 6- and 12-months (EQ-5D VAS).
# Murphy et al., 2024 [55]	General Anxiety Disorder	THC:CBD	302 (69.5)	38.06 (11.7)	3-m 6-m 12-m [Dec 2019 - Jan 2023]	Case series	yes	no	EQ-5D-5L [yes]	Improved HRQL at 3-, 6- and 12-months (index score).
Murphy et al., 2024b [41]	Multiple Sclerosis	THC:CBD	141 (48.9)	45.89 (11.1)	3-m 6-m [Dec 2019 - Aug 2022]	Cohort study	yes	no	EQ-5D-5L MSQoL-54 [yes]	Improved HRQL at 3 and 6 months (EQ-5D index score and MSQoL-54 physical and mental composite summary scores).
Naftali et al., 2021 [59]	Inflammatory Bowel Disease (Crohn's Disease)	THC:CBD	56 (33)	34.5 (11)	8-w [2013 - 2018]	RCT parallel	no	no	SF-36 [yes]	Improved HRQL compared with placebo at 8-weeks (total score).
Naftali et al., 2021b [60]	Inflammatory Bowel Disease (Ulcerative colitis)	THC	32 (56)	32 (10.86)	8-w [nr]	RCT parallel	yes	no	SF-36 [yes]	Improved HRQL compared with placebo at 8-weeks (total score).

Author, Year [ref]	Health Condition	MC composition	Total N (% male)	Mean Age (SD or range)	Follow-up [Recruitment dates]	Study Design	HRQL assessment justified?	HRQL definition? [citation?]	HRQL PROM(s) [citation?]	Summary of HRQL findings
Nathan et al., 2023 [51]	Cancer	THC:CBD	83 (58)	nr (65 - 81+)	3-m [Jan 2018 - Dec 2018]	Cohort study	no	no	ESAS [no]	No change in HRQL at 3-months (across all domains).
Nicholas et al., 2023 [75]	Headache Disorder	THC:CBD	97 (57)	37.9 (11.1)	3-m 6-m [Dec 2019 - Feb 2022]	Cohort study	yes	no	EQ-5D-5L [yes]	Improved HRQL at 3- and 6-months (index score).
Palmieri et al., 2019 [87]	Any condition	THC	20 (60)	40.7 (nr)	3-m [nr]	Cohort study	no	no	SF-36 [yes]	Improved HRQL at 3-months (across 6 domains). No change in role limitations and emotional state domains.
Peterson et al., 2021 [38]	Chronic Pain	THC:CBD	181 (47)	41.21 (12.9)	6-w ['Summer and Autumn' 2020]	Cohort study	yes	yes [yes]	EQ-5D-5L [yes]	Improved HRQL at 6-weeks (index score). Worsening in self-care domain.
# Rifkin-Zybutz et al., 2023 [57]	Anxiety disorder	THC:CBD	202 (68.6)	37 (11.5)	3-m 6-m [Dec 2019 - nr]	Cohort study	yes	no	EQ-5D-5L [yes]	Improved HRQL at 3- and 6-months (index score).
Russo et al., 2016 [45]	Multiple Sclerosis (Neuropathic Pain)	THC:CBD	20 (40)	46 (5.8)	1-month [nr]	Cohort study	no	no	MSQoL-54 [no]	Improved HRQL at 1-month (physical and mental composite summary scores).
Russo et al., 2016b [44]	Multiple Sclerosis spasticity	THC:CBD	61 (nr)	42 (8.9)	1-m 6-m [Jan 2014 - Dec 2014]	Cohort study	no	no	MSQoL-54 [yes]	Deterioration of HRQL at 1-month (physical composite summary score). Improved HRQL at 6-months (mental composite summary scores).
Safakish et al., 2020 [37]	Chronic Pain	THC:CBD	751 (43)	49.6 (14.3)	3-m 6-m 12-m [Oct 2015 - Mar 2019]	Cohort study	yes	no	SF-12 [yes]	Improved HRQL over 12-months (physical and mental composite summary scores).
Schloss et al., 2021 [53]	Cancer (Glioma)	THC:CBD	83 (51)	53.3 (12.6)	12-w [Nov 2018 - Dec 2019]	RCT parallel	no	no	FACT-Br [yes]	No change in HRQL at 12-weeks (total score). Improved sleep and physical wellbeing domains.
Sridharan et al., 2024 [65]	Fibromyalgia	THC:CBD	148 (19.6)	47.2 (13.5)	3-m 6-m 12-m [Dec 2019 - Jan 2023]	Cohort study	yes	no	EQ-5D-5L [yes]	Improved HRQL at 3-, 6- and 12-months (index score).

Author, Year [ref]	Health Condition	MC composition	Total N (% male)	Mean Age (SD or range)	Follow-up [Recruitment dates]	Study Design	HRQL assessment justified?	HRQL definition? [citation?]	HRQL PROM(s) [citation?]	Summary of HRQL findings
Stienrut et al., 2024 [84]	Any condition	THC:CBD	21,284 (52.5)	54.1 (15.3)	3-m [Sep 2019 - Oct 2020]	Cohort study	yes	no	EQ-5D-5L [yes]	Improved HRQL at 3-months (index score).
Sultan et al., 2024 [74]	Post-Traumatic Stress Disorder	THC	58 (66)	39.2 (8.9)	3-m 6-m [Aug 2020 - Apr 2023]	Cohort study	no	no	EQ-5D-5L [yes]	Improved HRQL at 3- and 6-months (EQ-5D VAS).
[†] Tait, J et al., 2023 [35]	Chronic Pain	THC:CBD	761 (47.3)	46.8 (15.4)	3-m 6-m [Dec 2019 - Jan 2022]	Cohort study	yes	no	EQ-5D-5L [yes]	Improved HRQL at 3- and 6-months (index score). No improvements at 6 months using MC flower.
[*] Tait, M et al., 2023 [85]	Any condition	CBD/ THC:CBD	2327 (37.2)	51 (15.4)	3-m [Nov 2020 - Dec 2021]	Cohort study	yes	yes [yes]	EQ-5D-5L QLQ-C30 [yes]	Improved HRQL at 3- months (EQ-5D index score and QLQ-C30 summary score).
[*] Tait, M et al., 2025 [80]	Any condition	CBD/ THC:CBD	2353 (37.2)	50.4 (15.4)	9-m 12-m [Nov 2020 - Mar 2023]	Cohort study	yes	yes [yes]	EQ-5D-5L QLQ-C30 [no]	Improved HRQL at 9- and 12-months (EQ-5D index score and QLQ-C30 summary score).
Ueberall et al., 2019 [31]	Chronic Pain	THC:CBD	800 (43)	46.3 (9.7)	12-w [Mar 2017 - Dec 2017]	Case series	yes	no	SF-12 [yes]	Improved HRQL at 12-weeks (physical and mental composite summary scores). Deterioration only in patients with nociceptive pain.
Varadpande et al., 2025 [49]	Cancer Pain	THC:CBD	168 (60.7)	54.2 (14.6)	3-m 6-m [Dec 2019 - Dec 2023]	Case series	no	no	EQ-5D-5L [yes]	Improved HRQL at 3- and 6-months (index score).
Vermersch et al., 2016 [43]	Multiple Sclerosis spasticity	THC:CBD	433 (44.8)	50.4 (10.4)	3-m [Aug 2013 - Oct 2015]	Cohort study	no	no	EQ-5D-5L [no]	Improved HRQL at 3-months (EQ-5D VAS).
Vickery et al., 2022 [97]	Any condition	CBD/THC/ THC:CBD	3961 (46)	56.1 (19.2)	3-m 24-m [Dec 2018 - Apr 2022]	Cohort study	no	no	SF-36 [yes]	Improved HRQL at 3-, 12-, and 24- months (physical and mental composite summary scores).
Vigano et al., 2023 [86]	Any condition	THC:CBD	2991 (49.8)	50.9 (18 - 96)	3-m 9-m 12-m [May 2015 - Oct 2018]	Cohort study	no	no	EQ-5D-5L [yes]	Improved HRQL at 3- and 12-months (global QoL).

Author, Year [ref]	Health Condition	MC composition	Total N (% male)	Mean Age (SD or range)	Follow-up [Recruitment dates]	Study Design	HRQL assessment justified?	HRQL definition? [citation?]	HRQL PROM(s) [citation?]	Summary of HRQL findings
Vivek et al., 2024 [70]	Insomnia	THC:CBD	61 (72)	41.3 (13.0)	3-m 6-m [Dec 2019 - Feb 2022]	Case series	yes	no	EQ-5D-5L [yes]	Improved HRQL at 3- and 6-months (index score).
Ware et al., 2015 [36]	Chronic Pain	THC:CBD	431 (51.6)	45.5 (19 - 82)	6-m 12-m [Jan 2004 - Apr 2008]	Cohort study	no	no	SF-36 [no]	Improved HRQL compared with control group at 6- and 12-months (physical composite summary score). No change in mental composite summary score.
# Warner-Levy et al., 2024 [56]	Generalised Anxiety Disorder	THC:CBD	302 (69.5)	38.06 (11.7)	3-m 6-m 12-m [Dec 2019 - Jan 2023]	Cohort study	yes	no	EQ-5D-5L [yes]	Improved HRQL at 3-, 6-, and 12-months (index score).

* Papers report HRQL from same study cohort (2353 patients in QUEST study) but at different follow-up assessment timepoints (n=2).

Papers report HRQL from same study cohort (302 patients with anxiety on UK Medical cannabis Registry) at same follow-up assessment timepoints (n=4).

‡ Papers report HRQL from same study cohort (1254 patients with chronic pain on UK Medical cannabis Registry) at overlapping follow-up assessment timepoints (n=7).

† Papers report HRQL from same study cohort (312 patients with any condition on UK Medical cannabis Registry) at overlapping follow-up assessment timepoints (n=2).

CBD, cannabidiol (only); **CBDV**, cannabidivarin; **EQ-5D-3L**, EuroQol quality of life -5 dimensions-3 levels; **EQ-5D-5L**, EuroQol quality of life -5 dimensions-5 levels; **ESAS**, Edmonton Symptom Assessment Score; **FACT-Br**, Functional Assessment of Cancer Therapy – Brain; **FIQ**, Fibromyalgia Impact Questionnaire; **HRQL**, health-related quality of life; **IBDQ**, Inflammatory bowel disease questionnaire; **m**, months; **MC**, medicinal cannabis; **MFHW**, Marburg questionnaire on habitual health; **MSQoL-54**, Multiple Sclerosis Quality of Life-54 items; **nr**, not reported; **PDI**, Pain Disability Index; **PEG**, 3-item scale assessing Pain Intensity and Interference; **PHQ-4**, Patient Health Questionnaire-4 items; **PROM**, patient-reported outcome measure; **PSQI**, Pittsburgh Sleep Quality Index; **QLQ-C30**, Quality of Life Questionnaire - Cancer 30 items; **QLQ-C15**, Quality of Life Questionnaire - Cancer 15 items for use in palliative care; **QoL**, quality of life; **QOLIE-89**, Quality Of Life In Epilepsy-89 items; **QOLIE-31-P**, Quality Of Life In Epilepsy-31items-plus 8 distress-related items; **QOLIE-10**, Quality Of Life In Epilepsy-10 items; **RCT**, randomised controlled trial; **ref**, reference; **SD**, standard deviation; **SF-36**, Short Form Health Survey -36 items; **SF-12**, Short Form Health Survey -12 items; **S-TOPS**, Treatment Outcomes in Pain Survey-Short Form; **THC**, delta-9-tetrahydrocannabinol (only); **THC:CBD**, combination of THC and CBD; **VAS**, visual analogue Scale **w**, weeks; **WHOQOL-BREF**, World Health Organisation Quality of Life Abbreviated Assessment.

QUALITY AND COMPLETENESS OF PRO REPORTING

When evaluating all 64 included studies for completeness of reporting using the composite STROBE and CONSORT-PRO criteria, 40/64 (63%) studies met 75% or more of PRO reporting criteria either fully or partially, and one study failed to meet more than 50% of criteria (Online Resource 5). Figure 3 displays the degree to which each PRO reporting criterion was met across all included studies. All studies reported recruitment procedures, baseline characteristics, and described PRO or HRQL domains. More than half of studies failed to describe sample size calculations or attempts to minimise bias. Looking specifically at the 52 observational studies, 32 (62%) reported no attempts to address bias (i.e., have high risk of bias).

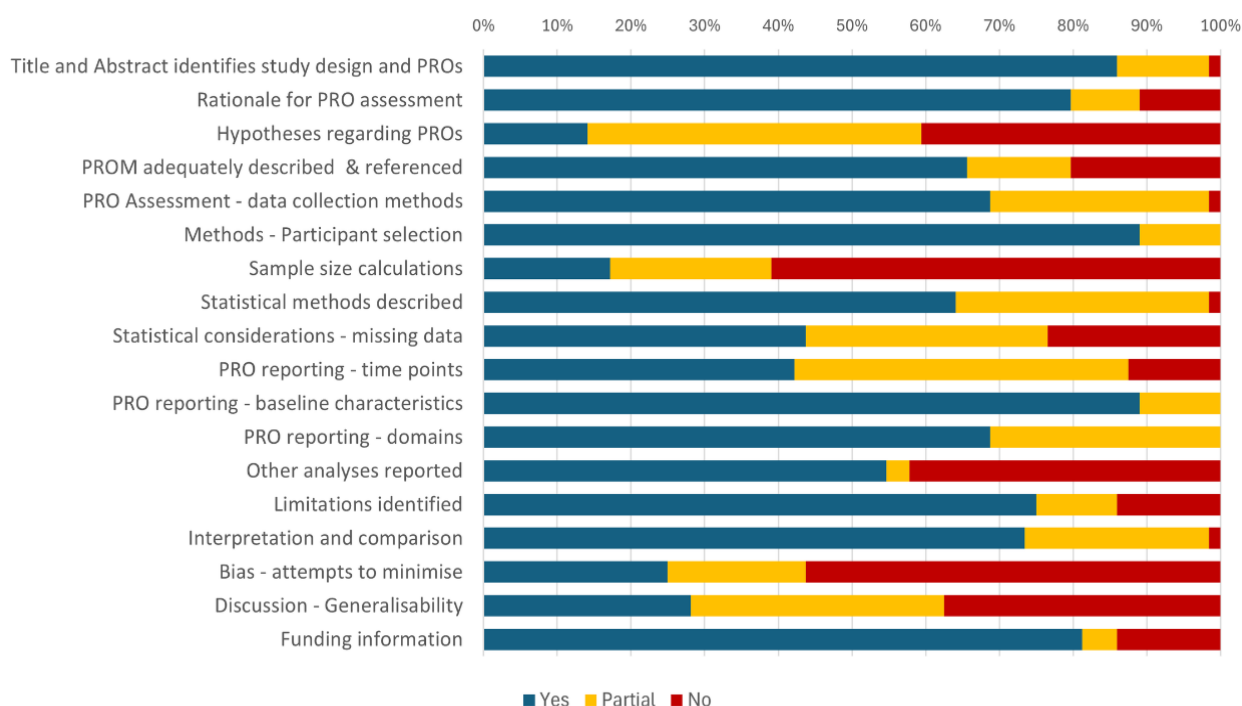


Figure 3. Completeness of PRO reporting for included studies (n = 64) displayed as % of criteria met.

None of the 8 RCTs included in the meta-analysis showed high risk of bias on any of the RoB 2 tool criteria and all were evaluated as having low risk of reporting bias (figure 4). Ratings for each RCT against RoB 2 items are presented in Online Resource 6, and overall RoB rating added to figure 5.

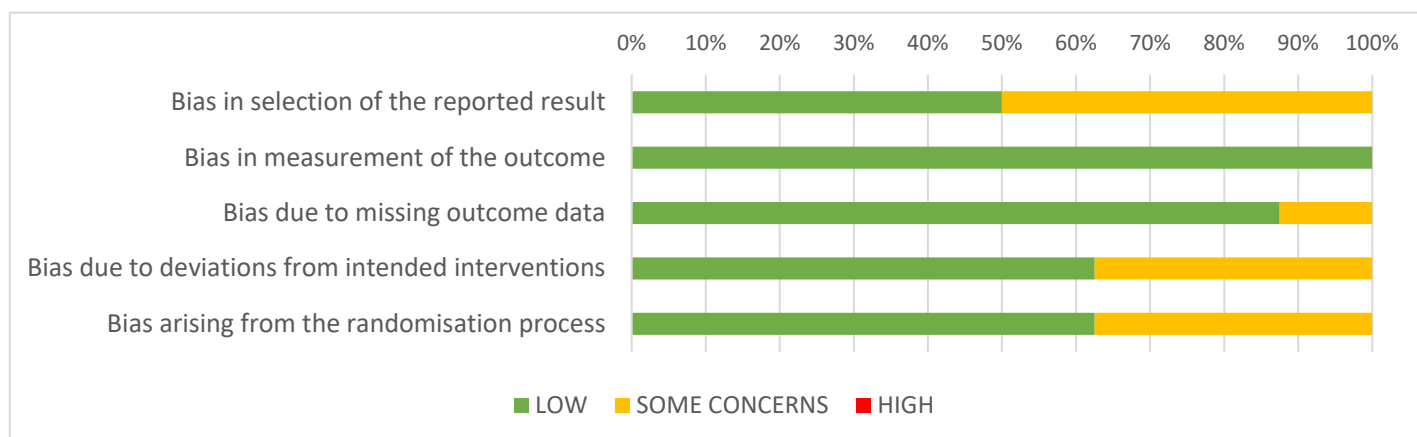


Figure 4. Risk of Bias graph: review of ratings for each RoB 2 criteria presented as percentage across 8 RCTs included in meta-analysis.

META-ANALYSES BY STUDY DESIGN

SHORT-TERM BETWEEN GROUP DIFFERENCES

Of the 12 studies comparing between group differences (cannabinoid treatment group vs placebo or controls), eight reported sufficient data to be included in a meta-analysis (Fig. 5). Of excluded studies, one did not report any measure of variability (standard deviations, IQR, or confidence intervals), one reported improvement from baseline but provided post-treatment HRQL scores only, one simply stated the difference was not significant, and one study reported >30% improvement responder rates across multiple domains. The eight included studies were all RCTs, either parallel (n=7) or crossover (n=1), with treatment

periods ranging from 4-weeks to 3-months (short-term). Between group effect sizes ranged from -0.03 to 1.74, with an overall effect size of 0.30 (95% CI: 0.03 to 0.57; $p=0.03$; $\tau^2=0.09$) favouring cannabinoids. Only two studies found statistically significant HRQL improvements. Across conditions, subgroup analyses by MC composition revealed THC interventions ($d=1.30$; 95%CI: 0.68 to 1.92; $p<0.001$) were more effective for improving HRQL than CBD alone ($d=0.07$; 95%CI: -0.13 to 0.27; $p=0.47$). Meta-analysis was conducted after removing the outlier with effect size greater than ± 1.5 (i.e., Chaves 2020), revealing a small overall effect size of 0.15 (95%CI: 0.01 to 0.30; $p=0.04$; $\tau^2=0.00$). Further subgroup analyses by health condition found MC least effective for improving HRQL in HIV-associated neuropathic pain and hypertension, with larger HRQL improvements in studies of fibromyalgia and Inflammatory Bowel Disease ($d=0.57$; 95%CI: 0.24 to 0.90; $p<0.001$).

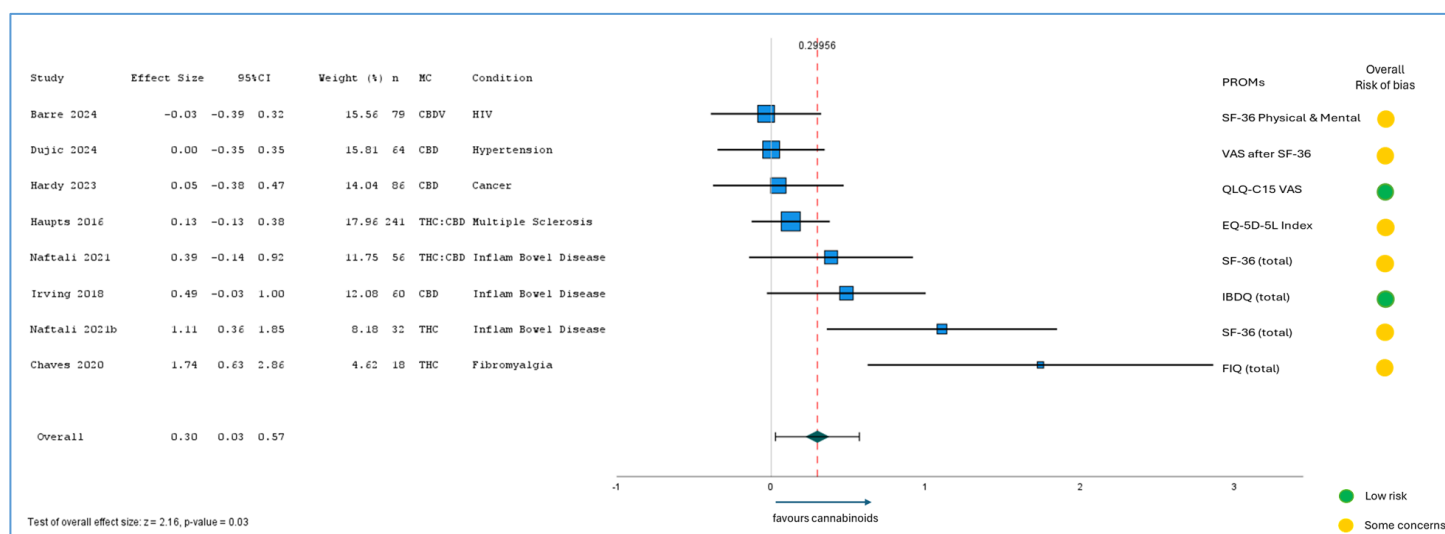


Figure 5. Meta-Analysis Results from RCTs ($n=9$) assessing short-term HRQL after MC (2-weeks to 3-months).

CBD, cannabidiol; CBDV, cannabidivarin; EQ-5D-5L, EuroQol quality of life -5 dimensions-5 levels; FIQ, Fibromyalgia Impact Questionnaire; HRQL, health-related quality of life; IBDQ, Inflammatory bowel disease questionnaire; PROM, patient-reported outcome measure; QLQ-C15, Quality of Life Questionnaire - Cancer 15 items for use in palliative care; RCT, randomised controlled trial; SF-36, Short Form Health Survey -36 items; THC, delta-9 tetrahydrocannabinol; VAS, visual analogue Scale.

SHORT-TERM WITHIN GROUP DIFFERENCES

Of the 46 studies evaluating short-term within group differences (pre- and post-cannabinoid treatment), 29 reported sufficient data and were eligible for meta-analysis (Fig. 6). Of the 17 excluded studies, 10 assessed participants from an already included study, and seven did not report a measure of variability or usable test statistic. The 29 included studies were all observational, either cohort (n=24) or case series (n=5), with treatment periods ranging from 3-weeks to 3-months (short-term). Seventy-nine percent (n = 23) of studies found significant improvements in HRQL over the first 3-months of MC therapy. Within group effect sizes ranged from -2.12 to 2.98, with an overall effect size of 0.43 (95% CI: 0.19 to 0.67; $p < 0.001$; $\tau^2 = 0.40$) favouring cannabinoids. As with RCTs, meta-analysis was also conducted after removing outliers with effect sizes greater than ± 1.5 (i.e., Russo 2016b, and Hershkovich 2023), maintaining an overall moderate effect size of 0.43 (95%CI 0.34 to 0.51; $p < 0.001$; $\tau^2 = 0.03$). Further subgroup analyses revealed similar HRQL improvements in studies investigating CBD only ($d = 0.48$; 95%CI: 0.36 to 0.60; $p < 0.001$) and those investigating various THC:CBD combinations ($d = 0.41$; 95%CI: 0.31 to 0.51; $p < 0.001$). Analyses by health condition revealed largest HRQL improvements for PTSD, anxiety, chronic pain ($d = 0.45$; 95%CI: 0.35 to 0.55; $p < 0.001$), and studies across any health condition ($d = 0.48$; 95%CI: 0.37 to 0.60; $p < 0.001$). Studies investigating headache, cancer ($d = 0.24$; 95%CI: -1.74 to 0.66; $p = 0.252$), and multiple sclerosis ($d = 0.38$; 95%CI: -0.21 to 0.96; $p = 0.204$) found no significant changes in HRQL. Short-term HRQL changes from baseline were most variable in studies of patients with multiple sclerosis, where an equal number of studies reported improved HRQL or no change.

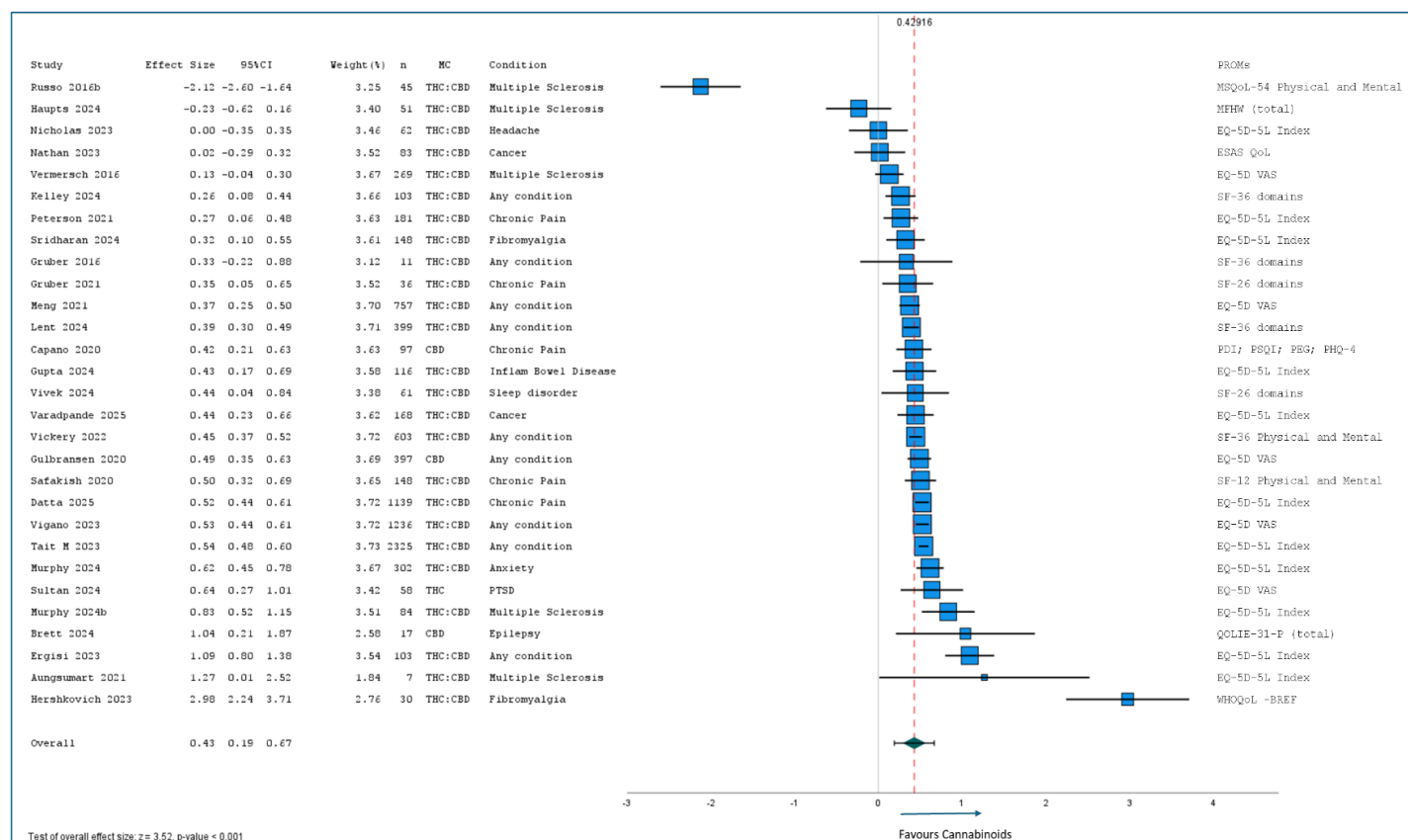


Figure 6. Meta-analysis of short-term (3-weeks to 3-months) results from cohort and case series studies (n=29) of HRQL after MC.

CBD, cannabidiol; EQ-5D-5L, EuroQol quality of life -5 dimensions-5 levels; HRQL, health-related quality of life; MC, medicinal cannabis; MFHW, Marburg questionnaire on habitual health; MSQoL-54, Multiple Sclerosis Quality of Life-54 items; PDI, Pain Disability Index; PEG, 3-item scale assessing Pain Intensity and Interference; PHQ-4, Patient Health Questionnaire-4 items; PROM, patient-reported outcome measure; PSQI, Pittsburgh Sleep Quality Index; QOLIE-31-P, Quality Of Life In Epilepsy-31items-plus 8 distress-related items; SF-36, Short Form Health Survey -36 items; SF-12, Short Form Health Survey -12 items; THC, delta-9 tetrahydrocannabinol; VAS, visual analogue Scale; WHOQOL-BREF, World Health Organisation Quality of Life Abbreviated Assessment.

MEDIUM-TERM WITHIN GROUP DIFFERENCES

Of the 30 studies evaluating medium-term within group differences (pre- and post-cannabinoid treatment), 19 were included in meta-analysis (Fig. 7). Of the 11 excluded studies, nine assessed participants from an already included study, and two did not report a measure of variability or usable test statistic. The 19 included studies were all observational,

either cohort (n=14) or case series (n=5), with treatment assessment periods of 5-months (n=1), 6-months (n=16), or 9-months (n=2). Ninety-five percent (n=18) of studies reported significantly improved HRQL. Within group effect sizes ranged from 0.24 to 2.03, with an overall effect size of 0.74 (95% CI: 0.52 to 0.96; $p < 0.001$; $\tau^2=0.21$) favouring cannabinoids. A few outliers with effect sizes greater than 1.5 influenced overall effect size. Meta-analysis was conducted after removing outliers with effect sizes greater than ± 1.5 (i.e., Brett 2024, Murphy 2024b, and Ergasi 2023), revealing an overall moderate effect size of 0.54 (95%CI: 0.45 to 0.64; $p < 0.001$; $\tau^2=0.02$). Further subgroup analyses revealed greater HRQL improvement over the medium term in studies investigating various THC:CBD combinations ($d = 0.56$; 95%CI: 0.46 to 0.66; $p < 0.001$) compared with THC only ($d = 0.47$; 95%CI: 0.05 to 0.89; $p = 0.029$). Larger HRQL improvements were seen across studies assessing patients with headache, multiple sclerosis, PTSD, chronic pain ($d = 0.48$; 95%CI: 0.35 to 0.62; $p < 0.001$) and any condition ($d = 0.64$; 95%CI: 0.58 to 0.71; $p < 0.001$).

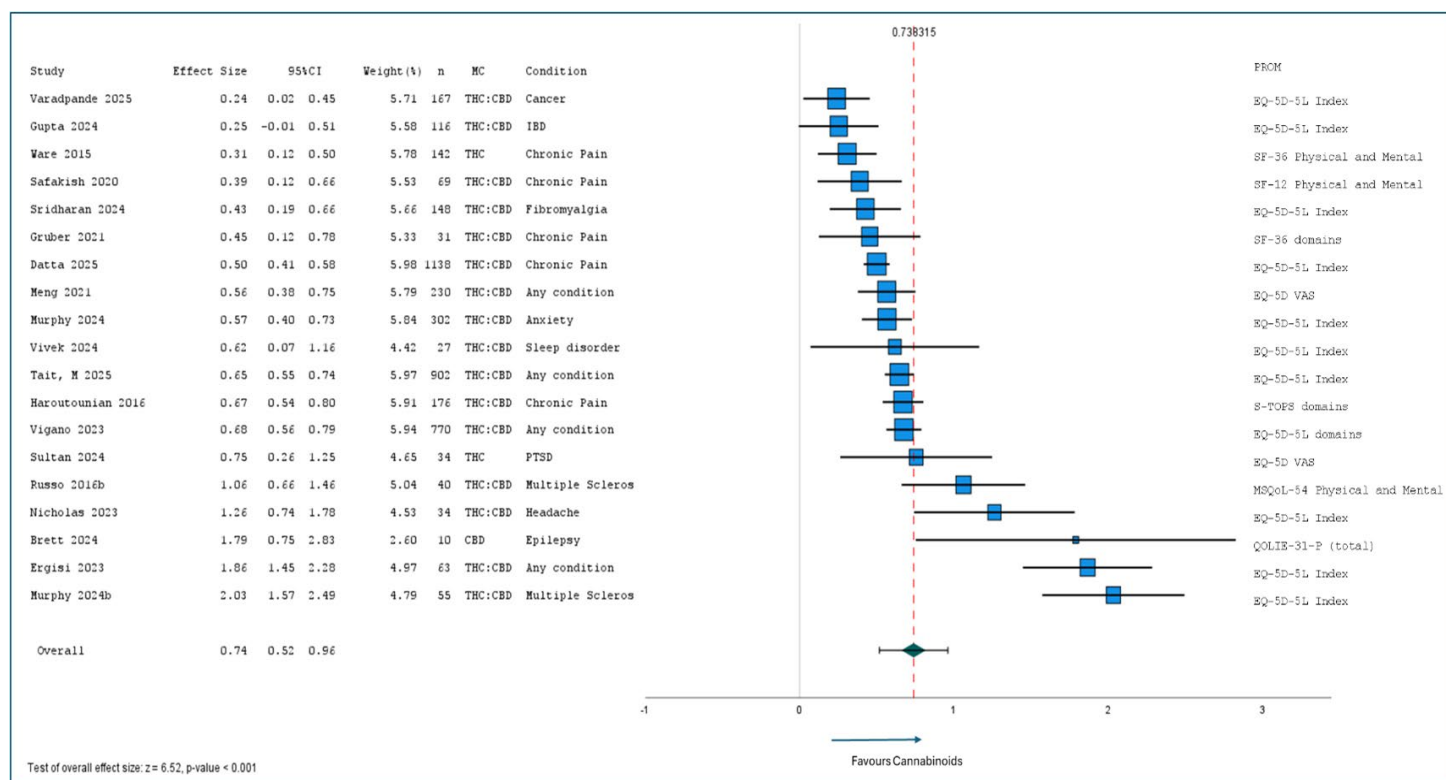


Figure 7. Meta-analysis of medium-term (5-9 months) results from cohort and case series studies (n=19) of HRQL after MC.

CBD, cannabidiol; EQ-5D-5L, EuroQol quality of life -5 dimensions-5 levels; HRQL, health-related quality of life; IBD, Inflammatory Bowel Disease; MC, medicinal cannabis; MSQoL-54, Multiple Sclerosis Quality of Life-54 items; PROM, patient-reported outcome measure; QOLIE-31-P, Quality Of Life In Epilepsy-31items-plus 8 distress-related items; SF-36, Short Form Health Survey -36 items; SF-12, Short Form Health Survey -12 items; S-TOPS, Treatment Outcomes in Pain Survey-Short Form; THC, delta-9 tetrahydrocannabinol; VAS, visual analogue Scale.

LONG-TERM WITHIN GROUP DIFFERENCES

Of the 17 studies evaluating long-term within group differences (pre- and post-cannabinoid treatment), five were excluded because they assessed participants from an already included study, leaving 12 studies with sufficient data to include in meta-analysis (Fig. 8). Included studies were all observational, either cohort (n=9) or case series (n=3), with treatment assessment periods of 12-months (n=9), 18-months (n=1), 20.7-months (n=1), or 24-months (n=1). Within group effect sizes ranged from 0.30 to 0.78, with an overall effect size of 0.53 (95% CI: 0.42 to 0.64; $p < 0.001$; $\tau^2 = 0.03$) favouring cannabinoids. All studies found significant

improvement in HRQL from 12-months. Further subgroup analyses found the largest HRQL improvements across studies investigating any health condition ($d = 0.67$; 95%CI: 0.55 to 0.80; $p < 0.001$), chronic pain ($d = 0.47$; 95%CI: 0.29 to 0.66; $p < 0.001$), and anxiety.

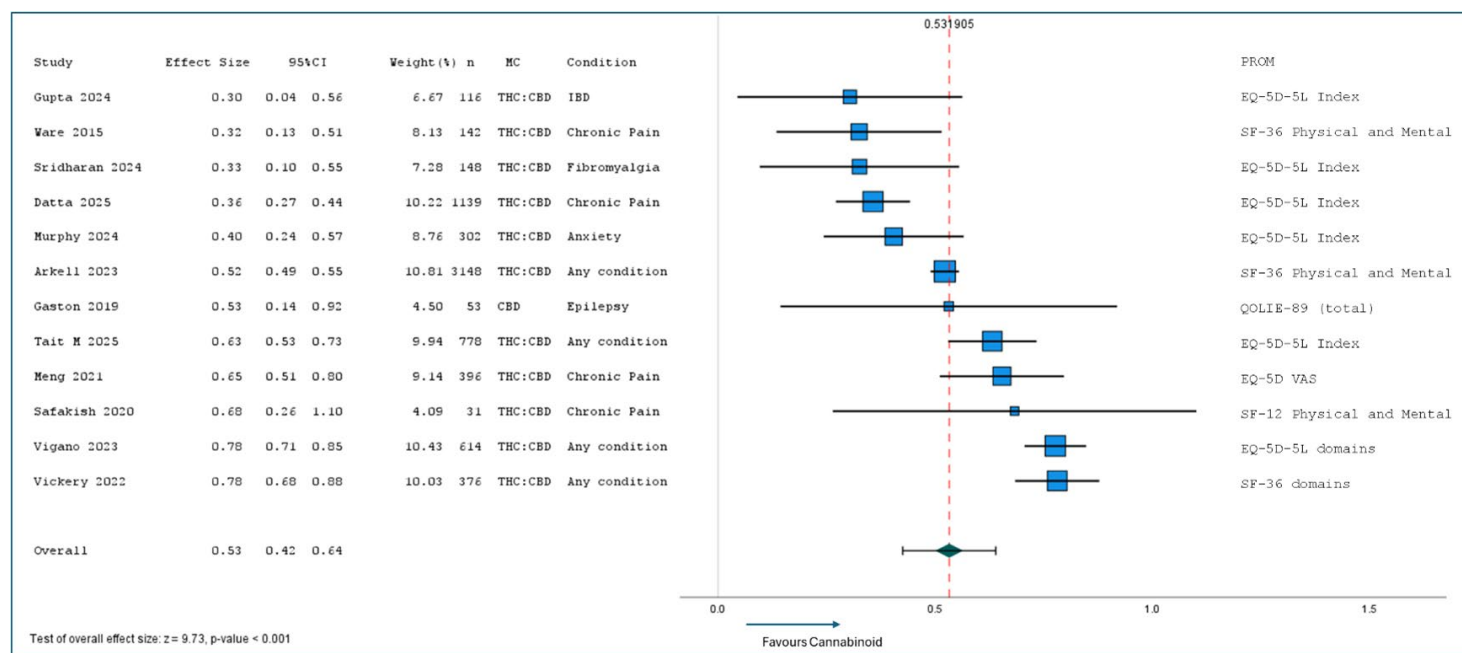


Figure 8. Meta-analysis of long-term (12-24 months) HRQL results from cohort and case series studies ($n = 12$) after MC therapy.

CBD, cannabidiol; EQ-5D-5L, EuroQol quality of life -5 dimensions-5 levels; HRQL, health-related quality of life; IBD, Inflammatory Bowel Disease; MC, medicinal cannabis; PROM, patient-reported outcome measure; QOLIE-89, Quality Of Life In Epilepsy-89 items; SF-36, Short Form Health Survey -36 items; SF-12, Short Form Health Survey -12 items; THC, delta-9 tetrahydrocannabinol; VAS, visual analogue Scale.

DISCUSSION

This systematic review with meta-analysis included all prospective studies between 2015 and 2025 reporting HRQL in patients treated with non-synthetic MC. The included studies are mostly representative of countries globally where MC is legal, apart from southeastern African countries where MC is legal, but no studies were identified.

Completeness of PRO reporting was adequate for most studies, however one study failed to meet more than 50% of reporting criteria. HRQL was rarely defined and a third of studies did not provide a rationale for assessing HRQL. Failing to define HRQL, justify its assessment, or provide a clear HRQL hypothesis suggests these studies may not have had a clear research objective regarding HRQL. PROs are increasingly being used in clinical studies,⁹⁸ following recommendations from professional and clinical organisations, health agencies, and regulatory bodies.^{10,99,100} It is important for researchers to be explicit about the meaning and context of HRQL in their studies to enable assessment of whether the chosen HRQL measure was fit-for-purpose.¹⁴ We found vastly different short-term HRQL results across the six observational studies assessing patients with multiple sclerosis treated with THC:CBD. Although not directly assessed, this may partly be due to a lack of HRQL definitions and rationales for evaluating HRQL, and the use of different HRQL PROMs across these studies. Having a clear HRQL definition helps inform the selection of appropriate PROMs, improves scientific rigor, and helps contextualise any discrepancies in findings. This is particularly important considering different PROMs have previously been shown to produce discrepant HRQL results within the same group of patients.¹⁴

Overall, our meta-analysis findings suggest that, compared with baseline, small to moderate HRQL improvements are apparent within 3 months of commencing MC, with moderate to large improvements between 5 and 9-months, and moderate levels long-term (12 to 24 months). However, HRQL did not improve for all conditions and improvements often varied depending on cannabinoids used. Findings across moderate- to high-quality RCTs indicated clinically meaningful short-term improvements in HRQL were mostly driven by studies of patients with irritable bowel disease or fibromyalgia. One study with HIV patients used a specific cannabinoid, Cannabidiol (CBDV), not investigated by any other included studies,

which focused on CBD and THC cannabinoids. The findings from this study suggest CBDV was not effective in this cohort for reducing pain or improving HRQL. Meta-analysis of short-term observational studies found moderate HRQL improvements overall, with similar findings across studies looking at CBD only and THC:CBD in combination. However, this was also dependent on health conditions treated, with no change seen across studies of patients with cancer or multiple sclerosis. Notably, the two observational studies providing extreme negative and positive effect sizes were also rated as having low completeness of PRO reporting. For example, HersHKovich et al. didn't specify the type of variability reported in results, however, after due diligence and investigation, we determined it was most likely standard deviation and included it in the meta-analysis. Although doubts were raised about the accuracy of reporting (e.g. whether standard error was mistakenly reported as standard deviation), we assumed research findings in peer-reviewed publications were reported correctly. However, to reduce possible bias from erroneous data, we crossed-checked all statistical information available for determining study effect sizes, including t tests and reported p-values, and where relevant, chose the most conservative estimation for inclusion in meta-analyses.

COMPARISONS WITH PREVIOUS REVIEW FINDINGS

In their review, Goldenberg et al. found no main effect of MC on HRQL.¹⁵ Along with synthetic cannabinoids, they reviewed six studies that used cannabis and seven that used non-synthetic cannabinoids (Sativex). Regarding the six cannabis studies, they found no main effect on HRQL, however, three of the studies were cross-sectional without pre- and post-therapy comparisons, two were prospective with small sample sizes (13 and 37), with the one RCT reporting significant but small improvements in mental HRQL in patients with

neuropathic pain.¹⁰¹ Across the seven non-synthetic cannabinoid studies, six found no main effect of MC on HRQL, and one observational study of 276 multiple sclerosis patients found significant HRQL improvements when assessed with MSQoL-54, but no HRQL change when the same patients were assessed using EQ-5D-3L.¹⁰² We observed similar disparate HRQL findings across studies assessing HRQL in multiple sclerosis patients using different PROMs, further highlighting the need to clearly define HRQL in this context to inform PROM selection. Goldenberg et al. concluded that where HRQL improvements were reported, this was mainly attributed to pain reduction.¹⁵ However, as summarised in table 1, we found that studies reported HRQL improvements in patients due not only to pain reduction, but also through resolving sleep, and physical and psychological issues.^{41,42,48,53-57,62-64,66,70,71,79}

STRENGTHS AND LIMITATIONS

A strength of this review is that all studies reviewed used non-synthetic cannabinoids derived from the cannabis plant, reflective of current MC products available in countries where MC prescribing is legal. Further, studies followed participants across short-, medium-, and long-term follow-up with meta-analyses comparing studies with similar follow-up assessment periods. A further strength of the current review is the wide coverage of 77 health conditions treated with MC in included studies (Online resource 4). This contrasts with previous reviews of HRQL in MC that included studies of synthetic cannabinoids, had limited coverage of health conditions, and short follow-up periods.^{15,16}

Generally, meta-analysis of observational studies should be interpreted cautiously, particularly over medium- and long-term assessment periods, due to possible attrition bias.¹⁰³ This is a limitation of review findings because participants remaining in observational studies are more likely those who are benefitting from therapy, inflating

positive findings. Across all studies included in this review, a quarter employed methods to reduce attrition bias including intention-to-treat analyses in RCTs,^{6,31,47,48,53,61} and applying the 'baseline observation carried forward approach'¹⁰⁴ for handling missing data in observational studies.^{30,33,49,54-56,58,65,68,69} However, when reasons for missing data are unknown, imputing data may potentially introduce other biases. We found most included observational studies did not report any attempts to reduce or address bias in their studies.

Another limitation of interpreting results of within group meta-analysis is that the correlation between pre and post therapy scores was often not reported in studies, thus introducing biased effect size variance, and without a control group it is unknown whether the effect is due to therapy, placebo, or natural recovery.¹⁰⁵ To account for this, we applied recommended correlations where available for repeated measures (including for RCT-crossover trials) and for multiple outcomes (HRQL domains) reported by the same group.^{28,29} This is in contrast to a previous meta-analysis that included multiple domains from one study alongside studies with single outcomes, inflating the overall effect size contributions from studies with multiple domains.¹⁵

CONCLUSIONS

We found a main effect of improved HRQL in patients using MC across studies published over the past decade. Improvements were observed across multiple health conditions over short-, medium- and long-term follow-up. However, disparate findings between studies of patients with the same health condition were also observed, possibly due to using different HRQL measures. This conflicting evidence may be better understood when researchers communicate how HRQL is defined and assessed in the context of their study and provide a justification for PROM selection.

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PART B

ASSESSING PATIENT-REPORTED OUTCOMES IN PATIENTS USING MEDICINAL CANNABIS

CHAPTER 3

PART B. PATIENT-REPORTED OUTCOMES WITH MEDICINAL CANNABIS

CHAPTER 3: PROTOCOL WITH STATISTICAL ANALYSIS PLAN

CHAPTER OVERVIEW

Findings from the systematic review in Chapter 2 revealed that studies vary on several factors, namely: their conclusions regarding the HRQL of patients accessing MC; the quality of research design and conduct; the completeness of reporting; and the generalisability of findings in practice. While randomised controlled trials are required for assessing the efficacy of drugs and other interventions, they seldom reflect real-world clinical practice and patient outcomes over the long-term. Chapter 3 presents a protocol for conducting a prospective study in a real-world setting to assess HRQL and other important PROs in patients prescribed MC by clinicians in Australia. Supplementary to the protocol, Appendix 2 contains the patient information, study invitations, and a comprehensive statistical analysis plan (SAP). The study protocol is required for ethical review and is essential for planning and conducting reproducible research. Publishing the protocol provides transparency on the aims, hypotheses, methods, and eventual findings of the study.¹ The SAP in Appendix 2 presents the principles of analysis in this study and discusses the main methodological and statistical concerns. Data from the longitudinal study were analysed at two timepoints reflecting short-term and long-term outcomes and follow the SAP to guide interpretation of the clinical relevance of findings.

¹ Cimino J, Braun C. Design a Clinical Research Protocol: Influence of Real-World Setting. *Healthcare (Basel, Switzerland)*. 2023;11(16).

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Margaret-Ann Tait made the following contributions.

- Conception and design of the research
- Funding acquisition
- Designed the data collection instrument
- Created study documents
- registered the study with Australian New Zealand Clinical Trials Registry
- Drafting and revising the paper
- Responding to reviewer comments
- Coordinating the submission of the paper for publication

All authors contributed towards the study concept and design, interpretation of data, and reviewed and provided critical feedback on the final manuscript.

As the primary supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

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ABSTRACT

BACKGROUND

Evidence supports several countries introducing legislation to allow cannabis-based medicine as an adjunctive treatment for the symptomatic relief of chronic pain, chemotherapy-induced nausea, spasticity in multiple sclerosis (MS), epileptic seizures, depression, and anxiety. However, clinical trial participants do not represent the entire spectrum of disease and health status seen in patients currently accessing medicinal cannabis in practice.

OBJECTIVE

This study aims to collect real-world data to evaluate health-related quality of life in patients prescribed medicinal cannabis oil and describe any differences over time from before starting therapy, to 3 and 12 months of therapy.

METHODS

Adult patients newly prescribed medicinal cannabis oil by authorized prescribers and under the Special Access Schemes across Australia will be screened for eligibility and invited to participate. A sample size of 2142 is required, with a 3-month follow-up. All participants will complete the EuroQol 5-Dimension; European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-30; Depression, Anxiety, and Stress Scale-21; Patients' Global Impression of Change; Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form (SF) version 1.0: Sleep Disturbance 8b; and PROMIS SF Fatigue 13a questionnaires. Patients with chronic pain conditions will also complete the PROMIS SF version 1.0: Pain Intensity 3a and PROMIS SF version 1.0: Pain Interference 8a. Patients with movement disorders will also complete Quality of Life in Neurological Disorders (Neuro-

QoL) SF version 1.0: Upper Extremity Function (Fine Motor and Activities of Daily Living) and if chorea is indicated, the Neuro-QoL SF version 2.0: Huntington's Disease health-related Quality of LIFE(HDQLIFE)-Chorea 6a. All questionnaires will be administered at baseline, 2 weeks (titration), monthly up to 3 months, and then every 2 months up to 1 year.

RESULTS

Recruitment commenced in November 2020. By June 2021, 1095 patients were screened for the study by 69 physicians in centres across 6 Australian states: Australian Capital Territory, New South Wales, Queensland, South Australia, Victoria, and Western Australia. Of the patients screened, 833 (39% of the target sample size) provided consent and completed baseline questionnaires. Results are expected to be published in 2022. Results of this study will show whether patient-reported outcomes (PROs) improve in patients accessing prescribed medicinal cannabis from baseline to 3 months and whether any changes are maintained over a 12-month period. This study will also identify differences in improvements in patient-reported outcomes among patients with different chronic conditions (eg, chronic pain, MS, epilepsy, Parkinson disease, or cancer).

CONCLUSIONS

This protocol contains detailed methods that will be used across multiple sites in Australia. The findings from this study have the potential to be integral to treatment assessment and recommendations for patients with chronic pain and other health indicators for accessing medicinal cannabis.

TRIAL REGISTRATION

Australian New Zealand Clinical Trials Registry: ANZCTR12621000063819;

<https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=380807&isReview=true>

INTRODUCTION

MEDICINAL CANNABIS

With the first accounts of cannabis being used as medicine dating back to China in 2600 BC, its use for medicinal purposes has been recorded on nearly every continent throughout history.¹ Many countries criminalised the consumption of cannabis in the 1900's, consequently limiting the potential therapeutic benefit and research into medicinal use. However, the identification of cannabinoids, cannabidiol (CBD) and Δ^9 -tetrahydrocannabinol (THC), as analgesics in 1940 refocused attention on using a cannabis-based medicine as adjunctive treatment for the symptomatic relief of chronic pain.¹ The past two decades have seen an increase in medicinal cannabis research particularly in response to growing concerns around the misuse and adverse events associated with opioids,² including increased risk of endocrinopathy, bowel dysfunction, cognitive decline, hospitalization, and death from overdose.³ Research to date has provided sufficient evidence for a number of countries to introduce legislations allowing its use for medicinal purposes. These policies help to avoid the potential risk of cannabis abuse by self-medicating,⁴ and enables appropriate monitoring for possible adverse drug-drug interactions.⁵ In 2020, there were about 400,000 medicinal cannabis patient registrations in Canada,⁶ over 60,000 in Germany,⁷ and more than 25,000 in Australia.⁸

Evidence from randomised controlled trials indicates that medicinal cannabis can reduce chronic pain,⁹⁻¹² neuropathic pain,¹³ cancer pain,¹⁴ chemotherapy-induced nausea,¹⁵ spasticity in Multiple Sclerosis,^{16,17} epileptic seizures,¹⁸ depression,^{10,12} and anxiety,¹² as well as improve sleep,¹⁹ and reduce opioid prescription numbers.²⁰ However, depression,

anxiety, and sleep problems may be exasperated with formulations containing high ratios of THC,²¹ and for some health indications, using medicinal cannabis in a *real world* setting may be confounded by drug-drug interactions.⁵ This supports the need for oversight by health care professionals and further research collecting *real world* evidence.

WHY PATIENT-REPORTED OUTCOMES ARE IMPORTANT

A PRO is any report coming directly from patients, without interpretation by physicians or others, about how the patient feels in relation to a health condition and its therapy.²² PROs can include symptoms, aspects of functioning, multidimensional constructs such as health-related quality of life (HRQL), and perceptions of treatment. PROs are regarded as the gold standard for assessing pain,²³ and are particularly important endpoints to include when assessing patients with chronic conditions where the primary aim is to palliate symptoms.²⁴ These patient-reports are captured and quantified by PRO measures (PROMs) using validated and reliable standardised questionnaires that allow comparisons between treatment groups, and within groups over time. The wide acceptance of PROM-based evidence by regulatory bodies is reflected in the Australian Commission on Safety and Quality in Health Care's support of the use of PROMs to drive quality improvement,²⁵ and the USA Food and Drug Administration's approval of PROs to support product labelling claims.²⁶

HEALTH INDICATIONS FOR ACCESSING MEDICINAL CANNABIS

The Australian Therapeutic Goods Administration (TGA) currently approves Special Access Scheme applications from health care providers who provide a clinical justification for prescribing medicinal cannabis where conventional therapies have failed.⁸ There are no TGA

imposed restrictions on the types of health conditions, however prescriptions are more commonly sought for chronic pain, and spasticity from neurological conditions.

CHRONIC PAIN

Chronic pain is a widespread health issue broadly defined as pain that lasts or recurs for more than three months,²⁷ and categorised as ‘chronic primary’, a disease in its own right such as with nonspecific low-back pain, or as ‘chronic secondary pain’ initiated as a symptom of an underlying disease, such as cancer-related pain or neuropathic pain.²⁸ In Australia, more than 15% of the adult population live with persistent chronic pain or recurring pain lasting longer than 6 months.²⁹ In the UK, as many as 35% of adults experience some level of chronic pain lasting more than 3 months, with more than 10% reporting moderate to severely limiting chronic pain.³⁰ In 2016, the Centers for Disease Control reported 20% of US adults had chronic pain, and 8% experienced chronic pain that severely interfered with daily functioning on most, or every, day for a 6 month period.³¹

Cancer-related pain is experienced by about one third of cancer patients at diagnosis and during treatment, and by about three quarters of patients with advanced stage cancer. However, 10-15% of patients are non-responsive to conventional pain therapy.³² Residual tissue damage from cancer and cancer treatment often results in chronic pain in cancer survivors that lasts many years post-treatment.³³

Neuropathic pain, pain that is caused by lesion or disease of the somatosensory nervous system,³⁴ is experienced by approximately 8% of the population,³⁵ and about 86% of patients with Multiple Sclerosis.³⁶ Neuropathic pain is associated with higher rates of unemployment,³⁵ poor physical, psychological, and social functioning, and significantly

impaired overall HRQL and sleep, and higher depression and anxiety than those with other chronic pain, and those without pain.³⁷ Less than 35% of patients with neuropathic pain respond to conventional therapy,³⁸ with others often receiving incomplete pain relief along with conventional treatment-related side effects.³⁹

The prevalence of chronic pain increases dramatically for those in palliative care.^{40,41} A study of patients in palliative care clinics in the USA found that the majority of patients were admitted with unrelieved pain, and that chronic pain assessment and management was inadequate.⁴² Added to this, a third of palliative care patients who experienced pain were significantly more likely to also suffer from depression,⁴¹ report insufficient sleep,⁴³ and were at higher risk of opioid misuse.⁴⁰ Effective pain and symptom management aimed at reducing suffering and improving overall HRQL are the primary goals of palliative care.

NEUROLOGICAL AND MOVEMENT DISORDERS

Multiple Sclerosis (MS) is a chronic inflammatory and demyelinating neurodegenerative disorder often involving symptoms such as spasms, tremor, pain, fatigue, bladder dysfunction, cognitive impairment, depression, and impairments in swallowing, speech, vision, and balance.⁴⁴ In 2018, MS Research Australia reported an estimated 24,600 Australians with MS, and on average their overall HRQL was 31% less than the Australian population norm (measured by the health state utility valuation).⁴⁵ As a currently incurable and often progressive condition, treatment and management largely focuses on improving the quality of everyday life by relieving symptoms.⁴⁴ A systematic review of reviews conducted in 2018 on the effects of CBD/THC in treating MS symptoms found sufficient evidence supporting cannabinoids in relieving both pain and spasticity symptoms.⁴⁶

Epilepsy is a chronic neurological disease characterized by two or more unprovoked seizures and affects about 50 million people worldwide.⁴⁷ High quality evidence from randomised clinical trials suggests CBD reduces seizure frequency, however further examination of patient-reported outcomes (PROs) is needed to assess whether CBD interacts with other anti-seizure medications to produce unwanted side-effects.⁴⁸

CRITICAL GAPS IN KNOWLEDGE ABOUT HRQL IN PATIENTS ACCESSING MEDICINAL CANNABIS

PRO assessment can assist health care professionals to monitor treatment outcomes over time from patients' perspectives. In 2020 there were no published results from a centralised PRO data collection for a large sample of patients accessing prescribed medical cannabis within Australia that covers all approved health indications using a comprehensive battery of PROMs. Participants studied under controlled clinical trial environments have not always been representative of the entire spectrum of disease and health status seen in people currently accessing medicinal cannabis in practice.⁴⁹ Therefore, while clinical trials provide evidence of the efficacy of medicinal cannabis, the true gauge of how effective it is in practice comes from real-world evidence from patients across all health conditions receiving prescribed medicinal cannabis.⁴⁹ Real-world data is needed to develop the scientific evidence base to inform regulation and policy-making.⁷

A scoping review conducted by the authors identified the following limitations in the current evidence on PROs for medicinal cannabis:

- Very few studies collected PRO data longitudinally including baseline, maintenance, and long-term use.⁴
- A large proportion of cannabinoid research was focused on pharmacokinetics, animal, and pre-clinical studies.

- Many cannabinoid clinical studies include case studies,⁴ or have small sample sizes.⁵⁰
- Early studies did not use the currently recommended individualized dosing titration paradigm of starting low and gradually escalating to achieve optimal effects.⁵⁰
- Formulations studied may not reflect current commercially available cannabinoid products.¹¹
- Many PROMs used have limited validity in the health conditions assessed.¹²
- Very few clinical studies used comprehensive pain assessments.

Therefore, the real-world collection of a comprehensive suite of PROs in a large sample of people across all health conditions, as approved by the TGA, accessing current formulations of prescribed medicinal cannabis in Australia is needed to enable clinically relevant assessment and provide ongoing evidence for decision making both in practice and at a policy level.

OBJECTIVES

The aim of this study is to evaluate PROs in patients who are prescribed medicinal cannabis by authorized prescribers and under the SAS across clinics within Australia. The findings from this study have the potential to be integral to treatment assessment and recommendations for chronic pain sufferers and other patients with chronic health conditions accessing medicinal cannabis.

PRIMARY OBJECTIVE

The primary objective of this study is to describe changes in the PROs (HRQL, pain, fatigue, sleep, anxiety, and depression) from baseline to 3 months for a large cohort receiving medicinal cannabis.

SECONDARY OBJECTIVES

The secondary objectives of this study are to describe changes in PROs (HRQL, pain, fatigue, sleep, anxiety, depression, and physical functioning) from baseline up to 12 months and to describe differences between patients accessing medicinal cannabis with different chronic health conditions, including, but not limited to, chronic pain, MS, epilepsy, Parkinson disease, and cancer.

EXPLORATORY OBJECTIVES

The exploratory objectives of this study are to explore (1) which individuals are more likely to have lower symptom burden and greater HRQL, (2) associations among PROs, with the hypothesis that a high symptom burden is associated with poorer HRQL, and (3) associations between PROs and resource and medication use over time, with the hypothesis that lower symptom burden is associated with reduced health care–resource use and reduced use of opioids and other prescribed medications for managing symptoms.

HYPOTHESES

The study includes 3 hypotheses: (1) PROs will improve from baseline to 3 months in patients accessing medicinal cannabis, (2) improvements in PROs at 3 months will be maintained over a 12-month period, and (3) no differences in PROs will be observed

between patients being treated for different conditions (e.g., chronic pain, MS, epilepsy, Parkinson disease, or cancer).

METHODS

OVERVIEW OF PROJECT RESEARCH DESIGN

This is a multicenter prospective longitudinal cohort study of patients newly prescribed with medicinal cannabis in Australia by authorized prescribers and under the SAS. The study is registered in the Australian New Zealand Clinical Trials Registry (ACTRN12621000063819).

STUDY ARRANGEMENTS

To be eligible to participate in the study, participants must have already been identified as eligible to receive a medicinal cannabis product from an authorized prescriber or under the SAS category B pathway, with approval given by the Australian TGA. This means that a suitable health practitioner has seen and assessed their patient, adhering to relevant standards of good medical practice, and successfully applied to the TGA for access to the particular medicinal cannabis product for the patient. Little Green Pharma Ltd (LGP) is responsible for the manufacture and quality of the products following the TGA guidelines. The prescriber is responsible for the prescription of the product for the patient and seeking TGA approval either as an authorized prescriber or under the SAS-B scheme, including the patient's informed consent for the product.

The University of Sydney researchers are responsible for the design of the cohort study and the data collection and analysis, as outlined in this protocol. LGP is responsible for arrangements for delivery of the product, any subsidization arrangements, and the

arrangements entered into with the participating sites and the physicians at these sites. The prescriber is responsible for identifying the patients suitable for the study and obtaining consent to email them an invitation to participate in the study.

ELIGIBILITY

The inclusion and exclusion criteria are provided in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patient is an adult (aged ≥ 18 years).
- Patient has been identified as eligible to receive medicinal cannabis by a Therapeutic Goods Administration–approved authorized prescriber or through the Special Access Scheme (or equivalent in other countries and jurisdictions) and the physician has sought and obtained Therapeutic Goods Administration approval for the Little Green Pharma Ltd product for their patient.
- Patient is able to read and understand English.
- Patient is able to provide informed consent.
- Patient has not started any prescribed medicinal cannabis therapy in the last 4 weeks or started prescribed Little Green Pharma Ltd medicinal cannabis therapy within the last 2 days (we expect no therapeutic benefit within 2 days) and did not receive any prescribed medicinal cannabis therapy in the last 4 weeks.
- Patient has a life expectancy of >3 months.

Exclusion criteria

- Patient is unconscious or confused.
- Patient has cognitive impairment (e.g., advanced Alzheimer disease).
- Patient is pregnant or breastfeeding.
- Patient is unable to read and write in English.
- Patient is denied access to medicinal cannabis under the relevant Special Access Scheme for their country of registration.

SAMPLE SIZE

SAMPLE SIZE CONSIDERATIONS

Our aim is to recruit a large, broad, and representative sample of medicinal cannabis users. Therefore, we will invite every eligible patient treated at each participating centre during a 12-month recruitment period. This large real-world cohort will enable several important analyses exploring differences in PROs between disease groups commonly treated with medicinal cannabis, as discussed in Objectives section.

MINIMUM SAMPLE REQUIRED FOR PRIMARY OBJECTIVE (CHANGE OVER TIME)

Following guidelines⁵¹ for the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30),⁵² and allowing for 20% loss to follow-up, a baseline sample size of 2142 is required with a minimum follow-up of 3 months. This sample size provides 95% power to detect the smallest effect size threshold of 0.1 for the insomnia domain of the QLQ-C30, using a two-sided significance level of 1%.⁵³

RECRUITMENT AND CONSENT PROCEDURES

SCREENING

Recruitment will take place between November 2020 and November 2021, with the aim of including all eligible patients receiving medicinal cannabis at participating sites during the recruitment period. Figure 1 provides an overview of the patient recruitment and data collection procedures.

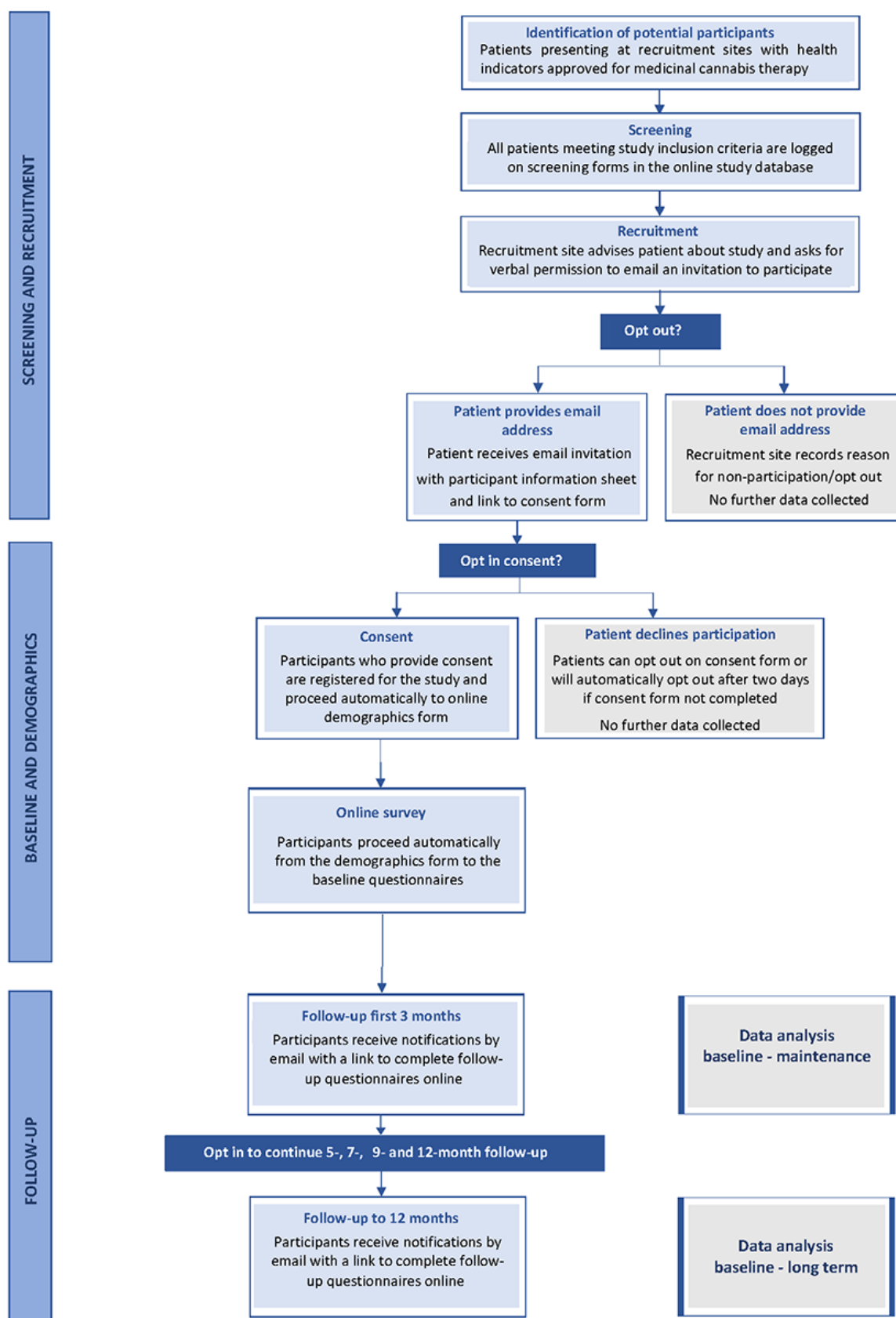


Figure 1. Patient recruitment and data collection process

LGP, following the World Health Organization Guidelines on Good Agricultural and Collection Practices for Medicinal Plants and European Union-Goods Manufacturing Practices standards, provides its medicinal cannabis products in Australia under the SAS. As part of this process, LGP engages with medical cannabis–focused clinics, authorized prescribers, and other health care professionals prescribing LGP products and will be responsible for identifying recruitment sites for this study. Advertising and information relevant to the study will be disseminated via a dedicated study website and social media platforms. Content on the study website will inform potential participants and recruitment sites of the study objectives, terms, and conditions, including eligibility criteria, and who to contact for more information. Approved recruitment sites will receive study-specific training from the University of Sydney researchers regarding participant screening and recruitment. Patients from participating centres who meet the eligibility criteria will be invited to participate in the study. Patients will be identified by physicians at recruitment sites and approached to participate by either the physician or site staff. A record of those identified as eligible and invited to participate will be logged in the web-based research database with the patient’s verbal consent. Physicians at recruitment sites will use a generic link to access the study database to create a new record for each patient screened.

The physician or staff at recruitment sites will ask if the patient agrees to have the Participant Information Statement and invitation sent to them through email. Patients will be informed that the process involves recruitment site staff entering the information, as per the Registration and Clinical Data section, into the research database, which then sends an invitation to them automatically. Participants will be informed that email addresses are stored within the Research Electronic Data Capture (REDCap) system and used solely for

sending reminders to complete questionnaires at scheduled time points. REDCap⁵⁴ is a secure web application that runs on The University of Sydney's servers, ensuring data stays within the Sydney University data centre.

All patients who provide their email address to receive an invitation for the study will receive their medicinal cannabis product at a standardized cost. As medicinal cannabis is still an unregistered product, it has been difficult to control the cost of the product; consequently, there has been considerable variability in what people pay for the product. LGP has partnered with several pharmacies across Australia to ensure that all participants taking part in this study will be charged the same amount for their product, eliminating variability in out-of-pocket costs and enabling a health economic evaluation.

As soon as an email address is entered in the web-based database, the patient will receive an email invitation with a link to the web-based forms for their record. The email will include the Participant Information Statement (Appendix 2) to be considered before giving consent on the web. The Participant Information Statement contains detailed information about the rationale, design, and personal implications of the study. Patients will then provide their consent to join the study by checking the consent box before being able to proceed to the data collection forms or they can opt out of study participation at this point. They have as much time as they need to consider their participation. The patient's right to refuse consent without giving reasons will be respected. If the patient does not respond to the invitation, 2 daily follow-up reminders will be sent via email, after which the system will automatically record the patient as having selected *opt out* without reason.

Participants will remain free to withdraw from the study at any time without giving reasons and without prejudicing any further treatment. Participants can withdraw responses from the study before the data have been analysed; otherwise, they will be included.

REGISTRATION

When physicians at recruitment sites complete the web-based screening form, REDCap will automatically generate a number to be used as the participant's study ID number for study registration.

DATA COLLECTION AND ASSESSMENT

Study data will be recorded by doctors at recruitment sites on case report forms and by participants in questionnaire booklets. These will be completed online through the University of Sydney research data capture system, REDCap⁵⁴.

Screening and registration and clinical data will be completed by the physician at the recruitment sites. The REDCap database will collect information only identifiable by REDCap-assigned study record ID numbers. Physicians at recruitment sites will maintain a record of participants' study ID numbers for each screened and registered participant entered. Where required, data can be updated for individual participants by notifying the study project manager of the corresponding study ID numbers (e.g., to record participant withdrawal). If 2 consecutive assessments are missed by participants, the study project manager will contact the physician at the recruitment site to determine the reasons for missed assessments, if known.

REGISTRATION AND CLINICAL DATA

The following patient screening details will be entered into the REDCap web-based registration form by physicians at recruitment sites: age, sex, country, email address, health indications for accessing medicinal cannabis, neuropathic pain screening using the short form Douleur Neuropathique en 4 Questions (S-DN4)^{55,56} (if pain is selected as a health indication), duration of pain (if pain is recorded as a health indication), comorbidities, medicinal cannabis type and dosage, date and dose of any previously prescribed medicinal cannabis, recruitment physician ID, and reasons for declining study participation (if applicable).

PATIENT CONSENT AND DEMOGRAPHICS

Patients who provide email addresses will receive an email with a link to the patient consent and demographic form corresponding to their study record ID. Patient consent and demographic questions include the following: consent to participate (or opt out), reasons for declining study participation (if applicable), ethnicity and cultural background, education, living arrangements, marital status, height, weight, gender identity, work status, access to health services, any medication other than medicinal cannabis taken during the last 4 weeks for health indication, and previous history of cannabis use.

PROM ADMINISTRATION

ADMINISTRATION

Baseline PROMs will be presented to participants on the web automatically after completing the demographic questions. Participants self-complete the questionnaires through the web-

based platform at home, accessible on a computer or other device with an internet connection, depending on their preference. All the questionnaires will be administered in the same order. It is anticipated that completion of baseline questionnaires may take up to 30 minutes. Follow-up questionnaires may take approximately 25 minutes. We estimate the time to complete questionnaires (including demographics questions) based on 10-12 seconds per item.⁵⁷

Patient-Reported Outcome Measures

All participants will complete the following PROMs.

GENERIC HRQL

Generic HRQL will be assessed in all participants using the EuroQol 5-Dimension questionnaire (EQ-5D-5L). The EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group to provide a simple, generic measure of health for clinical and economic appraisals.⁵⁸ EQ-5D-5L is designed for self-completion by respondents and consists of 5 items covering the dimensions of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Ratings for each item range from 1 (no problem) to 5 (extreme problem), with a recall period of *today*. In addition to the 5 items, there is a visual numeric scale of global health rated on a scale of 0-100. The questionnaire has validated language translations suitable for use in Australia.

To make the EQ-5D-5L suitable for use in economic evaluations, health states were valued using a preference-elicitation method in the general population. Australian national values have been collected and subsequently modeled and will be used for economic analysis.⁵⁹

All participants will receive the EORTC QLQ-C30 core quality of life cancer questionnaire,⁵² which includes core domains of functioning, cancer-specific symptoms, fatigue, and general pain. The QLQ-C30 core questionnaire was designed to be used by any patient participating in a cancer clinical trial; however, it has also been used to evaluate HRQL in other health conditions,⁶⁰⁻⁶⁴ as well as in large general population samples in Europe, the USA, and Australia.⁶⁵ It is a 30-item questionnaire with a recall period of 1 week and contains nine multi-item sub-scales and six single items. It incorporates five functional scales (physical, role, cognitive, emotional, and social functioning); three symptom scales (fatigue, pain, and nausea/vomiting); and a global health status/HRQL scale. The single items assess dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and perceived financial impact of disease and treatment. Ratings for each item range from 1 (not at all) to 4 (very much). The QLQ-C30 also produces a summary score of HRQL based on 13 scales.⁶⁶

The QLQ-C30 can be used for economic evaluation through the QLU-C10D,⁶⁷ a health state classification system derived from the QLQ-C30 for which Australian utility weights have been established.⁶⁸

OVERALL CHANGE IN HEALTH STATUS

Patients' subjective rating of overall change in health status related to their primary health condition will be assessed using the Patients' Global Impression of Change.⁶⁹ The Patients' Global Impression of Change contains 1 item rated from 1 (very much improved) to 7 (very much worse). The recall period is *since beginning medicinal cannabis treatment*.

ANXIETY AND DEPRESSION

Anxiety, depression, and stress will be assessed in all participants with the validated 21 item Short Version of the Depression, Anxiety, and Stress Scale (DASS).⁷⁰ The DASS21 includes three scales each containing 7 items, assessing: depression, anxiety, and stress. The Depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest / involvement, anhedonia and inertia. The Anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. The Stress scale assesses difficulty relaxing, nervous arousal, and being easily upset/agitated, irritable/over-reactive and impatient. Ratings for each item range from 0 (not at all) to 3 (very much or most of the time) with a recall period of one week.⁷¹

SLEEP AND FATIGUE

Sleep quality will be assessed in all participants with the PROMIS Short Form v1.0 Sleep Disturbance 8b.⁷² The PSF-SD is a universal, rather than disease-specific, 8 item assessment covering sleep quality, sleep depth, and restoration associated with sleep. Items are rated as 1 (not at all) to 5 (very much so), with a recall period of one week.

Fatigue will be assessed in all participants with the PROMIS Fatigue 13a/FACIT-Fat.⁷³ This 13 item measure has been validated in the general population, as well as in patients with cancer, anaemia, and arthritis.^{74,75} The scale consists of two domains; 5 items covering fatigue experience, and 8 items assessing the impact of fatigue on daily activities. Ratings for each item range from 0 (not at all) to 4 (very much so) with a recall period of one week.

CONDITIONAL PROMs

The following questionnaires will only be administered to patients with identified conditions or health status.

PALLIATIVE CARE

To reduce the burden on patients with a primary health indication of palliative care for advanced, symptomatic, incurable cancer with life expectancy of a few months, they will receive the EORTC QLQ-C15-PAL instead of the QLQ-C30. It is a shorter, 15 item, questionnaire that assesses the same outcomes of the QLQ-C30 questionnaire and is used extensively in the palliative care setting.⁷⁶ Palliative care participants will only complete the EQ-5D and QLQ-C15 questionnaires.

PAIN

Participants with pain as a health indication in their baseline clinical data will complete additional pain-specific questionnaires (excluding those in palliative care):

Pain intensity will be assessed using the PROMIS Scale version 1.0: Pain Intensity 3a.⁷⁷ The scale includes 3 items assessing pain intensity: 2 items cover pain at its worst, on average, over the last 1 week and 1 item about current pain. All items are rated from 1 (no pain) to 5 (very severe).

Pain interference will be assessed using the PROMIS Short Form version 1.0: Pain Interference 8a.⁷⁸ This measurement system contains 8 items measuring the degree to which pain interferes with physical, emotional, and social activities. Items are rated from 1 (not at all) to 5 (very much so), with a recall period of 1 week.

MOTOR FUNCTION

Participants with movement disorder, chorea, as a health indication will be assessed with the Quality of Life in Neurological Disorders Short Form version 2.0-HDQLIFE-Chorea 6a.⁷⁹

This 6-item scale producing 1 score was developed for patients with Huntington disease and is appropriate for patients experiencing irregular, random, involuntary movements of varying amplitude affecting the face, trunk, and limbs. The domains cover the impact of movement disorders on physical activity and participation, with each item rated from 1 (never or not at all) to 5 (always or very much), with a recall period of 1 week.

Participants with movement disorders affecting the upper body as a health indication will be assessed using the Quality of Life in Neurological Disorders version 1.0: Upper Extremity Function (Fine Motor and Activities of Daily Living) Short Form.⁸⁰ This 8-item scale assesses the ability to perform various activities involving digital, manual, and reach-related functions, ranging from fine motor to self-care (activities of daily living) for patients with stroke, MS, amyotrophic lateral sclerosis, Parkinson disease, epilepsy, and muscular dystrophy. Items are rated from 1 (unable to do) to 5 (without any difficulty) and emphasize current capabilities; therefore, they do not use a recall period.

WORK STATUS

For participants who indicate that they are working or would normally be working (ie, not retired or only studying), the impact of health on work performance will be assessed using the absenteeism and presenteeism questions of the World Health Organization's Health and Work Performance Questionnaire.⁸¹ The questionnaire contains 2 items covering absenteeism in the last 1 week and 2 items covering absenteeism in the last 4 weeks, rated

in number of days. Presenteeism is covered by 3 items rated from 0 (worst performance) to 10 (top performance).

FOLLOW-UP DATA COLLECTION

Participants will receive automatic reminders from the REDCap system to their email addresses at scheduled follow-up assessment time points (Table 1). Follow-up questionnaires can be completed using computers or mobile devices depending on their preference. Up to 2 email reminders to complete the follow-up questionnaires will be sent within the assessment time windows (Table 1). The following questions will be added to the front page of the follow-up questionnaires: current cannabis product and dose, any reduction in other medications taken for health indication because of using medicinal cannabis (including brand, strength, and dose), and work status.

PRO ASSESSMENT TIME POINTS

Prospective assessment of newly prescribed patients before and after treatment is required to assess changes in PROs over time. PROs will be completed at baseline before starting medicinal cannabis, at 2-3 weeks after starting medicinal cannabis (end of titration period), and then at 1, 2, 3, 5, 7, 9, and 12 months after the titration period. The acceptable PRO assessment time windows are indicated in Table 1.

Table 1. Patient-reported outcome assessment schedule.

PRO measure	Baseline	Titration ^a	1-month follow-up	2-month follow-up	3-month follow-up	5-month follow-up	7-month follow-up	9-month follow-up	12-month follow-up
		14-21 days after T0	4 weeks (and 3 days) after T1	8 weeks (and 7 days) after T1	13 weeks (and 7 days) after T1	21 weeks (and 7 days) after T1	30 weeks (and 7 days) after T1	39 weeks (and 7 days) after T1	52 weeks (and 14 days) after T1
	T0	T1	T2	T3	T4	T5	T6	T7	T8
EQ-5D questionnaire for measuring generic health status	✓	✓	✓	✓	✓	✓	✓	✓	✓
QLQ-C30	✓	✓	✓	✓	✓	✓	✓	✓	✓
Depression, Anxiety, and Stress Scale-21	✓	✓	✓	✓	✓	✓	✓	✓	✓
PROMIS Short Form for Sleep Disturbance	✓	✓	✓	✓	✓	✓	✓	✓	✓
PROMIS Short Form for Fatigue-Fat	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patients' Global Impression of Change		✓	✓	✓	✓	✓	✓	✓	✓
World Health Organization Health and Work Performance Questionnaire: Absenteeism and Presenteeism	✓		✓		✓		✓		✓
PROMIS Scale for Pain Intensity ^b	✓	✓	✓	✓	✓	✓	✓	✓	✓
PROMIS Short Form for Pain Interference ^b	✓	✓	✓	✓	✓	✓	✓	✓	✓
Neuro-QoL Short Form for chorea ^c	✓	✓	✓	✓	✓	✓	✓	✓	✓
Neuro-QoL Upper Extremity Function Short Form ^c	✓	✓	✓	✓	✓	✓	✓	✓	✓
15-item version of QLQ-C30 for Palliative Care patients receiving palliative care ^d	✓	✓	✓	✓	✓				

^a The titration period is approximately 2 weeks. As the EQ-5D assesses the current state (today), whereas the other patient-reported outcome questionnaires have a recall period of the past week, the time period is within 2-3 weeks to capture the end of titration across the questionnaires.

^b Pain questionnaires will be only administered to participants with a pain condition.

^c Impact on Motor Function Questionnaire will be only administered to patients with movement disorders.

^d Participants in palliative care with life expectancy of a few months will only complete the EuroQol 5-Dimension and Quality of Life Questionnaire, 15 items.

EQ-5D, EuroQol 5-Dimension; Neuro-QoL: Quality of Life in Neurological Disorders; PRO, patient-reported outcome; PROMIS, Patient-Reported Outcomes Measurement Information System; QLQ-C30, Quality of Life Questionnaire 30-items.

ANALYSES AND STATISTICAL CONSIDERATIONS

ANALYSIS SET

All analyses will be performed using SPSS software (version 26.0; IBM Corp). Baseline demographic and clinical data will be summarized descriptively for all patients registered for the study. Categorical data will be presented as frequencies and percentages. For continuous scale data, mean, SD, median, 25th and 75th percentiles, and minimum and maximum scores will be presented.

PRO analyses will explore changes over time using mixed linear models. Subgroup analyses will compare differences in PROs between underlying conditions, dose, and duration of pain and over time using linear mixed models.

STATISTICAL CONSIDERATIONS

A comprehensive PRO-specific statistical analysis plan will be produced by the study statistician. The key considerations include the following:

1. PRO questionnaire responses will be scored into PRO scales for outcome analysis according to standard scoring algorithms provided by the questionnaire developers and custodians.
2. Rates and reasons for missed PRO assessments will be summarized to assess likely missing data mechanisms against missing data assumptions of statistical modeling.
3. For each PRO, all participants with a score for that PRO at baseline and at least one time point after starting medicinal cannabis will be analyzed.

4. Linear mixed models will be used to compare groups in their PRO scores, adjusted for their PRO levels at baseline and with additional covariates such as duration of pain, previous cannabis use, use of other medications, and overall and prespecified subgroups.
5. If the scores are highly skewed, a suitable transformation will be sought to achieve normality.
6. As there are several PRO scales and time points and correlation among them is anticipated, statistical significance levels will be adjusted using an appropriate method.⁸²
7. The clinical significance of differences in the PRO questionnaires will be interpreted using existing guidelines (eg, QLQ-C30),⁸³ maintaining the overall type 1 error at 5% or less.

Missing items within the PRO questionnaires are not expected. This is because of the web-based administration platform alerting participants of missed items and the requirement to complete those items before progressing to the next page. Only those participants who complete at least 2 questionnaires (baseline and one other) will be included in the analysis. Single missed assessments will be imputed using the last value carried forward technique, that is, no change from that individual's last assessment. Pattern mixture models will be used to impute scores for missed assessments based on recorded reasons.⁸⁴

ECONOMIC EVALUATION

The economic evaluation will use collected data around pharmaceutical and other medical costs to explore the drivers of patient-level costs. As this study is not a comparative

randomized trial, we are not proposing to conduct a formal economic evaluation, resulting in a cost per quality-adjusted life year. We will instead use baseline resource use as an indicator of typical care and contrast resource use throughout the study with baseline data. We will explore the relationship between HRQL and resource use across the cohort, which is potentially important information for future economic evaluation of medicinal cannabis.

RESULTS

Participant recruitment in Australia commenced on November 27, 2020. By June 4, 2021, 1095 patients were screened for the study by 69 physicians in centers across 6 Australian states: Australian Capital Territory, New South Wales, Queensland, South Australia, Victoria, and Western Australia. Of the 1095 patients screened, 833 (76.07%) participants provided consent, completed baseline questionnaires, and remained on the study. Baseline recruitment is expected to end in March 2022 when the target sample size of participants has completed the baseline questionnaires and a 3-month follow-up. The final results for the primary objective are expected to be published in 2022.

DISCUSSION

PRINCIPAL FINDINGS

The results of this study will show whether PROs improve in patients accessing prescribed medicinal cannabis from baseline to 3 months and whether any changes are maintained over a 12-month period. This study will also identify whether there are differences in improvements in PROs among patients being treated for different conditions (eg, chronic pain, MS, epilepsy, Parkinson disease, or cancer).

CONCLUSIONS

The findings from this study have the potential to be integral to treatment assessment and recommendations for chronic pain sufferers and other patients with health indicators for accessing medicinal cannabis.

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CONFLICTS OF INTEREST

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CHAPTER 4

CHAPTER 4: SHORT-TERM HRQL IN MC PATIENTS: 3-MONTH FOLLOW-UP

RESULTS

CHAPTER OVERVIEW

Following the protocol and SAP described in Chapter 3, the prospective observational study examines short-term and long-term PROs. As an observational pre- and post-MC therapy study, it was essential clinicians notified me of eligible patients via our online screening forms before prescribing MC, which in turn triggered study invitations. To ensure the protocol was followed, clinicians were required to complete training sessions before using study screening forms. I provided doctors at each site with information about the study and conducted 112 site training sessions between November 2020 and December 2021.

Chapter 4 presents the overall short-term outcomes across the cohort after 3 months of MC therapy as a published manuscript. Shortly after publication, I discovered a scoring error on the sleep disturbance measure and re-ran the analysis. A post-publication correction request form was submitted to the journal, and I added the corrected sleep disturbance results to the publication's online comments section. The corrected manuscript is presented here and a copy of the submitted correction request form, detailing the corrections, can be found in Appendix 4.

Supplementary to the 3-month results, Appendix 2 contains participant information and study invitations, Appendix 3 contains the ethics approval letters, and Appendix 4 contains the supplementary material referenced in the publication, including the STROBE checklist for reporting observational studies. A parallel sub-study looking specifically at participants with cancer was conducted. Appendix 7 contains the sub-study findings as an abstract

presented at the Multinational Association of Supportive Care in Cancer Annual Meeting, Nara, Japan, 22 June 2023.

PUBLICATION DETAILS

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DATA AVAILABILITY STATEMENT:

All data files are available from the Sydney eScholarship database (<https://doi.org/10.25910/gtst-ve50>)

AUTHORSHIP ATTRIBUTION STATEMENT

The co-authors confirm the contribution of Margaret-Ann Tait as the primary author, in compliance with the international Committee of Medical Journal Editors (ICMJE) authorship criteria, for the following manuscript:

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Margaret-Ann Tait made the following contributions.

- Conception and design of the research
- Funding acquisition
- Designed the data collection instrument
- Created study documents
- Submitted and obtained ethics approvals
- Conducted recruitment site training
- Collected the data
- Data cleaning
- Analysis and interpretation of the data
- Drafted and revising the paper
- Responded to reviewer comments
- Coordinated the submission of the paper for publication

MT, CR, and LW made substantial contributions to the study concept and design, with critical feedback provided by RC, RN, DC, and SS. All authors contributed towards interpretation of data and reviewed and provided critical feedback on the final manuscript.

As the primary supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

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ABSTRACT

AIMS

Patients with chronic health conditions not responding to conventional treatment can access medicinal cannabis (MC) prescriptions from clinicians in Australia. We aimed to assess overall health-related quality of life (HRQL), pain, fatigue, sleep, anxiety, and depression in a large real-world sample of patients accessing prescribed medicinal cannabis. We hypothesized that all patient-reported outcomes (PROs) would improve from baseline to 3-months.

METHODS

The QUEST Initiative is a large prospective multicenter study of patients with any chronic health condition newly prescribed medicinal cannabis between November 2020 and December 2021. Eligible patients were identified by 120 clinicians at medical centers across six Australian states. Consenting participants completed the EuroQol Group EQ-5D-5L health status questionnaire; European Organization for Research & Treatment of Cancer Quality of Life questionnaire (QLQ-C30); Patient-Reported Outcomes Measurement Information System (PROMIS) Short Forms in Fatigue and Sleep Disturbance, and the Depression Anxiety Stress Scale (DASS-21) before starting therapy, at 2-weeks titration, then monthly for 3-months.

RESULTS

Of the 2762 consenting participants, 2327 completed baseline and at least one follow-up questionnaire. Ages ranged between 18-97 years (mean 51y; SD=15.4), 62.8% were female. The most commonly treated conditions were chronic pain (n=1598/2327; 68.7%),

insomnia (n=534/2327; 22.9%), generalized anxiety (n=508/2327; 21.5%), and mixed anxiety and depression (n=259/2327; 11%). Across the whole cohort both EQ-5D-5L utility scores and QLQ-C30 summary scores showed clinically meaningful improvement in HRQL from baseline to mean follow-up with $d=0.54$ (95%CI:0.47 to 0.59) and $d=0.64$ (95%CI:0.58 to 0.70) respectively; and clinically meaningful improvement in fatigue ($d=0.54$; 95%CI:0.48 to 0.59) and sleep ($d=0.67$; 95%CI: 0.61 to 0.73). There was clinically meaningful reduction of pain for those with chronic pain ($d=0.65$; 95%CI:0.57 to 0.72); significant improvements for those with moderate to extremely severe anxiety ($\chi^2=383$; $df=4$; $p<0.001$) and depression ($\chi^2=395$; $df=4$; $p<0.001$).

CONCLUSIONS

We observed statistically significant, clinically meaningful improvements in overall HRQL, sleep, and fatigue over the first 3-months in patients with chronic health conditions accessing prescribed medical cannabis. Anxiety, depression, and pain also improved over time, particularly for those with corresponding health conditions. The study continues to follow-up patients until 12-months to determine whether improvements in PROs are maintained long-term.

STUDY REGISTRATION

Australian New Zealand Clinical Trials Registry: ACTRN12621000063819

INTRODUCTION

More than 47% of Australians suffer from chronic health conditions¹ and nearly 20% live with persistent chronic pain,² negatively affecting their Health-Related Quality of Life (HRQL). In 2016, Australian legislation changes allowed patients with health conditions not responding to conventional treatment to access medicinal cannabis (MC) prescribed by clinicians with approval from the Therapeutic Goods Administration (TGA). This decision, driven by patient advocacy groups and community support,³ acknowledged only moderate-quality evidence that MC reduced chronic pain,⁴ and spasticity in multiple sclerosis,^{5,6} and low-quality evidence of benefit in chemotherapy-related nausea, vomiting, weight gain in HIV, sleep disorders and Tourette syndrome.⁷

Assessing and managing chronic conditions requires consideration of patient-reported outcomes (PROs).⁸ A PRO is any report coming directly from patients about their health status, without interpretation by clinicians or others,⁹ including symptoms, functioning, and multidimensional constructs such as HRQL. HRQL is defined as: “a multidimensional construct encompassing perceptions of the impacts – positive and negative – of a disease or its treatment on physical, emotional, social, and cognitive functions, as well as somatic discomfort and other symptoms.”¹⁰ PROs are the gold standard for assessing pain,¹¹ and important when assessing chronic conditions where the primary aim is to palliate symptoms.⁸ PROs are assessed with PRO measures (PROMs) - validated questionnaires allowing comparisons between groups and over time. PROM-based evidence is encouraged by regulatory bodies internationally,⁹ and the Australian Commission on Safety and Quality in Health Care recommends using PROMs to drive quality improvement.¹²

Real-world data on the effects of MC on HRQL is limited, and patients studied in controlled clinical trials seldom represent the range of chronic health conditions seen in practice.¹³ Considering the TGA has approved MC prescription applications for over 200 health conditions,¹⁴ real-world evidence from patients prescribed MC is needed to truly gauge how HRQL changes in practice and inform regulation and policy-making.^{13,15}

This study is reporting the 3-month interim results of the QUEST initiative (**Q**uality of life **E**valuation **S**tudy), which is assessing patient-reported overall HRQL, pain, fatigue, sleep disturbance, anxiety, and depression for 12-months in a large sample of chronic health patients in Australia prescribed MC. We hypothesized that all PROs would improve from baseline to 3-months in patients accessing MC, and that patients with specific conditions would see improvements in symptoms related to those conditions.

METHODS

STUDY POPULATION AND DESIGN

The QUEST initiative is an Australia-wide, multicenter, prospective study of patients with chronic health conditions newly prescribed MC by 120 clinicians between November 2020 and December 2021. Patients were eligible if they: a) were prescribed Little Green Pharma (LGP) MC oil products by a medically registered clinician with TGA approval, b) were ≥ 18 years old, c) were able to read and self-complete online PROMs and study documents in English, and d) had not accessed prescribed MC within the previous 4-weeks. Clinicians completed screening forms via the web-based research data capture system, REDCap.¹⁶ Eligible patients were assigned study ID numbers and emailed generic invitations with Participant Information directly from REDCap. The authors had no access to information

that could identify individual participants during or after data collection. To enable future health economic evaluation, clinicians prescribed their study-eligible patients LGP products at a study-standardized price, AUD\$150/50ml (GBP £88), representing a 15-38% discount on standard retail prices. The four LGP products prescribed were contained phytocannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), dissolved in a medium chain triglyceride (MCT) carrier oil in the following ratios: LGP Classic 1:20 (1mg THC and 20mg CBD per ml), LGP Classic 10:10 (10mg THC and 10mg CBD per ml), LGP Classic 20:5 (20mg THC and 5mg CBD per ml), LGP Classic CBD 50 (50mg CBD per ml). As full-spectrum MC oil, products also contained trace amounts of other naturally occurring phytocannabinoids and terpenoids from the cannabis plant.

Ethical approval was granted by University of Sydney Human Research Ethics Committee (HREC) Project#:20789 and informed written consent to participate in the study was obtained from all participants. Full details for study design, eligibility, recruitment procedures, PROM administration, and sample size calculations are provided in the study protocol.¹⁷

DATA COLLECTION

Clinician-completed screening forms collected basic patient demographics, MC products prescribed, clinical characteristics, and up to two health conditions being treated with MC. Consent, demographics, and patient-reported HRQL, pain, sleep, anxiety, and depression were completed electronically by participants. All PROMs were administered at baseline prior to commencing MC therapy, again after titration (approximately 2-weeks after commencing therapy), then monthly for 3 months. The '2-weeks after commencing therapy' timepoint was chosen because it is when the therapy is expected to be titrated to achieve

optimal benefit. Monthly follow-up for 3-months was selected because it aligned with TGA guidance for MC monitoring,¹⁸ matched The Centers for Disease Control and Prevention guidelines of 3 months or more frequently for chronic pain management,¹⁹ and clinical guidelines of monthly assessments for insomnia.²⁰ REDCap automatically emailed reminders to participants for follow-up assessments. PROMs were made available to participants to complete within 7 days of the assessment timepoint, after which, the timepoint was recorded as a missed assessment. A detailed description of each PROM administered is in Table 1.

Table 1. Outcomes assessed and characteristics, scoring, and details of use for patient-reported outcome measures (PROMs) administered to QUEST participants.

Outcome	PROM	Number of items	Domains	Rating	Recall period	Scoring	Details
HRQL	EQ-5D-5L Health status questionnaire developed by the EuroQoL Group. ²¹	5	Mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.	Items rated 1 (no problem) to 5 (extreme problem or inability)	'today'	EQ-5D responses were transformed using Australian population utility weights ²² and combined to produce a health index ranging from 0 (death) to 1 (perfect health). Negative values reflect a perceived health state worse than being dead. Higher scores indicate better HRQL.	EQ-5D has been used in published cannabis studies of HRQL in people with neuropathic pain, ^{23, 24} and irritable bowel disease. ²⁵
	QLQ-C30 The European Organization for Research & Treatment of Cancer (EORTC) core quality of life questionnaire (QLQ-C30). ²⁶	30	Functioning (physical, role, emotional, cognitive and social), global health status quality of life, and symptoms (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea) and financial impact.	Items rated 1 (not at all) to 4 (very much), except global health items rated 1 (very poor) to 7 (excellent)	past week	A QLQ-C30 summary score ²⁷ was generated from 27 of the 30 items, excluding the global health and financial impact items, to produce a score between 0 and 100. Higher scores indicate better HRQL.	QLQ-C30 was designed for assessing patients in cancer clinical trials, however it has also been used in other health conditions, ²⁸⁻³² the Australian general population, ³³ and medical cannabis studies in people with cancer pain. ^{34, 35}
	QLQ-C15-PAL[†] EORTC quality of life questionnaire for use in Palliative care setting. ³⁶	15	Functioning (physical, emotional), global quality of life, and symptoms (fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation).	Same as QLQ-C30	past week		QLQ-C15-PAL has also been used in other palliative care settings, ^{37, 38} and chosen because the subscales correspond with, and can be analyzed alongside, the QLQ-C30.
Pain	QLQ-C30 Pain subscale (and QLQ-C15-PAL Pain subscale)	2	Pain: <i>Have you had pain?</i> and <i>Did pain interfere with your daily activities?</i>	Items rated 1 (not at all) to 4 (very much).	past week	Pain scale produces a score between 0 and 100, with a higher score representing greater pain. The QLQ-C15-PAL and QLQ-C30 pain scales are the same, providing pain scores for all participants.	This pain scale has previously been used in studies of palliative care patients, ³⁹ diabetes, ⁴⁰ chronic pain, ⁴¹ and medical cannabis studies in people with cancer pain. ³⁵
Sleep disturbance	PROMIS Sleep Disturbance 8b The Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form	8	Sleep quality, sleep depth, and restoration.	Items rated 1 (not at all) to 5 (very much so).	past 7 days	PROMIS sleep measure generates a T-score with a mean of 50 and standard deviation of 10 in a reference population of the US general population (US 2000 Census) in combination with a clinical sample. ⁴³ Higher scores reflect greater sleep disturbance. [‡]	PROMIS Sleep disturbance has been shown to be valid and sensitive to changes in sleep in women with fibromyalgia, a condition associated with widespread pain, fatigue, and poor sleep quality. ⁴⁴

Outcome	PROM	Number of items	Domains	Rating	Recall period	Scoring	Details
	v1.0 Sleep Disturbance 8b. ⁴²						
Fatigue	PROMIS Fatigue 13a PROMIS Short Form v1.0 Fatigue 13a, also known as Functional Assessment of Chronic Illness Therapy – Fatigue Scale (FACIT-Fatigue). ⁴⁵	5	Experience of fatigue, and the impact of fatigue on daily activities.	Items rated 1 (not at all) to 5 (very much so).	past 7 days	PROMIS fatigue measure generates a T-score with a mean of 50 and standard deviation of 10 in a reference population of US general population (US 2000 Census). ⁴³ Higher scores reflect greater fatigue. [‡]	FACIT-Fatigue has been validated in the general population as well as in patients with cancer, anemia, and arthritis. ^{46, 47}
	DASS-21 Depression, Anxiety, Stress Scale -21 ⁴⁸ is a short version of the DASS-42. ⁴⁹	21	Three subscales assessing depression, anxiety, and stress.	Items rated 1 (not at all) to 5 (very much so or most of the time).	past week	For consistent interpretation, DASS-21 scores between 0 and 42 were generated by summing the responses and multiplying by 2 to align with the DASS-42. ⁵⁰ Higher scores reflect greater symptom burden	
Depression	DASS-21 Depression subscale	7	Dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest/involvement, anhedonia, and inertia.	Items rated 0 (not at all) to 3 (very much or most of the time)	past week	DASS-depression scores were categorized into severity levels at each timepoint as follows: 0-9 normal, 10-13 mild, 14-20 moderate, 21-27 severe, 28+ extremely severe. ⁵⁰	DASS-21 is a validated PROM of depression and anxiety used in routine assessment of in-patients, ⁴⁸ patients with multiple sclerosis, ⁵¹ pain, ⁵² and in the general population. ⁵³
Anxiety	DASS-21 Anxiety subscale	7	Autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect.	Items rated 0 (not at all) to 3 (very much or most of the time)	past week	DASS-anxiety scores were categorized into severity levels at each timepoint as follows: 0-7 normal, 8-9 mild, 10-14 moderate, 15-19 severe, 20+ extremely severe. ⁵⁰	

DASS Depression, Anxiety, Stress Scale; HRQL health-related quality of life; PROM patient-reported outcome measure.

[†] To reduce burden, palliative care patients with advanced, symptomatic, incurable conditions, only completed two PROMs at each timepoint (QLQ-C15-PAL and EQ-5D-5L). Non-palliative care participants completed all PROMs at each timepoint (except QLQ-C15-PAL).

[‡] The HealthMeasures Scoring Service recommended for PROMIS instruments was used to calculate T-scores because it uses item level calibrations more accurately than manually transforming total raw scores.⁵⁴

PROMs

We aimed to assess PROs using validated PROMs as described in Table 1. PROMs used to assess HRQL were designed to cover all dimensions of HRQL as defined in the introduction.

STATISTICAL ANALYSES

STATISTICAL SIGNIFICANCE

For each PRO, participants with a score at baseline and at least one follow-up assessment were analyzed. All PROMs were scored according to standard scoring algorithms provided by the PROM developers.

PROMIS measures generate T-scores with a mean of 50 and standard deviation of 10 in a reference population of the US general population (US 2000 Census) in combination with a clinical sample.⁴³ The HealthMeasures Scoring Service recommended for PROMIS instruments was used to calculate T-scores because it uses item level calibrations more accurately than manually transforming total raw scores.⁵⁴ Statistical analyses were carried out using the IBM SPSS Statistics 28.0 program.

Means, standard deviations (SD), and standardized mean-difference effect sizes with 95% confidence intervals were calculated for each assessment timepoint. Differences in baseline patient characteristics were explored using linear regression on QLQ-C30 scores, and where significant, adjusted for in the longitudinal analyses. Linear mixed models were used to examine change over time in PRO scores, with time included as a random factor. To adjust for possible Type I error inflation due to the analysis of multiple dependent variables, we used the Hochberg adjustment.⁵⁵ The model adjusted for PRO levels at baseline and

potential confounders, such as cannabis use within previous 12-months and sex, with duration of pain and age modelled as fixed factor covariates. Analyses compared mean scores at baseline with mean scores at each follow-up timepoint and the mean of post-intervention scores and analyzed trends over time and interactions between groups. In the linear mixed models, we probed change over time in two ways: (1) by analyzing contrasts representing linear and quadratic trends, to determine whether there was constant change over time (linear only) or change at a changing rate (linear + quadratic); (2) by analyzing a contrast comparing baseline scores to the mean of post-intervention scores. Additionally, change in DASS-anxiety and DASS-depression severity categories from baseline to follow-up were analyzed using Pearson Chi-squared.

As per the study protocol,¹⁷ a sample size of 2142 was powered to detect the smallest effect size threshold (Cohen's $d=0.1$) of difference in QLQ-C30 insomnia domain.⁵⁶

CLINICALLY MEANINGFUL CHANGE

This study, and others with large sample sizes, may detect statistically significant changes that are not large enough to be clinically meaningful or important in practice. A minimally clinically important difference (MCID) is “the smallest difference which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management.”⁵⁷ The EQ-5D-5L index score MCID in general populations falls between 0.037 and 0.069.⁵⁸ While there are recommended QLQ-C30 subscale MCIDs,⁵⁶ currently there are no published QLQ-C30 Summary Score MCIDs. The recommended threshold for evaluating meaningful within-group change using PROMIS measures generally ranges between 2 and 6 T-score points⁵⁹ with PROMIS Group consensus on 3 T-score points. The MCID for DASS-21 depression and anxiety scales is movement from

one severity level to another (e.g., from 'severe' to 'moderate'), as well as a change of 5 points.⁶⁰

Clinically meaningful differences on PROs over time were interpreted using existing guidelines where available. In the absence of guidelines, the threshold for discriminating HRQL changes for chronic diseases has generally been found to be approximately half of the standard deviation of change score (i.e. Cohen's $d=0.5$).⁶¹ A threshold of Cohen's $d=0.5$ was used as the MCID for the QLQ-C30 Summary Score.

PATIENT AND PUBLIC INVOLVEMENT

Patients were involved in this research as participants providing self-rated PROM responses reflecting their personal experiences while prescribed MC. PROMs used were previously developed and validated elsewhere in collaboration with patients and public who provided feedback on relevance and comprehension of questionnaire items. Patient participation was voluntary. Patients and public were not directly involved in developing the research question or study design. A summary of study findings will be emailed to participants and their clinicians.

RESULTS

Of 3302 eligible patients emailed invitations, 2762 provided consent and completed baseline PROMs and demographic information. Of those, 2327 completed at least one follow-up PROM and were included in the analysis (Fig 1). Those who dropped out after completing baseline were generally younger than those who continued. Participants were aged between 18-97 years (mean 51y; SD= 15.4), 62.8% female, and 37.6% University educated. Due to illness, 25.4% were either unemployed, on leave, or on limited work duties

(Table 2). S1 Appendix A shows numbers of patients screened and participating from each Australian state and territory, and further demographic information on gender identity and ethnicity.

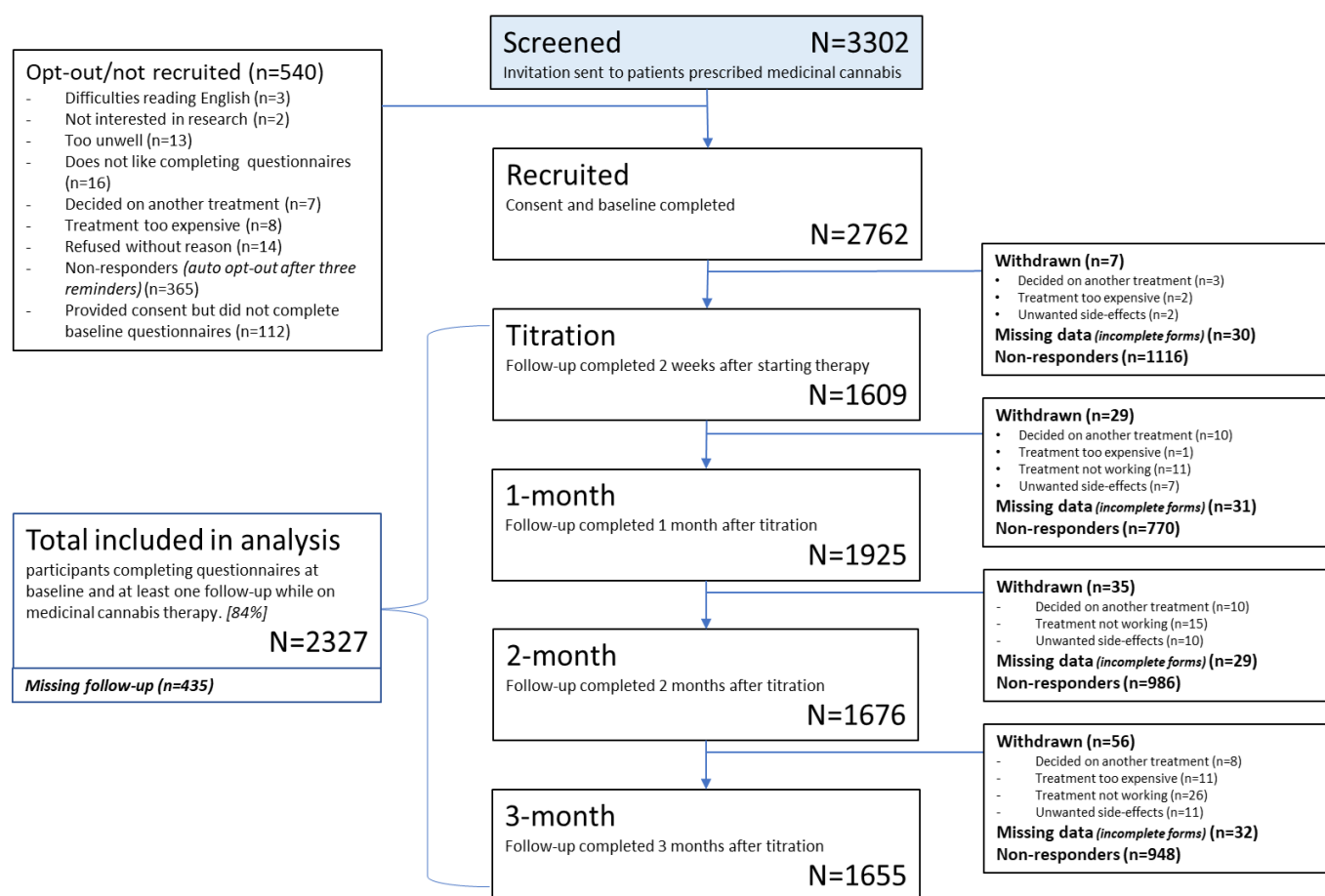


Figure 1. Study Recruitment Flow

Table 2. Baseline characteristics of 3302 eligible patients invited to QUEST grouped by those screened but not joined, participants completing baseline questionnaires only, and participants included in the analyses (completed baseline plus at least one follow-up).

Characteristics	Screened - not joined	Completed baseline only	Included in analysis	P value (χ^2)
Total (<i>n</i> =3302)	540	435	2327	
Age (years), mean (SD)	51 (17.6)	47 (16.9)	51 (15.4)	>0.001
Sex, <i>n</i> (%)				>0.001
Male	249 (46.1)	172 (39.5)	863 (37.1)	
Female	291 (53.9)	262 (60.2)	1462 (62.8)	
Indeterminate/Intersex	0	1 (0.2)	2 (0.1)	
Palliative care, <i>n</i> (%)	8 (1.5)	7 (1.6)	27 (1.2)	0.67
Currently treated for Cancer (any), <i>n</i> (%)	23 (4.3)	24 (5.5)	98 (4.2)	0.47
Living arrangements, <i>n</i> (%)				0.23
Live alone		84 (19.3)	467 (20.1)	
Live with partner		249 (57.2)	1414 (60.8)	
Live with carer		11 (2.5)	42 (1.8)	
Live with other		88 (20.2)	394 (17.0)	
Live in assisted care home		3 (0.7)	7 (0.3)	
Missing		-	3	
Marital Status, <i>n</i> (%)				0.02
Single		116 (26.7)	507 (21.8)	
Married		184 (42.3)	1104 (47.5)	
Separated		24 (5.5)	93 (4.0)	
Divorced		37 (8.5)	251 (10.8)	
Widowed		21 (4.8)	70 (3.0)	
Cohabiting		53 (12.2)	299 (12.9)	
Missing		-	3	
Work Status, <i>n</i> (%)				0.50
Full time		138 (32.2)	658 (28.6)	
Part time		68 (15.9)	361 (15.7)	
At work but limited hours/duties		27 (6.3)	131 (5.7)	
Retired		68 (15.9)	449 (19.5)	
Unemployed due to illness		78 (18.2)	394 (17.2)	
Unemployed NOT due to illness		6 (1.4)	43 (1.9)	
On leave due to illness		10 (2.3)	57 (2.5)	
Home duties		15 (3.5)	99 (4.3)	
Studying only		9 (2.0)	65 (2.8)	
Voluntary work		6 (1.4)	25 (1.1)	
Retraining		4 (0.9)	15 (0.7)	
Missing		6	30	
Education, <i>n</i> (%)				0.05
Primary School		8 (1.8)	23 (1.0)	
High School		132 (30.3)	588 (25.3)	
Certificate or Diploma		149 (34.3)	839 (36.1)	
University or higher		146 (33.6)	874 (37.6)	
Missing		-	3	

SD standard deviation; P values in bold are significant

After titration, median MC daily doses were: LGP Classic 1:20 = 1.0ml (IQR: 0.50, 1.50); LGP Classic 10:10 = 0.75ml (IQR: 0.37, 1.36); LGP Classic 20:5 = 0.57ml (IQR: 0.30, 1.10); and LGP Classic CBD 50 = 1.0ml (IQR: 0.50, 1.63). MC had previously been prescribed for 108/2327 (4.6%) participants (but not within 4-weeks prior to joining the study), and 521/2327 (22.4%) had used cannabis recreationally, or medicinally without a prescription, within 12-months prior to joining. Of those who had accessed cannabis illicitly, 239/521 (45.9%) used cannabis daily.

Half of participants were prescribed MC for more than one health condition (n=1233/2327; 53%), with the majority treated for chronic pain (n=1598/2327; 68.7%). Other common conditions included insomnia (n=534/2327; 22.9%), anxiety (n=508/2327; 21.5%), and mixed anxiety and depression (n=259/2327; 11%). S2 Appendix B shows participant health conditions and MC products prescribed at baseline.

PROs

Analyses, where appropriate, were adjusted for age, sex, duration of pain condition, and exposure to cannabis within the previous 12-months (recreational or medicinal). These patient characteristics were identified as significant covariates using linear regression on baseline QLQ-C30 summary scores; however not all were significant covariates in the longitudinal analyses. For example, exposure to cannabis in previous 12-months rarely predicted changes in PROs over time. Similarly, age was not associated with QLQ-C30 scores over time, however younger age was associated with higher EQ-5D-5L scores. Two participants identified as intersex were excluded from adjusted analyses.

Results in Table 3 summarize the clinical meaningfulness of change scores using Cohen's $d=0.5$ as the MCID threshold for HRQL, pain, sleep, fatigue, depression, and anxiety from baseline to each follow-up timepoint, and baseline to overall post-treatment mean.

Table 3. Clinical meaningfulness of change by effect size in patient-reported outcomes from baseline to each timepoint (2 weeks titration, then 1-, 2-, and 3-months post-titration) and mean post-treatment follow-up in patients with any health condition prescribed medical cannabis.

PROM			Mean scores at baseline and each follow-up timepoint										Mean post-treatment overall			
	Baseline	Titration	ES (95% CI)	Baseline	1- Month	ES (95% CI)	Baseline	2- Month	ES (95% CI)	Baseline	3- Month	ES (95% CI)	Baseline	Mean Follow-up	ES (95% CI)	<i>P</i> ^c
HRQL ^a																
EQ-5D-5L Utility Score																
<i>N</i>	1608	1608		1925	1925		1672	1672		1653	1653		2325	2325		
<i>Mean</i>	0.42	0.55	0.46	0.42	0.55	0.46	0.41	0.58	0.59	0.41	0.58	0.60	0.41	0.57	0.54	<0.001
<i>(SD)</i>	(0.29)	(0.27)	(0.39, 0.53)	(0.29)	(0.28)	(0.39, 0.52)	(0.30)	(0.28)	(0.52, 0.65)	(0.29)	(0.28)	(0.53, 0.67)	(0.29)	(0.28)	(0.47, 0.59)	
QLQ-C30 Summary Score																
<i>N</i>	1574	1574		1900	1900		1648	1648		1629	1629		2297	2297		
<i>Mean</i>	60.20	69.74	0.62	59.81	70.26	0.63	59.75	71.02	0.66	59.56	71.16	0.68	59.85	70.54	0.64	<0.001
<i>(SD)</i>	(16.41)	(16.30)	(0.55, 0.69)	(16.46)	(16.49)	(0.57, 0.70)	(16.88)	(17.02)	(0.59, 0.73)	(16.75)	(17.22)	(0.61, 0.75)	(16.63)	(16.75)	(0.58, 0.70)	
Pain ^b																
QLQ-C30 (or QLQ-C15Pal) Pain subscale																
<i>N</i>	1598	1598		1921	1921		1667	1667		1645	1645		2326	2326		
<i>Mean</i>	58.80	47.26	0.37	59.42	45.75	0.45	59.62	44.70	0.49	59.64	43.99	0.52	58.86	45.42	0.45	<0.001
<i>(SD)</i>	(31.71)	(29.95)	(0.30, 0.44)	(31.11)	(29.29)	(0.39, 0.52)	(31.20)	(29.92)	(0.42, 0.56)	(31.10)	(29.61)	(0.45, 0.58)	(31.34)	(29.69)	(0.38, 0.50)	
Sleep ^b																
PROMIS Sleep Disturbance 8b T-scores																
<i>N</i>	1566	1566		1894	1894		1633	1633		1619	1619		2298	2298		
<i>Mean</i>	61.04	55.26	0.69	61.14	54.87	0.71	61.3	54.76	0.71	61.24	54.72	0.69	61.03	54.9	0.67	<0.001
<i>(SD)</i>	(8.66)	(9.23)	(0.64, 0.75)	(8.49)	(9.27)	(0.66, 0.76)	(8.48)	(9.31)	(0.66, 0.76)	(8.53)	(9.54)	(0.64, 0.75)	(8.6)	(9.33)	(0.61, 0.73)	
Fatigue ^b																
PROMIS Fatigue 13a T-scores																
<i>N</i>	1568	1568		1895	1895		1635	1635		1619	1619		2299	2299		
<i>Mean</i>	58.30	54.50	0.47	58.32	54.25	0.50	58.51	53.97	0.55	58.34	53.92	0.53	58.37	54.16	0.54	<0.001
<i>(SD)</i>	(8.17)	(8.14)	(0.39, 0.54)	(8.07)	(8.30)	(0.43, 0.56)	(8.09)	(8.36)	(0.48, 0.62)	(8.09)	(8.55)	(0.46, 0.60)	(8.11)	(7.60)	(0.48, 0.59)	
Depression ^b																
DASS-21 Depression subscale																
<i>N</i>	1570	1570		1895	1895		1639	1639		1624	1624		2299	2299		
<i>Mean</i>	15.10	11.15	0.38	15.09	10.90	0.41	14.96	10.55	0.43	14.97	10.34	0.45	15.20	10.73	0.44	<0.001
<i>(SD)</i>	(10.95)	(10.06)	(0.31, 0.45)	(10.86)	(9.79)	(0.34, 0.47)	(10.83)	(9.83)	(0.36, 0.50)	(10.71)	(9.81)	(0.38, 0.52)	(10.90)	(9.87)	(0.37, 0.49)	
Anxiety ^b																
DASS-21 Anxiety subscale																
<i>N</i>	1570	1570		1895	1895		1639	1639		1624	1624		2299	2299		
<i>Mean</i>	10.26	7.33	0.37	10.42	7.28	0.40	10.36	6.94	0.43	10.57	7.10	0.43	10.57	7.17	0.45	<0.001
<i>(SD)</i>	(8.67)	(6.86)	(0.30, 0.44)	(8.69)	(6.97)	(0.33, 0.46)	(8.76)	(7.03)	(0.36, 0.50)	(8.74)	(7.18)	(0.36, 0.50)	(8.75)	(7.01)	(0.37, 0.49)	

ES: standardized mean-difference effect size (Cohen's d), **bold** indicates clinically meaningful change determined by effect size (d≥0.5)

^a Higher scores indicate better HRQL

^b Higher scores indicate worse symptoms

^c p-value for mean difference of baseline to mean post-treatment follow-up across all participants (2-tailed T-test)

OVERALL HRQL

EQ-5D-5L index scores (n= 2325) displayed significant linear ($t_{(9172)}= 18.45$, $p<0.001$) and quadratic ($t_{(6697)}= -16.45$, $p<0.001$) trends over time, showing rapid initial improvement that was maintained over 3-months (Fig 2a). Mean EQ-5D-5L index scores improved by 0.152 (SD= 0.28) from baseline (0.414; SD= 0.29) to mean follow-up (0.566; SD= 0.28), indicating a clinically meaningful improvement ($d= 0.54$; 95%CI: 0.47 to 0.59). This observed change was greater than the recommended EQ-5D-5L index score MCID for general populations, which falls between 0.037 and 0.069.[45]

QLQ-C30 summary scores (n= 2297) also showed significant linear ($t_{(8912)}= 22.79$; $p<0.001$) and quadratic ($t_{(6513)}= -23.41$; $p<0.001$) trends of improvement over time (Fig 2b). Mean change in QLQ-C30 summary score of 10.7 (SD= 16.72) from baseline (59.85; SD= 16.63) to mean follow-up (70.54; SD= 16.75) indicated a clinically meaningful improvement ($d= 0.64$; 95%CI: 0.58 to 0.70).

FATIGUE

PROMIS Fatigue T-scores (n=2299) displayed significant linear ($t_{(8995)}= -16.77$; $p<0.001$) and quadratic ($t_{(6559)}= 16.6$; $p<0.001$) trends of improvement over time (Fig 2c). Fatigue improved on average by 4.21 T-scores (SD= 7.73) from baseline (T= 58.37; SD= 8.11) to mean follow-up (T= 54.16; SD= 7.60), indicating clinically meaningful improvement ($d= 0.54$; 95%CI: 0.48 to 0.59). This improvement was greater than the recommended PROMIS MCID of 3 T-scores.

SLEEP

PROMIS Sleep Disturbance, completed by 2298 participants, displayed significant linear ($t_{(8961)} = -18.98$; $p < 0.001$) and quadratic ($t_{(6826)} = 21.93$; $p < 0.001$) trends of improvement over time (Fig 2d). Sleep improved on average by 5.95 T-scores (SD= 8.49) from baseline (T= 61.03; SD= 8.6) to mean follow-up (T= 54.9; SD= 9.33), indicating clinically meaningful improvement ($d = 0.67$; 95%CI: 0.61 to 0.73) greater than the recommended PROMIS MCID of 3 T-scores. Similarly, analysis of 534 participants with an insomnia diagnosis (of which 460 (86%) had a secondary diagnosis), mean T-scores improved by 8.13 (SD=8.36) from baseline (64.1; SD= 7.42) to follow-up (55.74; SD= 9.37), indicating clinically meaningful improvement ($d = 0.94$; 95%CI: 0.82 to 1.06).

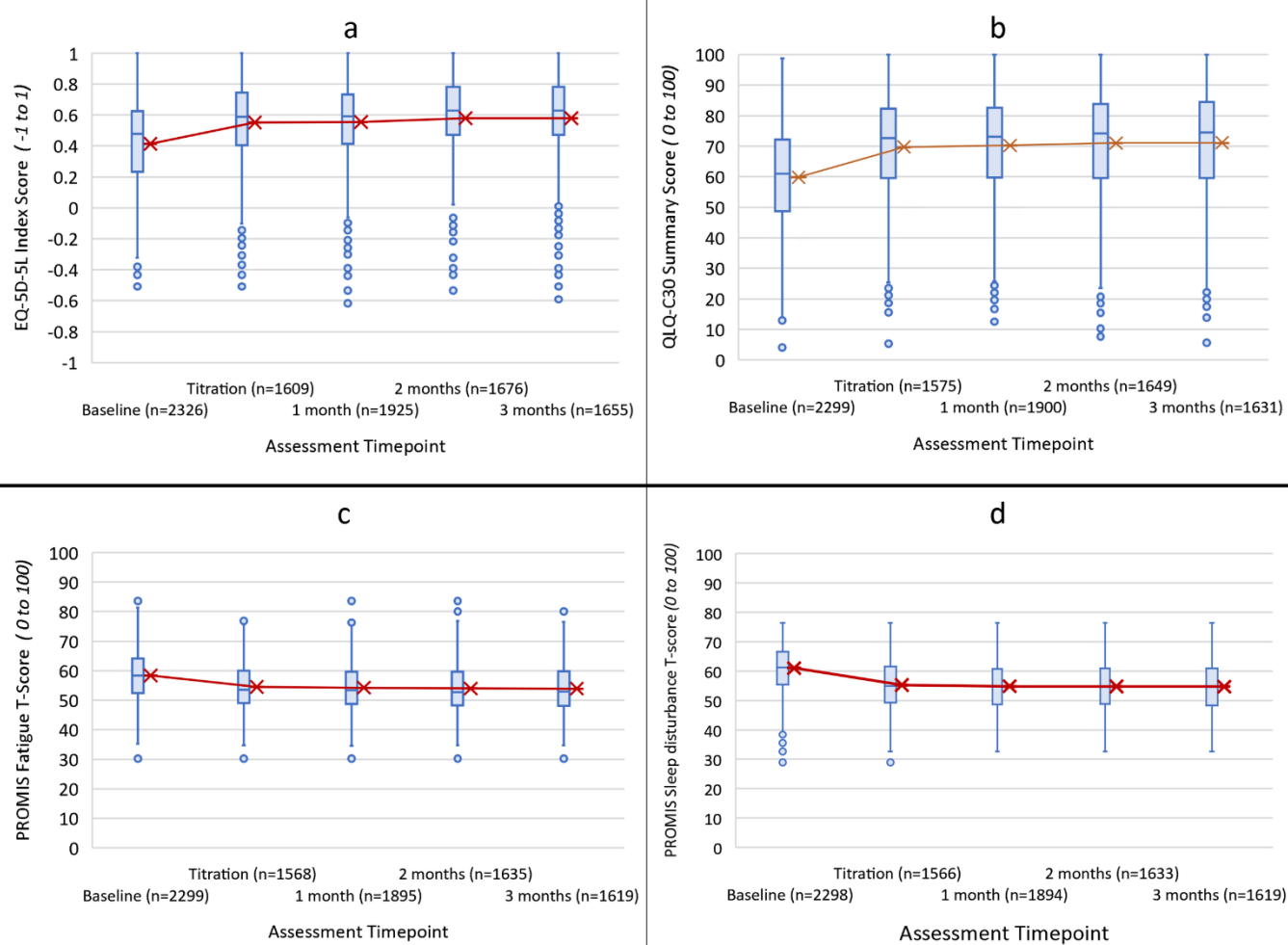


Figure 2. Score distribution (blue) and mean trends (red) from baseline to 3-months following titration for **a)** EQ-5D-5L Australian weighted Index Scores, **b)** QLQ-C30 Summary Scores, **c)** PROMIS-Fat T-scores, and **d)** PROMIS Sleep disturbance T-scores. Higher scores indicate better quality of life (a & b). Higher scores indicate worse symptom burden (c & d).

PAIN

QLQ-C30 pain scores (calculated from QLQ-C30 or QLQ-C15 PAL) improved from baseline to follow-up with significant linear ($t_{(9149)} = -16.73$; $p < 0.001$) and quadratic ($t_{(6693)} = 14.46$; $p < 0.001$) trends of improvement over time (Fig 3). When comparing participants with a chronic pain diagnosis with those not being treated for pain, improvements from baseline to mean follow-up were greater for the pain group ($t_{(4511)} = 9.79$, $p < 0.001$) (Fig 3).

Looking specifically at the 1592 participants with a chronic pain diagnosis, mean pain scores improved by 16.51 (SD= 26.07) from baseline (71.24; SD= 24.53) to follow-up (54.73; SD= 26.56), indicating clinically meaningful improvement ($d = 0.65$; 95%CI: 0.57 to 0.72).

Following guidelines for interpreting QLQ-C30 subscale change scores, more than 14 points on the pain subscale is regarded as a large improvement.⁶²

ANXIETY

Mean DASS-Anxiety scores displayed significant linear ($t_{(8962)} = -13.76$; $p < 0.001$) and quadratic ($t_{(6402)} = 15.29$; $p < 0.001$) trends of improvement over time (Fig 3). Mean difference between baseline (10.57; SD= 8.75) and mean follow-up (7.17; SD= 7.01) was 3.4 (SD= 7.49), with $d = 0.45$ (95%CI: 0.37 to 0.49). Although mean scores moved from moderate severity into mild severity range, the difference did not reach the recommended 5-point threshold. Comparing participants with anxiety health conditions with those not treated for anxiety, the improvement in DASS-anxiety scores from baseline to mean follow-up was greater for the anxiety group ($t_{(8661)} = 11.71$; $p < 0.001$) (Fig 3). After categorizing baseline and average follow-up anxiety scores, comparisons using Chi-square goodness of fit test showed significant movement from more severe anxiety categories towards the normal range ($\chi^2 = 383$; $df = 4$; $p < 0.001$; Appendix 4).

Looking specifically at the 748 participants with anxiety health conditions (i.e. generalized anxiety or mixed depression and anxiety), the mean difference between baseline (14.56; SD= 8.92) and mean follow-up (8.79; SD= 7.59) was 5.77 (SD= 7.96), with $d = 0.72$ (95%CI: 0.59 to 0.80) indicating clinically meaningful improvement. On average, scores shifted from moderate/severe down to mild anxiety with more than 5-point change, meeting the recommended threshold for clinically meaningful improvement.

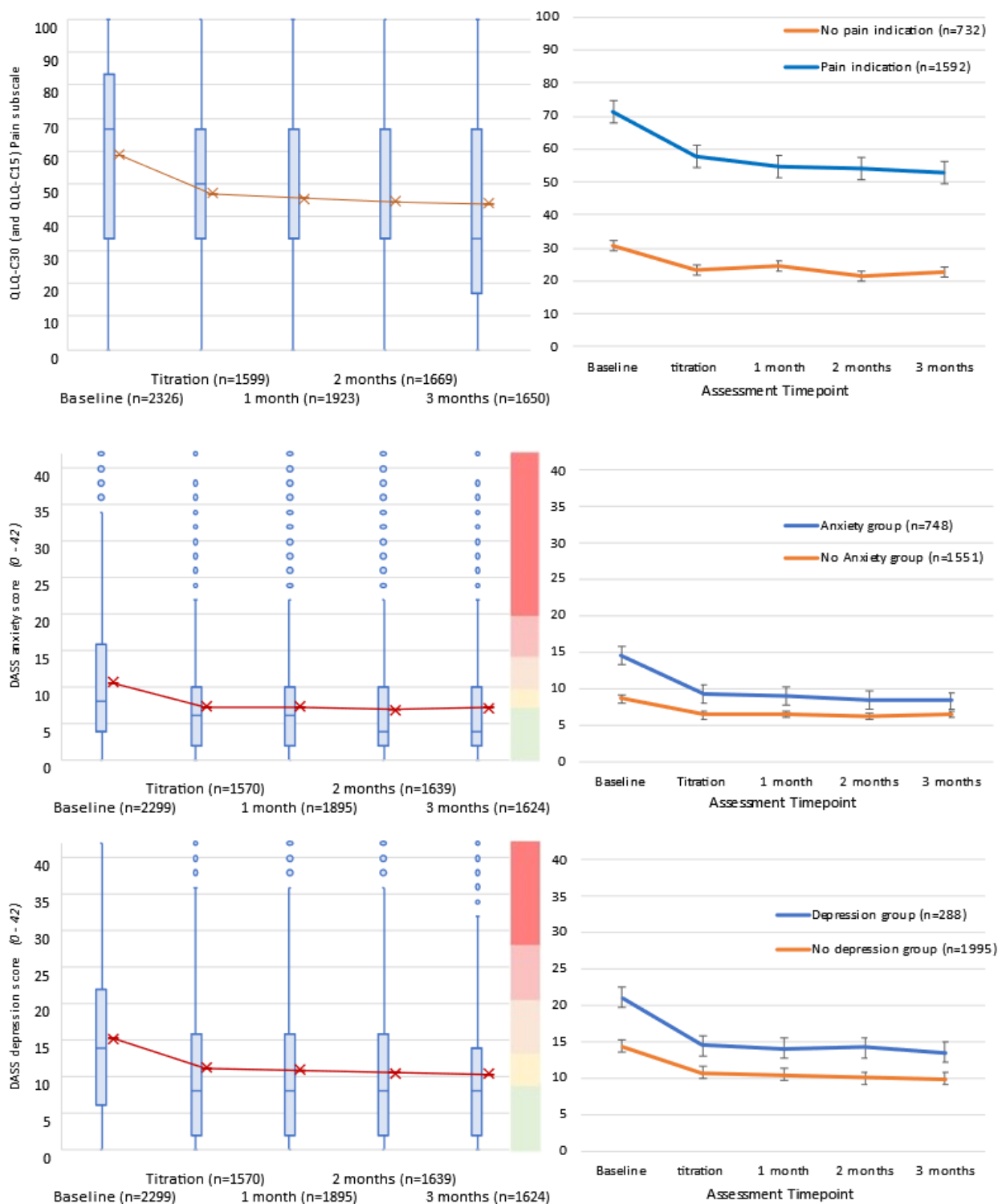


Figure 3. Score distribution and group comparisons of mean scores for Pain, Anxiety, and Depression from baseline to 3-months following titration. Higher scores indicate greater symptom burden. Pain group includes participants with any diagnosed pain condition (listed in Appendix 4). Anxiety group includes participants diagnosed with generalized anxiety disorder or mixed depressive and anxiety disorder. Depression group includes participants diagnosed with recurrent depressive disorder, mixed depressive and anxiety disorder, or bipolar disorder.

DEPRESSION

Mean DASS-Depression Scores displayed significant linear ($t_{(8921)} = -14.69$; $p < 0.001$) and quadratic ($t_{(6451)} = 14.33$; $p < 0.001$) trends of improvement over time (Fig 3). Mean difference between baseline (15.20; SD= 10.90) and follow-up (10.73; SD= 9.87) was 4.47 (SD= 10.14), with $d = 0.44$ (95%CI: 0.37 to 0.49). Although scores shifted from moderate severity into mild severity range, the difference did not reach the 5-point threshold for clinically meaningful improvement. Comparing participants with depression health conditions with those not being treated for depression, the change in DASS-depression scores from baseline to mean follow-up was greater for the depression group ($t_{(8601)} = 5.30$, $p < 0.001$) (Figure 3). After categorizing baseline and mean follow-up depression scores, comparisons using Chi-square goodness of fit test showed significant improvement from more severe categories towards the normal range ($\chi^2 = 395$; $df = 4$; $p < 0.001$; Appendix 4).

Looking at the 288 participants with depression health conditions (i.e. mixed depressive and anxiety, recurrent depressive disorder, and bipolar disorder), mean improvement from baseline (21.04; SD= 11.22) to mean follow-up (14.06; SD= 10.79) was 6.98 (SD= 10.91), with $d = 0.64$ (95%CI: 0.47 to 0.80). On average, respondents shifted from the severe category to moderate depression with more than 5-points difference indicating clinically meaningful improvement.

MISSED ASSESSMENTS

During the 3-month follow-up period, 127 participants formally withdrew from the study. Recorded reasons for withdrawal included changing treatment ($n = 31$), treatment too expensive ($n = 14$), treatment not working ($n = 52$), or unwanted side-effects ($n = 30$). Follow-

up data collected from these participants were included in the analysis up to the time they withdrew, however seven participants withdrew before completing any follow-up assessment (Figure 1).

Appendix 4 shows EQ-5D and QLQ-C30 results stratified by those who dropped out or failed to complete follow-up after each timepoint. Participants only completing baseline (n= 435) had poorer HRQL than those who continued on the study (QLQ-C30 Summary score MD= 2.03; SD= 16.8; p= 0.02). Those who only completed baseline and titration showed less improvement in HRQL compared with those who continued. At each follow-up timepoint, between 28% and 40% of participants failed to complete PROMs (Figure 1).

DISCUSSION

PRINCIPAL FINDINGS

As hypothesized, this study found overall HRQL improved over 3-months in patients accessing prescribed MC in Australia. Results showed both statistically significant and clinically meaningful improvements in overall HRQL, sleep, and fatigue for people with chronic health conditions. Similar improvements were found in pain scores for participants with chronic pain; depression scores for patients with depression; and anxiety scores in patients with anxiety.

Although HRQL improvement was similar between the EQ-5D-5L index and QLQ-C30 summary scores, differences were observed when looking at responses from participants who dropped out after baseline (Appendix 4), and when adjusting for age. As participant age increased, EQ-5D-5L index scores decreased slightly over time, whereas QLQ-C30 summary scores were not affected. The association between increased age and declining EQ-5D utility

scores has previously been reported for the Australian population,⁶³ whereas a previous Australian population study using QLQ-C30 found that increased age was only associated with some QLQ-C30 subscales while decreased age influenced other subscales.³³ Other differences may be due to the PROMs' comprehensiveness and recall period. The QLQ-C30 summary score covers 15 domains of HRQL across a longer timeframe (1-week) whereas the EQ-5D only captures five domains over the past 1-day and may be more sensitive to daily fluctuations in symptom burden.

COMPARISON WITH OTHER MEDICINAL CANNABIS STUDIES ASSESSING PROs

Our HRQL findings are consistent with findings from a registry study published in 2021 that found improvements on EQ-5D-5L scores after 1-month in 92 chronic pain patients prescribed MC, which was maintained at 3-months (n=51).⁶⁴ In contrast, an open-label study comparing MC with usual treatment in 101 neuropathic pain patients, found no improvements in EQ-5D scores after 6-months.²⁴ While the lack of 3-month data limits direct comparison, it suggests HRQL may return to baseline, reflecting diminishing efficacy, or a response-shift over time.⁶⁵ This will be explored further in our 12-month follow-up.

Findings from a double-blind randomized control trial (RCT) published in 2010 investigating 177 cancer pain patients found clinically meaningful and significant improvement in pain intensity Numeric Rating Scores after 2-weeks in the THC:CBD group, but not the THC group, when compared to placebo, however improvements in QLQ-C30 pain scores were not significant.³⁴ Participants (n=43) were subsequently followed-up in an open-label study where their QLQ-C30 pain scores improved by 24% over 5-weeks.³⁵ While our sample was not limited to cancer pain, overall this is consistent with our findings of clinically meaningful

improvements in pain scores for chronic pain patients after 2-weeks and maintained over 3-months.

Similar to our findings, significant improvements in fatigue after 3-months of MC therapy have previously been reported in observational studies of patients with multiple sclerosis (n=389),⁶⁶ chronic pain (n=248),⁶⁷ and cancer (n=743).⁶⁸

Similar to our findings, an observational study published in 2021 found significant improvements in Pittsburgh Sleep Quality Index scores after 3-months in 36 chronic pain patients prescribed CBD:THC.⁶⁹ Although limited by a small sample size, similar improvements were found for 25 insomnia patients with CBD oil over a 1-month period.⁷⁰ Another observational study of real-time symptom relief in 409 people with self-reported insomnia found significant improvements in a single-item sleep outcome when inhaling cannabis flower with higher levels of CBD,⁷¹ although the authors did not report follow-up time periods, use validated PROMs, or confirm diagnoses. Nevertheless, their findings suggest the way in which MC is administered (inhaled vs ingested) may affect efficacy, and that MC products with a higher ratio of CBD to THC may help promote sleep. Previous research has found that THC and CBD can disrupt the normal sleep cycle by reducing the production of melatonin, a hormone involved in regulating sleep, and that this was dose-dependent.⁷² Although, an RCT of 21 chronic pain patients found smoking cannabis containing THC improved sleep outcomes when compared with placebo.²³ Participants with insomnia in our study received a variety of MC products, more than half had formulations containing both CBD and THC (Appendix 4), and a large proportion of participants (86%) had more than one health condition.

An observational study of MC patients (n=51) found significant improvements in depression scores after 3-months,⁷³ while another larger study found improvements in depression after 1-month (n=787) and 3-months (n=757) in chronic pain patients,⁷⁴ however neither study reported the clinical meaningfulness. Similar to our findings, clinically meaningful improvements in depression scores were reported for MC patients in a real-world setting with moderate to severe depression (n=115) after 3-months, but not for MC patients with mild symptoms (n=157).⁷⁵ The same study reported improvements in anxiety were also limited to patients with high baseline anxiety scores, which was similar to our study findings for patients with anxiety-related conditions.

STRENGTHS AND LIMITATIONS

Our study assessed a large real-world cohort with a wide range of chronic conditions using validated, condition-relevant PROMs at clinically meaningful time-points and reported the clinical meaningfulness of findings referencing predefined MCIDs. We included everyone within a year time-period, recruited from multiple sites across different Australian states. Product dosing reflected clinical practice use rather than the typically large CBD or THC doses in RCTs.⁷⁶ The use of de-identified electronic data collection, with outcomes blinded to doctors and participants throughout the study, reduced the risk of response bias and biases that may be introduced by researchers or clinicians when collecting (or failing to collect) questionnaire data in person.

However, our findings should be interpreted in the context of a single arm study without a control group. A systematic review of cannabis and HRQL studies revealed small effect sizes in RCTs and large effect sizes without control groups.⁷⁷ There is a chance that observed improvements are partly due to placebo effect,⁷⁸ with the widespread public discussion

(press and social media) on the benefits of medicinal cannabis and its interaction with the endocannabinoid system increasing patients' expectations.

Considering MC is a relatively new therapy in Australia, it is likely that patient outcomes are correlated with clinician experience, particularly experience prescribing MC. Unfortunately, we did not collect data related to clinician experience and we were unable to run an analysis clustered by clinician due to the large number of clinicians involved in the study (n=120) and their uneven participant recruitment numbers (ranging from 1 to 214). For example, two clinicians enrolled more than 200 participants each in the study, whereas 61 clinicians had less than 10 (with 25 clinicians only recruiting one participant). Future research should include clinicians' MC prescribing experience.

Participants completing follow-up PROMs were likely to be those still using MC because it was helpful to them. The only financial incentive for participants was in accessing discounted MC. Even with the discount, many participants would likely have experienced some financial burden, particularly those who were unemployed or had lower levels of income. This may introduce further bias in the results. Many participants failed to complete PROMs at scheduled follow-up timepoints and did not provide a reason. Some of these participants may have paused or informally withdrawn due to side-effects or lack of MC therapy benefit. Our 12-month follow-up study will identify those who withdrew (rather than missed assessments) and adjust analyses accordingly.

We did not measure adverse events as part of the study. However, follow-up PROMs asked participants to indicate whether they were currently using MC and to select a reason for pausing or withdrawing from the study, which included an option 'not taking MC due to side-effects.' Participants and clinicians were also advised to report concerning side-effects

to the product manufacturer. No participants reported significant adverse effects, or side-effects that they were unable to self-manage through dose-reduction. Similarly, we did not screen participants for cannabis use disorder before or during the study. As 239 participants had previously been using illicit cannabis daily, there is a possibility some of them met the criteria for cannabis use disorder.

We did not include an overall analysis of outcomes by MC product because the participant data we collected did not specify which condition was being treated by each MC product. Many participants (23%) were prescribed more than one MC product, and over half of the total sample (n=1233) were treated for multiple conditions. This limitation is also noted in Appendix 4 which shows participants' health conditions and prescribed MC products at baseline. Future analyses of outcomes for specific groups will explore this further.

Lastly, our study only observed four MC oil products which further limits the generalization of results to other MC products.

CLINICAL IMPLICATIONS

Our findings suggest that prescribing MC in clinical practice may alleviate symptoms of pain, fatigue, sleep disorders, anxiety, and depression in patients with chronic health conditions and improve overall HRQL. More research is needed to understand the full effects of MC for treating sleep-related conditions, and possibly identify optimal MC formulations, dosing, and routes of administration. Current clinical guidelines recommend clinicians consider trialing MC with patients who have chronic conditions not responding to first line treatments,⁷⁹ but acknowledge more evidence and education is needed for clinicians to put

this into practice. At the very least, prescribing MC may avoid potential risks of cannabis abuse by self-medicating while enabling clinicians to monitor possible adverse effects.

CONCLUSION

Short-term findings over 3-months indicate that patients prescribed MC in practice have improved HRQL and sleep, and reduced fatigue. Patients experiencing anxiety, depression, or chronic pain also improved in those outcomes over 3-months. The study continues to follow patients over 12 months to determine whether improvements in PROs are maintained long-term. In addition, further subgroup analyses will be undertaken to determine whether patients with specific health conditions have better outcomes compared with others when using validated condition-specific questionnaires. The findings from this study contribute to the ongoing evidence for decision making both in clinical practice and at policy level.

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COMPETING INTERESTS

The University of Sydney received funding from Little Green Pharma Pty Ltd. to support MT and CR to conduct the submitted work; LW is a paid employee of Little Green Pharma Pty Ltd.; no other relationships or activities that could appear to have influenced the submitted work. All authors have completed the ICMJE uniform disclosure form. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

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CHAPTER 5

CHAPTER 5: ASSESSING HRQL IN PATIENTS PRESCRIBED MC: 12-MONTH FOLLOW-UP RESULTS

CHAPTER OVERVIEW

Chapter 5 extends the study reported in chapter 4, with a follow-up analysis of the cohort at 12-months, to determine whether changes observed at 3-months were maintained long-term. As outlined in the protocol presented in chapter 3, the objective of the 12-month follow-up study was also to describe differences between patients accessing MC with different chronic health conditions. This was important to explore due to the wide use of MC across multiple conditions, the prevalence of chronic health comorbidities, and the interrelationship between mental health, sleep, and pain discussed in chapter 1. While a previous review by Goldenberg et al. concluded improved pain was the main driver of improved HRQL in MC studies,² the systematic review presented in chapter 2 found HRQL improvements were not only associated with pain reduction, but also through resolving sleep, and physical and psychological issues. Therefore, the following study assessed whether there were group differences in change scores for condition-specific outcomes and if the different cannabinoid compositions of MC therapy were associated with different outcomes in patients with the same condition.

Supplementary to the 12-month results, Appendix 2 contains the study invitations and participant information, and Appendix 3 contains the ethics approval letters. Appendix 5 contains the supplementary material referred to in the publication as well as the completed STROBE checklist for reporting observational studies.

² Goldenberg M, Reid MW, IsHak WW, Danovitch I. The impact of cannabis and cannabinoids for medical conditions on health-related quality of life: A systematic review and meta-analysis. *Drug and alcohol dependence*. 2017;174:80-90

As reported in Appendix 7, the parallel sub-study looking specifically at participants with cancer found clinically meaningful improvements in pain and HRQL following titration and maintained over 3 months. Further analysis was conducted at 12-months to determine whether HRQL improvements were maintained long-term. Appendix 7 contains the sub-study findings at 12-months as an abstract presented at the New South Wales Cancer Conference, Sydney, Australia, 19 September 2023.

PUBLICATION DETAILS

Tait M, Costa D, Warne LN, Norman R, Campbell R, Stephan Schug, Rutherford C.

Improvements in health-related quality of life are maintained long-term in patients prescribed medicinal cannabis in Australia: The QUEST Initiative 12-month follow-up observational study, PLOS One, 2025 20(4):e0320756. doi: 10.1371/journal.pone.0320756

DATA AVAILABILITY STATEMENT

All data files are available from the Sydney eScholarship database

(<https://url.au.m.mimecastprotect.com/s/7U2CCzvkyVC84v8AOs4gfPO?domain=hdl.handle.net>).

AUTHORSHIP ATTRIBUTION STATEMENT

The co-authors confirm the contribution of Margaret-Ann Tait as the primary author, in compliance with the international Committee of Medical Journal Editors (ICMJE) authorship criteria, for the following manuscript:

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Margaret-Ann Tait made the following contributions.

- Conception and design of the research
- Funding acquisition
- Designed the data collection instrument
- Created study documents
- Submitted and obtained ethics approvals
- Conducted recruitment site training
- Collected the data
- Data cleaning
- Analysis and interpretation of the data
- Drafted and revising the paper
- Responded to reviewer comments
- Coordinated the submission of the paper for publication

MT, CR, and LW made substantial contributions to the study concept and design, with critical feedback provided by RC, RN, DC, and SS. All authors contributed towards interpretation of data and reviewed and provided critical feedback on the final manuscript.

As the primary supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

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ABSTRACT

AIMS

Since 2016, more than one million new patients with chronic health conditions have been prescribed medicinal cannabis in Australia. We aimed to assess overall health-related quality of life (HRQL), pain, fatigue, sleep, anxiety, depression, and motor function in a large real-world sample of patients prescribed medicinal cannabis. We previously found all patient-reported outcomes improved in the first 3-months and hypothesised that improvements would be maintained to 12-months.

METHODS

The QUEST Initiative, a multicentre prospective study, recruited adult patients with any chronic health condition newly prescribed medicinal cannabis oil between November 2020 and December 2021. Participants identified by 114 clinicians across Australia completed validated questionnaires at baseline, then 2-weeks titration, and 1-,2-,3-,5-,7-,9- and 12-months follow-up.

RESULTS

Of 2744 consenting participants who completed baseline assessments, 2353 also completed at least one follow-up questionnaire and were included in analyses, with completion rates declining to 778/2353 (38%) at 12-months. Ages ranged between 18-97 years (mean 50.4y; SD=15.4), 62.8% were female. Chronic conditions commonly treated included musculoskeletal pain (n=896/2353; 38.1%), neuropathic pain (n=547/2353; 23.2%), insomnia (n=546/2353; 23.2%), anxiety (n=520/2353; 22.1%), and mixed depressive and anxiety disorder (n=263/2353; 11.2%). Clinically meaningful improvements were observed in

HRQL: EQ-5D-5L index ($d=0.52$) and QLQ-C30 summary scores ($d=0.91$), PROMIS fatigue ($d=0.51$) and sleep disturbance ($d=0.76$). Participants diagnosed with chronic pain experienced clinically meaningful improvement in scores on QLQ-C30 pain ($d=0.5$), PROMIS pain intensity ($d=0.76$), and PROMIS pain interference ($d=0.76$). There was significant improvement in DASS anxiety ($d=0.69$) and DASS depression ($d=0.65$) for those with anxiety or depressive conditions, but no motor function improvements observed for participants with movement disorders. All observed improvements were statistically significant.

CONCLUSIONS

Statistically significant and clinically meaningful improvements in overall HRQL, fatigue, and sleep disturbance were maintained over 12-months in patients prescribed medical cannabis for chronic health conditions. Anxiety, depression, insomnia, and pain also improved over time for those with corresponding health conditions.

STUDY REGISTRATION

Australian New Zealand Clinical Trials Registry: ACTRN12621000063819

INTRODUCTION

Almost half of the Australian population suffers from chronic health conditions,¹ with an estimated 3.6 million living with chronic pain,² 3.3 million with anxiety disorders, and 1.5 million with sleep disorders,³ all negatively impacting their Health-Related Quality of Life (HRQL). Research into the therapeutic benefits of medicinal cannabis (MC) has increased since discovery of the analgesic properties in cannabis plant compounds, delta-9-tetrahydrocannabinol and cannabidiol (THC and CBD),⁴ and fuelled by growing concerns around opioid misuse and adverse events,⁵ including bowel dysfunction, cognitive decline, endocrinopathy, hospitalization, and death from overdose.⁶ With support from the community, advocacy groups lobbied the Australian government to bring about legislation changes in 2016,⁷ which allows patients not responding to conventional treatment to access MC with a prescription from clinicians regulated by the Therapeutic Goods Administration (TGA). TGA records to date show that more than one million new patients in Australia have received MC prescriptions,⁸ for over 200 health conditions.⁹

Regarded as the gold standard for assessing pain,¹⁰ a patient-reported outcome (PRO) is any report about health status that comes directly from patients,¹¹ and is important when evaluating the impact of new treatments for chronic health conditions where the main goal is to alleviate symptoms.¹² HRQL is a PRO that encompasses the overall impact of disease or treatment across areas such as physical, emotional, social, and cognitive function, as well as bodily discomfort and symptoms like pain.¹³ Regulatory bodies on safety and quality in health care in Australia¹⁴ and those overseeing medical research funding, health service delivery, and product labelling internationally,^{11,15-17} often require evidence gathered using validated PRO measures (PROMs) to assess the value of treatment. To better inform

regulation and policymaking, evidence from patients prescribed MC in clinical practice is needed to evaluate change in HRQL and other PROs in the real-world.^{18,19}

The QUEST initiative (**Q**uality of life **E**valuation **S**Tudy) assessed patient-reported HRQL, pain, fatigue, sleep disturbance, anxiety, depression, and motor function in patients with chronic health conditions prescribed MC in Australia. Our short-term results, reported elsewhere,²⁰ found that within the first three months of MC therapy, participants reported clinically meaningful improvements in HRQL, fatigue, and sleep disturbance, and in health conditions associated with anxiety, depression, and pain. It is typical when evaluating clinical care outcomes in chronic conditions to assess 12-month follow-up.²¹ This study aimed to assess 12-month follow-up data to determine if our previously reported improvements at 3-months were maintained long-term and to explore differences across health conditions and MC compositions. We hypothesised that improvements in PROs from baseline would be maintained long-term in patients prescribed MC, and that patients with specific conditions would have sustained improvements in condition-specific symptoms.

METHODS

The STROBE statement for reporting observational studies was followed.²² Ethical approval was granted by University of Sydney Human Research Ethics Committee (HREC) Project#:2020/589 and informed written consent to participate in the study was obtained from all participants. This study was registered with the Australian New Zealand Clinical Trials Registry: ACTRN12621000063819. Full details of study design, eligibility, recruitment procedures, and data collection are reported in the published study protocol.²³

STUDY POPULATION AND DESIGN

The QUEST initiative is a multicentre prospective study of patients with chronic health conditions newly prescribed MC across Australia between 27 November 2020 and 23 December 2021. All clinicians prescribing Little Green Pharma (LGP) MC oil products across Australia were informed of the study and invited to contact the researchers to receive the study training and information required to screen their patients for eligibility. Clinicians entered clinical information on eligibility screening forms via the web-based research data capture system, REDCap.²⁴ Eligibility for the 12-month follow-up study included patients ≥ 18 years old with prescriptions for LGP MC oil products, and able to read and self-complete online PROMs in English. To achieve a pre-therapy baseline, patients were excluded if they had accessed prescribed MC within the previous 4-weeks; selected because it ensured the minimum wash-out period of 13-30 days had passed,^{25,26} and was greater than the maximum recall period of PROMs used in the study. Palliative care patients were identified by clinicians following the ICD-11 definition of having a life expectancy of only a few months.²⁷ Accordingly, PROMs were only administered to palliative care patients for the first 3-months of the QUEST study, excluding them from the 12-month analysis. Our 3-month findings for participants receiving end of life palliative care are reported elsewhere.²⁰ Invitations were emailed to eligible patients directly from REDCap. All participants purchased LGP products at the same price of AUD\$150 (USD \$98) per 50ml bottle, standardised to allow future health economic evaluation. Depending on individual dosing needs, each 50ml bottle typically lasts between 6-12 weeks. The four LGP products were full-spectrum MC oil containing the following ratios of THC and CBD dissolved in a medium chain triglyceride carrier oil: LGP Classic 1:20 (1mg THC and 20mg CBD per ml), LGP Classic

10:10 (10mg THC and 10mg CBD per ml), LGP Classic 20:5 (20mg THC and 5mg CBD per ml), LGP Classic CBD 50 (50mg CBD per ml).

DATA COLLECTION

Clinicians completed basic patient demographics (age and sex), clinical characteristics, and selected up to two health conditions that were being treated with MC. Informed written consent, further demographics, and PROMs were completed electronically by participants. All PROMs were completed at baseline prior to commencing MC therapy, after approximately 2-weeks titration (optimal benefit of therapy was expected to be achieved 2-weeks after commencing therapy), monthly for 3 months, then at 5-, 7-, 9-, and 12-months post titration. Follow-up assessment timepoints were selected to align with TGA guidance for MC monitoring,²⁸ and clinical guidelines.^{29,30} At each assessment timepoint, participants received automated reminders to complete PROMs within 7-days, with non-responders recorded as missed assessments. Data collection ended 19 March 2023.

PROMs

We assessed PROs using validated PROMs for HRQL (EQ-5D-5L Index; QLQ-C30 Summary score), pain (QLQ-C30-pain subscale), fatigue (PROMIS fatigue 13a), sleep (PROMIS sleep disturbance 8b), anxiety (DASS-anxiety scale), and depression (DASS-depression scale). A description and justification for each PROM administered to all participants is reported in detail elsewhere.^{20,23} Additional PROMs for pain (PROMIS pain intensity 3a; PROMIS pain interference 8a) and motor function (Neuro-QoL Upper extremity function) were administered to participants with diagnosed chronic pain conditions or movement disorder in this 12-month study and are described in S1 Table.

STATISTICAL ANALYSES

STATISTICAL CONSIDERATIONS

Participants' PROs were included in the analyses if they had a score at baseline and at least one follow-up assessment. Our target sample size of 2142 was determined *a priori* with power to detect the smallest QLQ-C30 effect size threshold³¹ using a two-sided significance level of 1%, as reported in the study protocol.²³ All PROMs were scored following instructions provided by the PROM developers. The HealthMeasures Scoring Service³² calculated PROMIS measure T-scores with a mean of 50 and standard deviation of 10 in the general population (US 2000 Census) for assessing pain, fatigue, and motor function, and in combination with a clinical sample for assessing sleep disturbance.³³ EQ-5D responses were transformed using the most recent Australian population utility weights³⁴ and combined to produce a health index ranging from 0 (death) to 1 (perfect health).

Means, standard deviations (SD), and standardized mean change from baseline (Cohen's d) with 95% confidence intervals were calculated for each assessment timepoint. Linear mixed models were used to examine change over time in PRO scores (including baseline to 3-months), with time included as a random factor.

The model adjusted for PRO response levels at baseline and sex, with duration of pain and age modelled as fixed factor covariates. Participant age, sex, and duration of pain condition, were previously identified as significant covariates in this cohort.²⁰ Change over time was analysed by looking at linear and quadratic trends to determine whether there was constant change over time (linear) or change at a changing rate (linear + quadratic); and baseline was compared to mean of all follow-up scores when assessing differences between groups.

Averaging follow-up was justified by results from the 3-month analyses, which

demonstrated that the largest changes occurred shortly after MC-therapy initiation with minimal change thereafter.²⁰ Paired sample t-tests compared mean change from baseline to each follow-up timepoint. In addition, the average follow-up scores for DASS anxiety and depression subscales were coded into severity categories and compared to the distribution of severity categories at baseline using a One-Sample Chi-squared test. Statistical significance, defined as p-value <0.05, was Hochberg-adjusted to account for multiple comparisons,³⁵ and analyses conducted with IBM SPSS Statistics 28.0 program.

Findings from our 3-month study revealed that participants were often prescribed more than one product,²⁰ therefore total daily dosage of THC and CBD was calculated and grouped into four of the five active ingredient categories used by the TGA:³⁶ CBD-only (CBD $\geq$ 98%); CBD-dominant (CBD $\geq$ 60% and <98%); CBD:THC-balanced (CBD <60% and $\geq$ 40%); and THC-dominant (THC 60-98%); with the fifth TGA category, THC-only (THC $\geq$ 98%), not available in this study.

CLINICALLY MEANINGFUL CHANGE

The primary focus of our analyses was to examine clinically meaningful change in PROs. This is important because our large sample size provided power to detect small changes as statistically significant that may not actually be regarded as clinically relevant or important to patients. Minimally clinically important differences (MCIDs)³⁷ in PROs over time were evaluated using existing guidelines where available. The MCID for EQ-5D-5L index score falls between 0.037 and 0.069 in general populations,³⁸ and evaluating meaningful within-group change using PROMIS measures is between 2 and 6 with consensus on 3 T-score points.^{39,40} The MCID for DASS-21 depression and anxiety scales is change of 5 points from one severity

category to another.⁴¹ The recommended QLQ-C30 pain subscale MCID is 5 points,³¹ however there are currently no published MCIDs for the QLQ-C30 Summary Score.

In the absence of guidelines, Cohen's $d=0.5$ was used for the QLQ-C30 Summary Score MCID. This threshold of half of the standard deviation of change score has previously been determined as suitable for discriminating HRQL change in chronic diseases,⁴² and is reported for all PROs.

PATIENT AND PUBLIC INVOLVEMENT

Patient participants voluntarily provided self-rated PROM responses. Participants received a summary of findings at the end of the study but were not directly involved in developing the research question or study design.

RESULTS

Of 3302 invited eligible patients by 114 clinicians, 2744 (83%) provided consent and completed baseline PROMs and demographics. Of those, 2353 (86%) completed at least one follow-up PROM and were included in the analysis (Figure 1). During study follow-up, 322 (11.7%) enrolled participants withdrew due to lack of therapeutic benefit (132, 41%), finding an alternative treatment (70, 22%), unwanted side-effects (64, 20%), and financial cost (57, 17%). PROM completion rates for participants remaining on the study at each follow-up ranged from 82.8% at 1-month to 38% at 1-year. The 391 who dropped out after only completing baseline without providing a reason were generally younger, male, less educated, and less likely to be married, than those who continued on the study (Table 1). When looking at the 2353 participants who continued, those still remaining at 12-months were slightly older and less likely to have been diagnosed with an anxiety disorder.

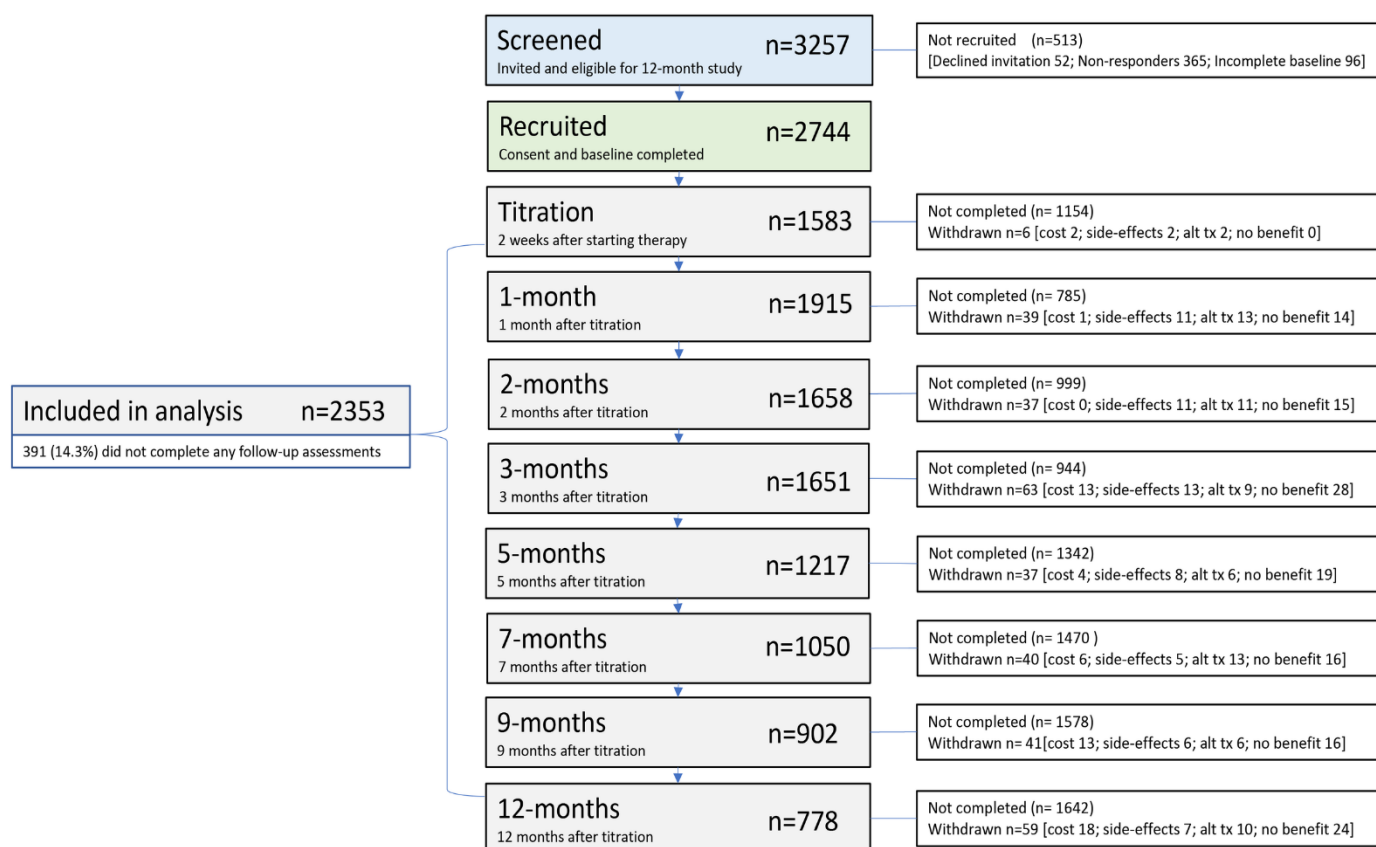


Figure 1. Study Recruitment Flow

Table 1. Baseline characteristics of QUEST participants grouped by participants who completed baseline PROMs only, and those included in the 12-month analyses (completed baseline plus at least one follow-up).

Characteristics	Completed baseline only	Included in analysis	P value (χ^2)
Total ($n=2744$)	391	2353	
Age (years), mean (SD)	47.7 (17.1)	50.4 (15.4)	0.002
Sex, n (%)			
Male	157 (40.2)	874 (37.1)	0.230
Female	232 (59.3)	1477 (62.8)	
Indeterminate/Intersex	1 (0.3)	2 (0.1)	
Living arrangements, n (%)			
Live alone	76 (19.4)	479 (20.4)	0.124
Live with partner	226 (57.8)	1423 (60.5)	
Live with carer	10 (2.6)	41 (1.7)	
Live with other	74 (18.9)	401 (17)	
Live in assisted care home	3 (0.8)	7 (0.3)	
Missing	2 (0.5)	2 (0.1)	
Marital Status, n (%)			
Single	96 (24.6)	525 (22.3)	0.032
Married	169 (43.2)	1106 (47)	
Separated	22 (5.6)	92 (3.9)	
Divorced	35 (9.0)	252 (10.7)	
Widowed	20 (5)	72 (3.1)	
Cohabiting	47 (12.0)	304 (12.9)	
Missing	2 (0.5)	2 (0.1)	
Work Status, n (%)			
Full time	138 (32.2)	658 (28.6)	0.792
Part time	68 (15.9)	361 (15.7)	
At work but limited hours/duties	27 (6.3)	131 (5.7)	
Retired	68 (15.9)	449 (19.5)	
Unemployed due to illness	78 (18.2)	394 (17.2)	
Unemployed NOT due to illness	6 (1.4)	43 (1.9)	
On leave due to illness	10 (2.3)	57 (2.5)	
Home duties	15 (3.5)	99 (4.3)	
Studying only	9 (2.0)	65 (2.8)	
Voluntary work	6 (1.4)	25 (1.1)	
Retraining	4 (0.9)	15 (0.7)	
Missing	6 (1.4)	30 (1.3)	
Education, n (%)			
Primary School	6 (1.5)	23 (1.0)	0.033
High School	120 (30.7)	599 (25.5)	
Certificate or Diploma	129 (33.0)	850 (36.1)	
University or higher	134 (34.3)	879 (37.4)	
Missing	2 (0.5)	2 (0.1)	

SD standard deviation; χ^2 Pearson's chi-squared; P values in bold are significant.

Participants were aged between 18-97 years (mean 50.4y; SD=15.4), 62.8% female, 37.4% University educated, and more than a quarter were either unemployed, on leave, or on limited work duties, due to their poor health (Table 1). S2 Table provides additional demographic information on gender identity and ethnicity.

The range and proportion of conditions being treated were similar for participants included in the analysis compared with those who dropped out at baseline (S3 Table). Half of participants were prescribed MC for more than one condition (n=1244/2353; 53%), with the majority treated for chronic pain conditions (n=1615/2353; 68.6%). Other common conditions included insomnia (n=546/2353; 23.2%), anxiety (n=520/2353; 22.1%), and mixed anxiety and depression (n=263/2353; 11.2%). Ninety participants had a cancer diagnosis (receiving cancer-treatment), of which only 28 were prescribed MC for cancer-related pain.

Within each MC composition category, the median daily doses were: CBD-only – 50mg (IQR: 25, 100) equivalent to 1ml LGP Classic CBD; CBD-dominant – 30mg CBD (IQR: 15, 55) and 3mg THC (IQR: 1, 8) similar to 1.5 ml LGP Classic 1:20; CBD:THC-balanced – 7.5mg CBD (IQR: 3, 15) and 7.5mg THC (IQR: 3, 15) equivalent to 0.75ml LGP Classic 10:10; and THC-dominant – 5mg CBD (IQR: 2, 10) and 20mg THC (IQR: 8, 30) equivalent to 1ml LGP Classic 20:5. The number of participants at each follow-up timepoint taking the different combinations of active ingredients are shown in Figure 2.

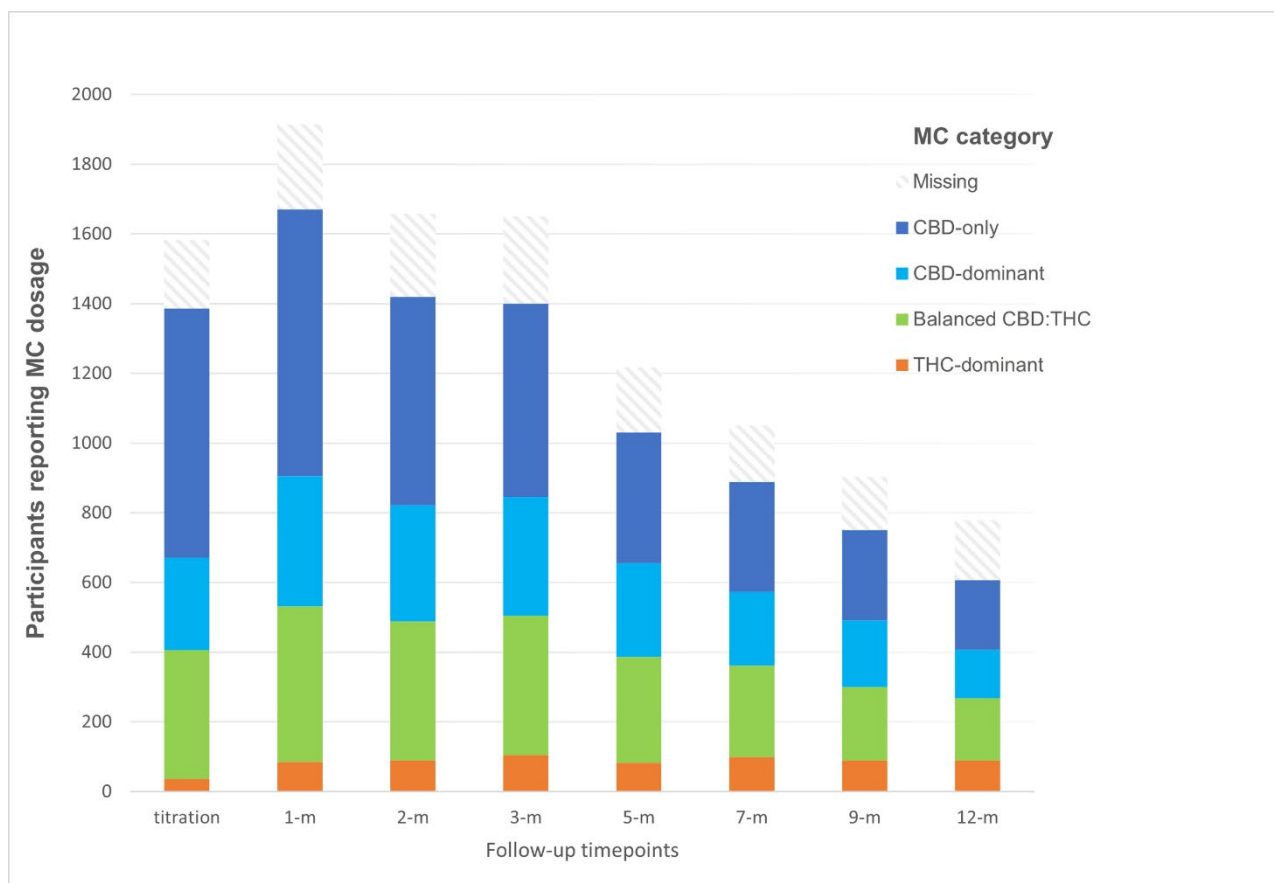


Figure 2. Number of participants at each follow-up timepoint taking MC doses containing average daily CBD to THC ratios within the four categories of active ingredients.

Less than 5% (109/2353) of participants had been prescribed MC previously (but not within 4-weeks prior to joining the study), and 576/2353 (24.5%) had used cannabis recreationally, or medicinally without a prescription, within 12-months prior to joining. At baseline, two-thirds of participants (1621/2353) were taking medications other than MC on a regular daily basis to manage their condition, of which 488 (30%) were opioids, with an additional 38 participants taking opioids occasionally. In total, 526 (22.6%) participants were regularly taking opioids daily or as needed when they joined the study. During the study 1100 (47%) participants reported that due to taking MC they had reduced their use of at least one of their other prescribed medications to manage their symptoms. Of these, 526 (48%) had

completely stopped taking one or more medications due to taking MC. By the end of the 12-month follow-up period, 370/526 (70%) participants had reduced their opioid medications, of which, 138 (26%) completely stopped.

PROs

Results in Table 2 show mean differences in HRQL, pain, sleep, fatigue, depression, and anxiety scores across the whole cohort from baseline to 5-, 7-, 9-, and 12-months follow-up and clinically meaningful significance of effect sizes (results for first three months of the QUEST study are reported elsewhere²⁰).

HRQL

EQ-5D-5L index scores (n=2353) displayed significant linear ($t_{(9028)}=9.79$, $p<0.001$) and quadratic ($t_{(13037)}=-10.05$, $p<0.001$) trends over time, signifying a large initial improvement maintained thereafter (Figure 3a). Adjusted scores improved on average by 0.114 (SD=0.219; 95%CI:0.111, 0.122) from 0.625 (SD=0.240) at baseline to mean follow-up of 0.739 (SD=0.224), indicating a clinically meaningful improvement ($d=0.52$) greater than the recommended MCID.[45]

QLQ-C30 summary scores (n=2353) also showed significant linear ($t_{(2351)}= 17.32$, $p<0.001$) and quadratic ($t_{(5595)}= 19.46$, $p<0.001$) trends, suggesting initial improvement maintained over 12-months (Figure 3b). The adjusted mean difference from 58.92 (SD=16.7) at baseline to 69.63 (SD=17.66) mean follow-up was 10.71 (SD=11.77) indicating a clinically meaningful improvement ($d=0.91$; 95%CI: 0.85, 0.97).

Table 3 reports change in HRQL from baseline to mean post-MC therapy across different health conditions, for participants having only one of the listed conditions.

Table 2. Change in HRQL, pain, sleep, fatigue, depression, and anxiety from baseline to 5-, 7-, 9-, and 12-months post-titration in 2353 participants with any health condition prescribed medical cannabis.

Outcome	PROM	Follow-up timepoint	N	MD	SD	ES	95% CI	p
HRQL	EQ-5D-5L utility index	5 months	1217	0.127	0.201	0.630	0.569, 0.692	<.001
		7 months	1050	0.137	0.204	0.669	0.602, 0.736	<.001
		9 months	902	0.134	0.208	0.646	0.574, 0.718	<.001
		12 months	778	0.142	0.226	0.631	0.554, 0.708	<.001
	QLQ-C30 summary score	5 months	1205	12.06	14.63	0.824	0.759, 0.890	<.001
		7 months	1044	12.41	14.80	0.839	0.768, 0.909	<.001
		9 months	898	12.47	15.32	0.814	0.738, 0.889	<.001
		12 months	773	13.51	15.93	0.848	0.766, 0.930	<.001
Pain	QLQ-C30 pain subscale	5 months	1206	17.27	26.34	0.656	0.593, 0.718	<.001
		7 months	1047	17.78	26.40	0.673	0.606, 0.740	<.001
		9 months	899	17.52	27.59	0.635	0.563, 0.706	<.001
		12 months	775	19.66	28.37	0.693	0.614, 0.771	<.001
Sleep	PROMIS sleep disturbance 8b	5 months	1195	6.890	9.358	0.736	0.672, 0.800	<.001
		7 months	1037	6.862	9.464	0.725	0.656, 0.793	<.001
		9 months	891	6.922	9.348	0.741	0.666, 0.814	<.001
		12 months	768	7.828	10.06	0.778	0.697, 0.859	<.001
Fatigue	PROMIS fatigue 13a	5 months	1198	5.415	8.298	0.653	0.590, 0.715	<.001
		7 months	1037	5.685	8.394	0.677	0.610, 0.745	<.001
		9 months	893	5.685	8.756	0.649	0.577, 0.721	<.001
		12 months	768	6.090	8.886	0.685	0.607, 0.764	<.001
Depression	DASS-21 depression subscale	5 months	1199	4.832	9.010	0.536	0.476, 0.597	<.001
		7 months	1039	5.207	8.817	0.591	0.525, 0.656	<.001
		9 months	895	5.377	8.697	0.618	0.526, 0.690	<.001
		12 months	768	5.492	9.105	0.603	0.526, 0.680	<.001
Anxiety	DASS-21 anxiety subscale	5 months	1200	3.597	7.068	0.509	0.449, 0.569	<.001
		7 months	1039	3.731	7.122	0.524	0.459, 0.589	<.001
		9 months	895	3.423	6.988	0.490	0.420, 0.559	<.001
		12 months	768	3.716	7.459	0.498	0.423, 0.573	<.001

CI confidence interval of effect size; ES standardized mean-difference effect size (Cohen's d); HRQL health-related quality of Life; MD mean difference in direction of improvement; PROM patient-reported outcome measure; SD standard deviation of mean difference. p values reported are from paired t-tests. **bold** indicates clinically meaningful change ($d \geq 0.5$).

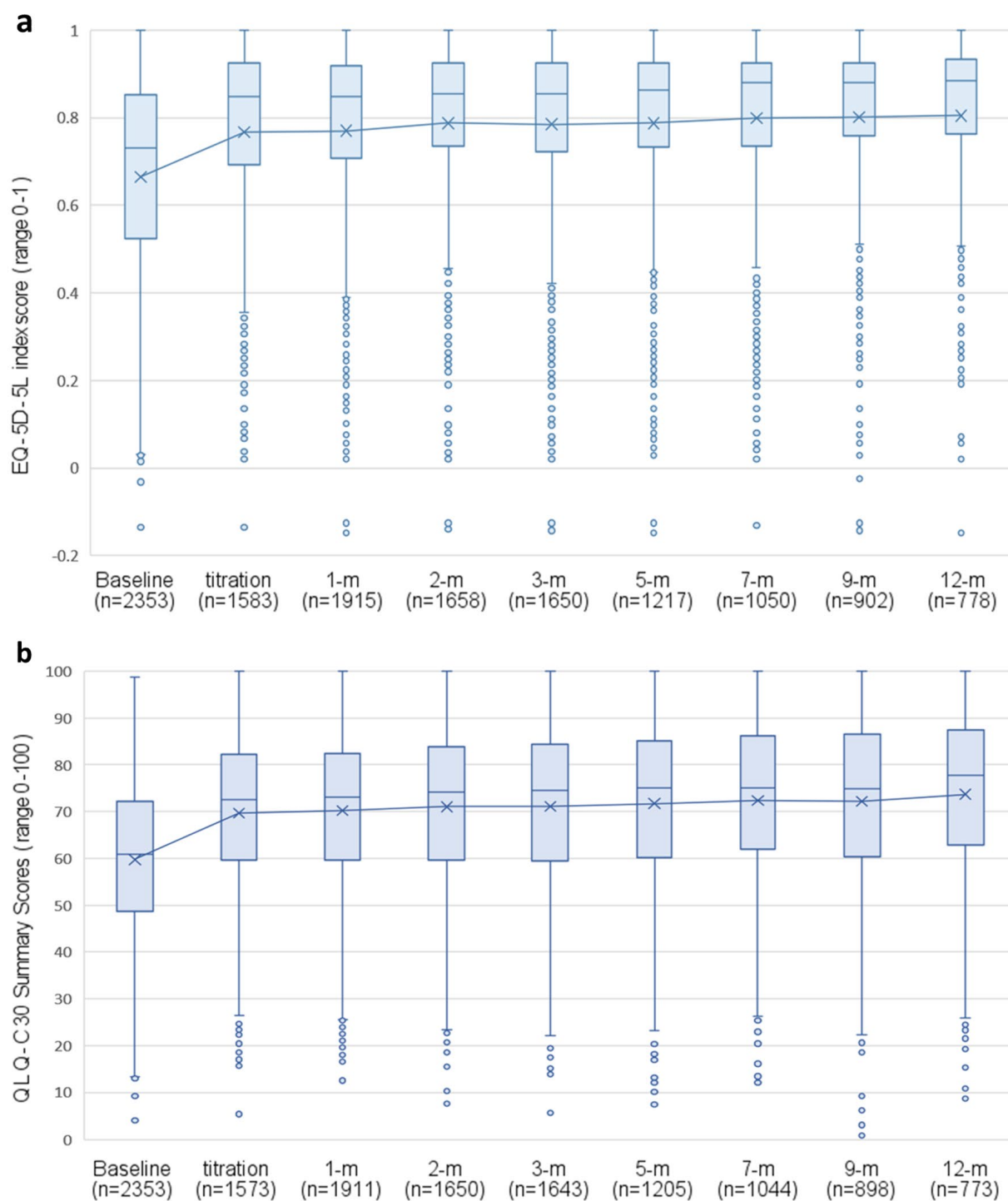


Figure 3. Score distribution from baseline to 12-months following titration box plots with median bars and mean line for **a)** EQ-5D-5L Australian weighted Index Scores, and **b)** QLQ-C30 Summary Scores. Higher scores indicate better quality of life.

Table 3. Change in self-reported HRQL from baseline to mean post-therapy scores for participants exclusively treated for each health condition.

PROM	Health condition [^]	N	MD	SD	ES	95% CI	p
EQ-5D-5L utility index							
	Chronic pain [†]	1024	0.118	0.186	0.64	0.57, 0.70	<.001
	Sleep disorder	93	0.057	0.108	0.53	0.31, 0.75	<.001
	Generalised anxiety disorder	202	0.090	0.145	0.62	0.47, 0.77	<.001
	Movement disorder [‡]	15	0.004	0.156	0.03	-0.48, 0.53	0.923
	PTSD	22	0.106	0.194	0.55	0.09, 0.99	0.018
	Mixed anxiety and depression	94	0.061	0.146	0.42	0.21, 0.63	<.001
	Epilepsy	10	0.000	0.091	0.00	-0.62, 0.62	0.99
QLQ-C30 summary score							
	Chronic pain [†]	1022	9.559	11.88	0.81	0.73, 0.88	<.001
	Sleep disorder	93	10.22	9.653	1.06	0.80, 1.31	<.001
	Generalised anxiety disorder	200	10.68	10.79	0.99	0.82, 1.16	<.001
	Movement disorder [‡]	15	5.204	11.90	0.45	-0.09, 0.97	0.106
	PTSD	19	12.85	10.86	1.18	0.58, 1.77	<.001
	Mixed anxiety and depression	93	8.304	13.212	0.63	0.41, 0.85	<.001
	Epilepsy	10	6.28	8.694	0.72	0.01, 1.35	0.048
ES: standardized mean-difference effect size (Cohen's d), bold indicates clinically meaningful change (d≥0.5)							
Higher scores indicate better health related quality of life (HRQL)							
PTSD post-traumatic stress disorder							
[^] participants exclusively treated for the health condition listed							
[†] Chronic pain conditions include neuropathic, widespread (fibromyalgia), primary and secondary musculoskeletal, primary and secondary headache or orofacial, primary and secondary visceral, cancer-related, and post-traumatic.							
[‡] movement disorders included: Parkinsonism, tremor, paroxysmal dyskinesias, dystonia, ataxia, and tic disorders.							

PAIN

QLQ-C30 pain subscale scores across the cohort showed significant linear ($t_{(9002)}= 10.60$, $p<0.001$) and quadratic ($t_{(13012)}=8.90$, $p<0.001$) trends of improvement over time (Figure 4a). Mean scores improved by 14.39 (SD= 28.99; 95%CI: 14.19, 15.55; $d= 0.5$) with significantly greater improvements observed over time in participants with a chronic pain diagnosis ($n=1615$) compared to those without ($t_{(5144)}= 11.17$, $p<0.001$) (Figure 4b). Following guidelines, change of more than 14 points is considered a large clinical improvement.⁴³

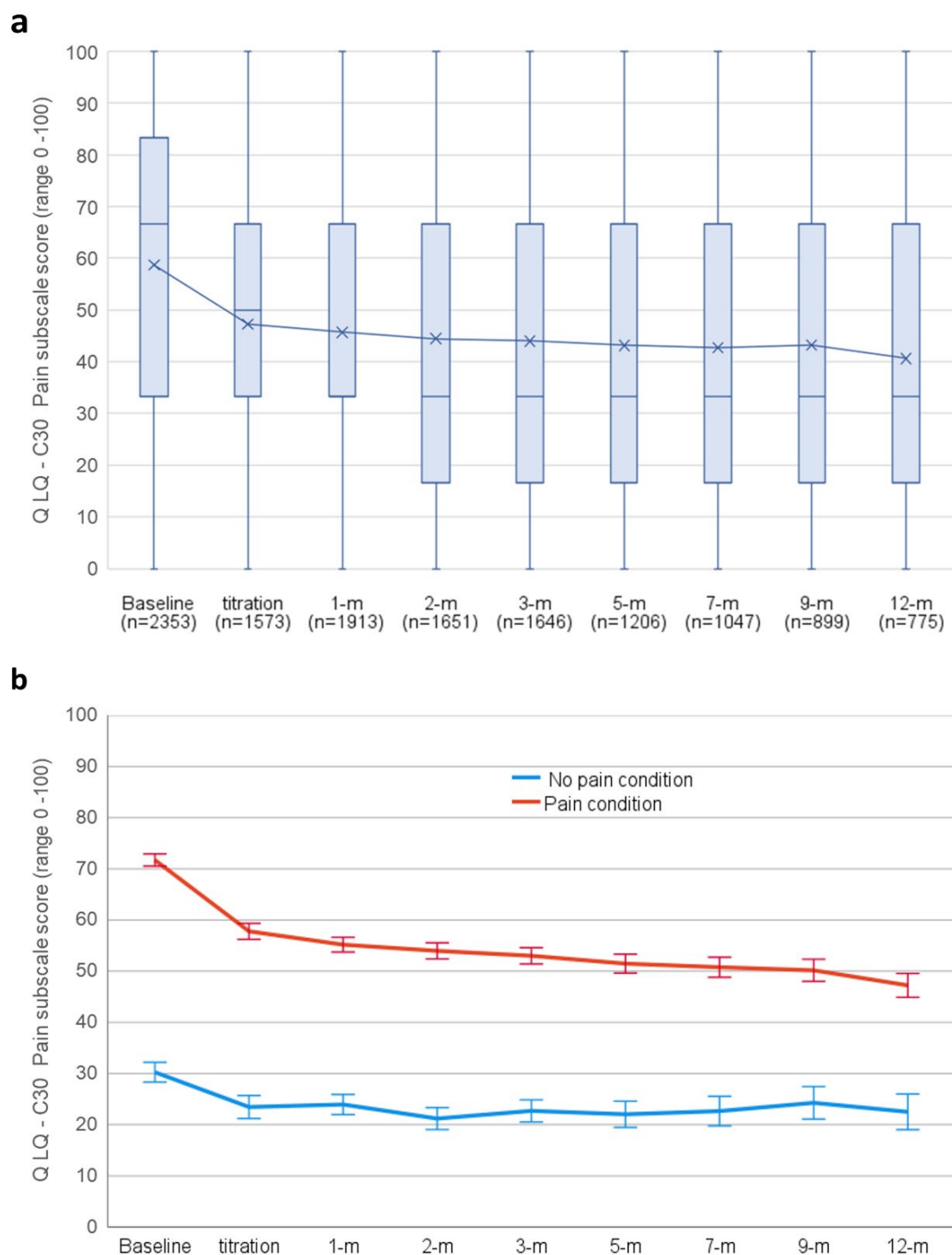


Figure 4. QLQ-C30 Pain subscale scores from baseline to 12-months following titration for **a)** Score distribution box plot with median bars and mean line for whole cohort and **b)** Comparisons of mean scores for participants with a pain diagnosis vs no pain diagnosis. Higher scores indicate greater symptom burden. Error bars are 95%CI.

PAIN INTENSITY

PROMIS Pain Intensity 3a scores showed significant linear ($t_{(1640)} = 15.39$, $p < 0.001$) and quadratic ($t_{(4072)} = 11.74$, $p < 0.001$) trends of improvement over time for participants with chronic pain (Figure 5a). Mean improvement in pain intensity T-scores from baseline to follow-up was 4.94 (SD=6.53; 95%CI: 4.62, 5.26) indicating clinically meaningful improvement ($d = 0.76$) greater than the recommended PROMIS MCID of 3 T-scores.

When comparing change scores from baseline to follow-up across the different pain conditions (visceral, headache, musculoskeletal, neuropathic, cancer-related, or post-surgery), significant differences were observed between neuropathic and musculoskeletal pain ($p = 0.028$), neuropathic and headache pain ($p = 0.019$), and between headache and widespread pain ($p = 0.027$) (Figure 5b).

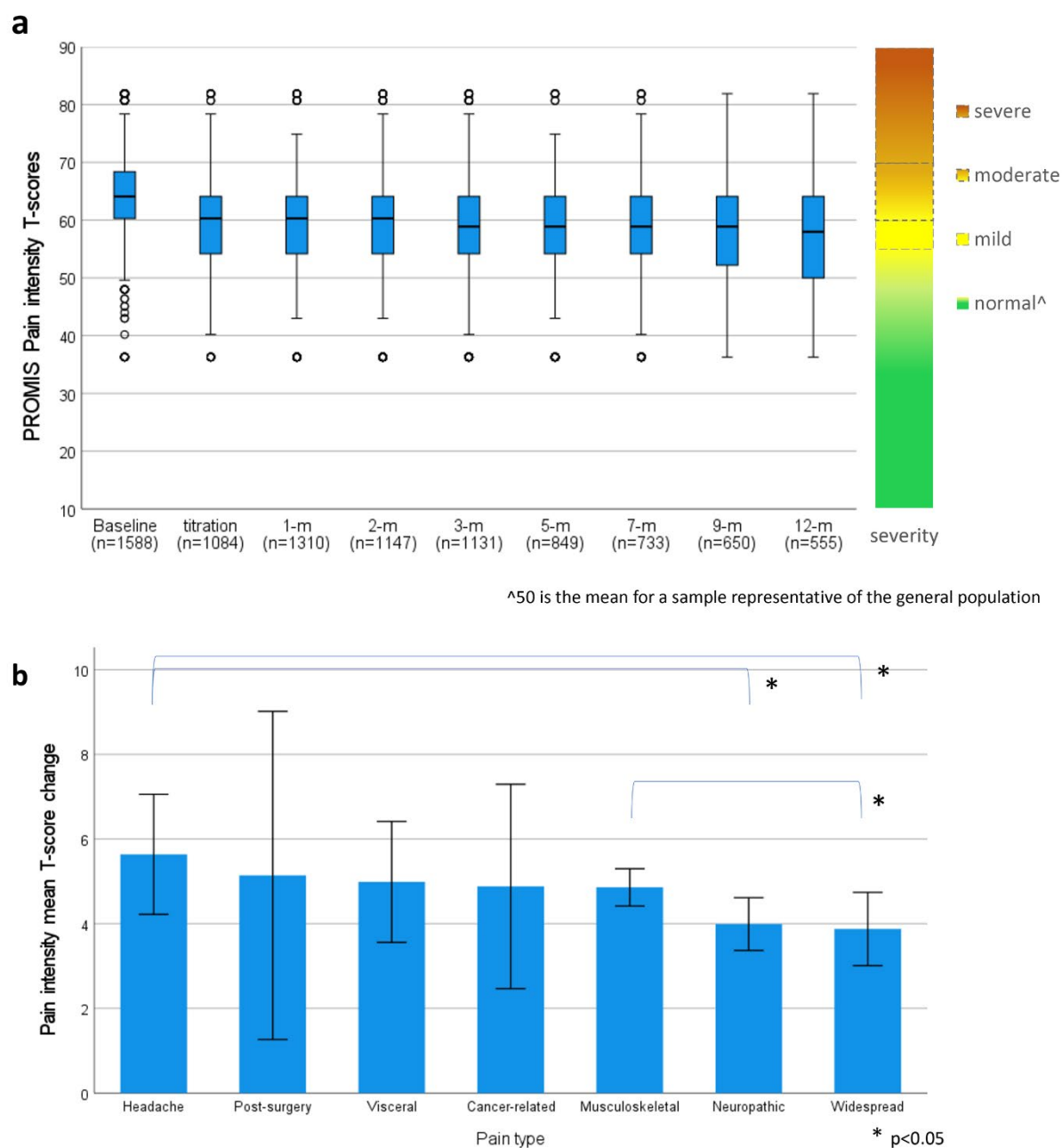


Figure 5. PROMIS T-scores for participants with a pain diagnosis for **a)** Pain intensity T-score distribution from baseline to 12-months following titration with PROMIS severity scale **b)** Pain intensity mean difference from baseline to average follow-up across different pain conditions.

PAIN INTERFERENCE

PROMIS Pain Interference 8a scores also showed significant linear ($t_{(1651)}=15.16$, $p<0.001$) and quadratic ($t_{(3853)}=12.07$, $p<0.001$) trends of improvement over time for participants with chronic pain (Figure 6a). Mean improvement in pain interference T-scores from baseline to average follow-up was 4.87 (SD=6.44; 95%CI: 4.56, 5.19) indicating clinically meaningful improvement ($d=0.76$) greater than the recommended PROMIS MCID of 3 T-scores.

When comparing change scores from baseline to follow-up across the different pain conditions, significant differences were observed between visceral and neuropathic pain ($p<0.001$), visceral and widespread pain ($p=0.008$), visceral and musculoskeletal pain ($p=0.001$), and between headache and neuropathic pain ($p=0.002$), headache and widespread pain ($p=0.014$), and headache and musculoskeletal pain ($p=0.002$)(Figure 6b).

Table 4 reports mean difference of pain interference and pain intensity T-scores and effect size from baseline to each follow-up timepoint for participants with a pain condition.

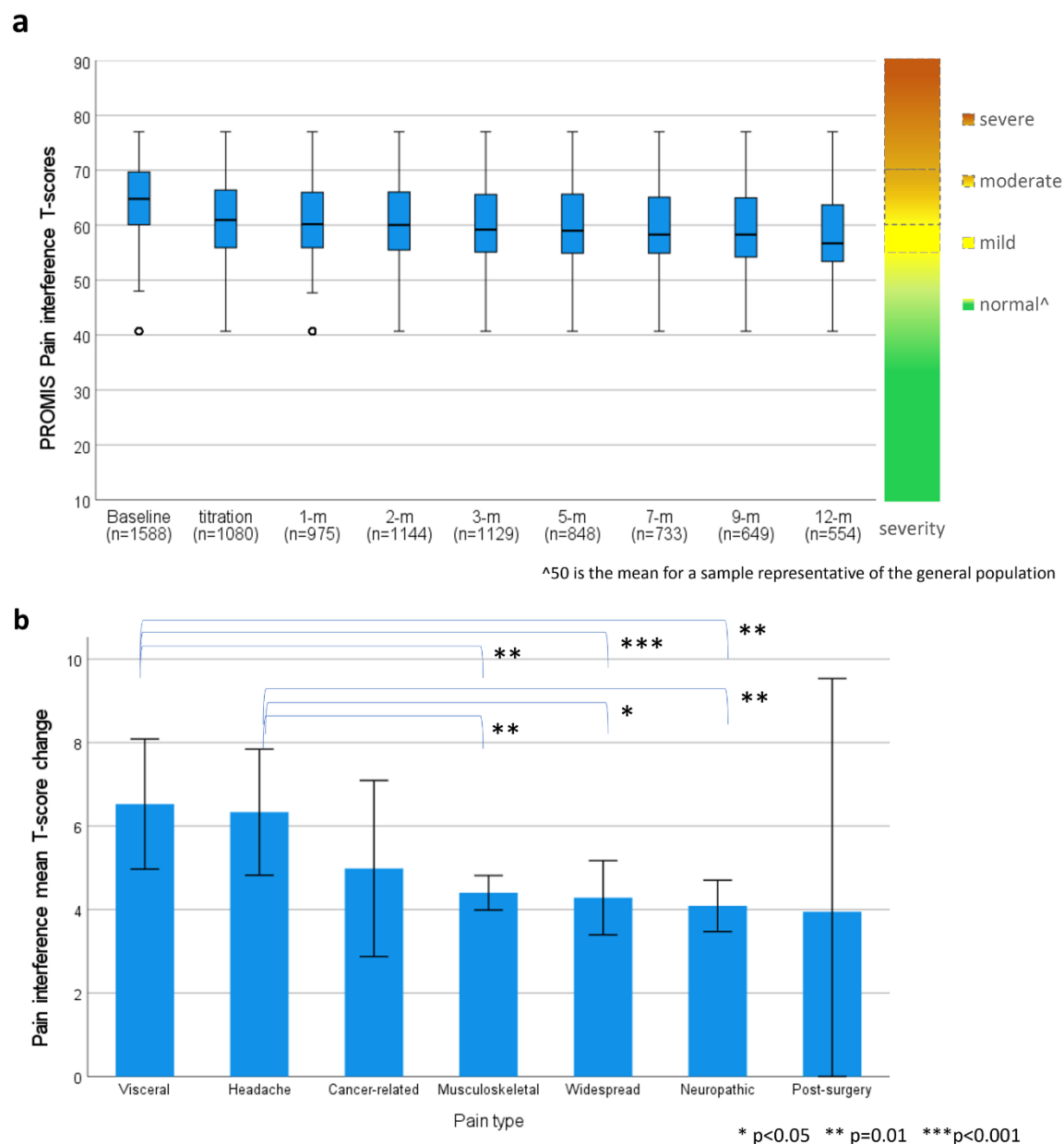


Figure 6. PROMIS T-scores for participants with a pain diagnosis for **a)** Pain interference T-score distribution from baseline to 12-months following titration with severity scale, and **b)** Pain interference mean difference from baseline to average follow-up across different pain conditions.

Table 4. Mean difference in condition-specific PROM scores from baseline to each follow-up for participants receiving MC for those conditions.

Condition	PROM	Follow-up	N	MD	SD	ES	95% CI	p
Chronic Pain (n=1588)	PROMIS pain intensity 3a	Titration	1084	3.80	6.32	0.60	0.54, 0.67	<.001
		1 month	1310	4.49	7.24	0.62	0.56, 0.68	<.001
		2 months	1147	5.02	7.59	0.66	0.60, 0.73	<.001
		3 months	1131	5.39	7.50	0.72	0.65, 0.78	<.001
		5 months	849	5.59	8.31	0.67	0.60, 0.75	<.001
		7 months	733	5.50	8.07	0.68	0.60, 0.76	<.001
		9 months	650	5.94	8.30	0.72	0.63, 0.80	<.001
		12 months	555	6.57	8.47	0.77	0.68, 0.87	<.001
	PROMIS pain interference 8a	Titration	1080	3.66	6.19	0.59	0.59, 0.66	<.001
		1 month	975	4.42	7.07	0.63	0.56, 0.69	<.001
		2 months	1144	5.00	7.58	0.66	0.60, 0.72	<.001
		3 months	1129	5.39	7.46	0.72	0.66, 0.79	<.001
		5 months	848	5.55	7.81	0.71	0.64, 0.79	<.001
		7 months	733	5.61	8.00	0.70	0.62, 0.78	<.001
		9 months	649	5.84	8.09	0.72	0.64, 0.81	<.001
		12 months	554	6.49	8.23	0.79	0.69, 0.88	<.001
Anxiety Disorders (n=775)	DASS-anxiety subscale	Titration	511	4.95	7.00	0.71	0.61, 0.80	<.001
		1 month	608	5.69	7.28	0.78	0.69, 0.87	<.001
		2 months	501	5.84	7.76	0.75	0.65, 0.85	<.001
		3 months	504	5.99	8.03	0.75	0.65, 0.84	<.001
		5 months	349	5.91	7.83	0.76	0.64, 0.87	<.001
		7 months	307	6.24	7.52	0.83	0.70, 0.96	<.001
		9 months	254	6.21	7.80	0.80	0.65, 0.94	<.001
		12 months	216	6.53	8.17	0.80	0.64, 0.95	<.001
Depressive Disorders (n=296)	DASS-depression subscale	Titration	195	6.50	9.60	0.68	0.52, 0.83	<.001
		1 month	239	7.07	9.11	0.78	0.63, 0.92	<.001
		2 months	203	6.51	9.18	0.71	0.55, 0.86	<.001
		3 months	202	7.06	9.88	0.71	0.56, 0.87	<.001
		5 months	143	7.83	11.13	0.70	0.52, 0.89	<.001
		7 months	136	8.54	9.61	0.89	0.69, 1.09	<.001
		9 months	116	8.34	9.07	0.92	0.70, 1.14	<.001
		12 months	103	8.85	9.77	0.91	0.68, 1.13	<.001
Insomnia (n=546)	PROMIS sleep disturbance 8b	Titration	382	7.89	8.34	0.95	0.82, 1.07	<.001
		1 month	455	7.82	8.54	0.92	0.81, 1.03	<.001
		2 months	389	8.99	9.00	1.00	0.88, 1.12	<.001
		3 months	379	9.23	9.35	1.00	0.86, 1.11	<.001
		5 months	287	8.94	8.63	1.04	0.89, 1.18	<.001
		7 months	246	8.93	9.00	0.99	0.84, 1.14	<.001
		9 months	204	9.14	8.58	1.07	0.89, 1.24	<.001
		12 months	183	9.67	9.34	1.04	0.86, 1.21	<.001
Movement Disorders (n=49)	Neuro-QoL Upper function^	Titration	22	1.23	4.91	0.25	0.67, 0.18	0.252
		1 month	41	2.00	6.20	0.32	0.63, 0.01	0.046
		2 months	35	1.95	4.51	0.43	0.78, 0.08	0.015
		3 months	41	1.55	5.50	0.28	0.59, 0.03	0.079
		5 months	30	1.30	6.00	0.22	0.58, 0.15	0.246
		7 months	10	0.02	3.32	0.01	0.63, 0.61	0.985
		9 months	28	1.29	6.78	0.19	0.56, 0.18	0.322
		12 months	24	1.72	6.46	0.27	0.67, 0.14	0.206

ES standardized mean-difference effect size (Cohen's d); CI confidence interval of effect size; MC medicinal cannabis; MD mean difference in direction of improvement; SD standard deviation of mean difference; PROM patient-reported outcome measure **bold** indicates clinically meaningful change ($d \geq 0.5$ with 95%CI above 0.5)

SLEEP

PROMIS Sleep Disturbance T-scores showed a significant linear ($t_{(2546)}=12.18$, $p<0.001$) and quadratic ($t_{(4877)}=16.96$, $p<0.001$) trends of initial large improvement that was maintained over 12-months for the whole cohort(Figure 7a). Adjusted mean baseline scores ($T=61.35$; $SD=8.61$) improved by 5.96 points ($SD=7.81$; 95%CI: 5.64, 6.27) to mean follow-up ($T=55.38$; $SD=9.59$), indicating clinically meaningful improvement greater than the recommended PROMIS MCID of 3 T-scores ($d=0.76$), with participants having diagnosed insomnia improving significantly more than those without ($t_{(4806)}=6.831$, $p<0.001$)(Figure 7b).

Analysis of 546 participants with an insomnia diagnosis revealed statistically significant and clinically meaningful improvements in sleep disturbance of 7.96 ($SD=7.83$; 95%CI: 7.30, 8.62; $p<0.001$) from baseline ($T=63.91$; $SD=7.42$) to mean follow-up ($T=55.95$; $SD=9.64$), well above the recommended MCID ($d=1.02$). Mean difference and effect size in sleep disturbance T-scores from baseline to each follow-up timepoint for participants with insomnia are reported in Table 4.

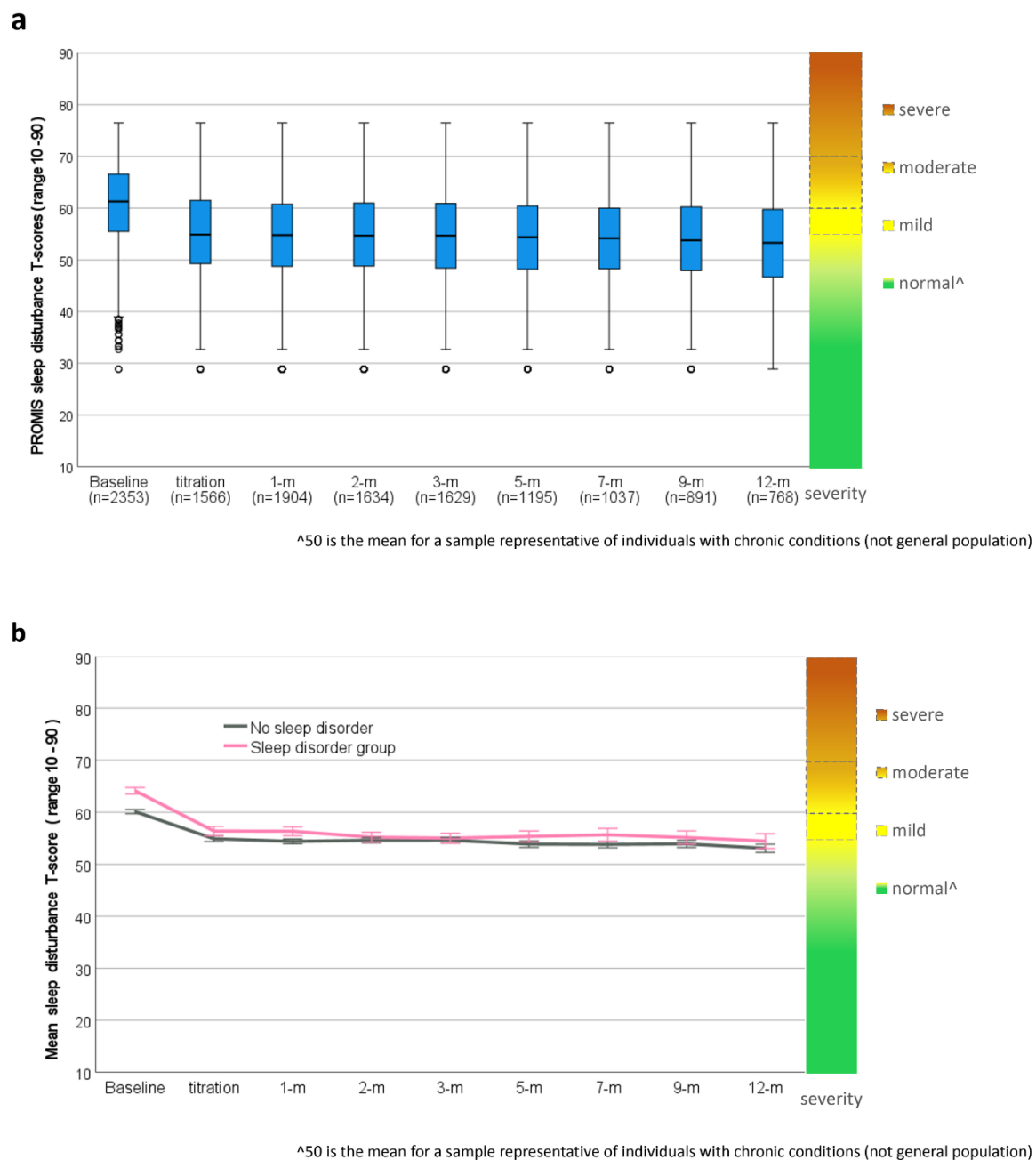
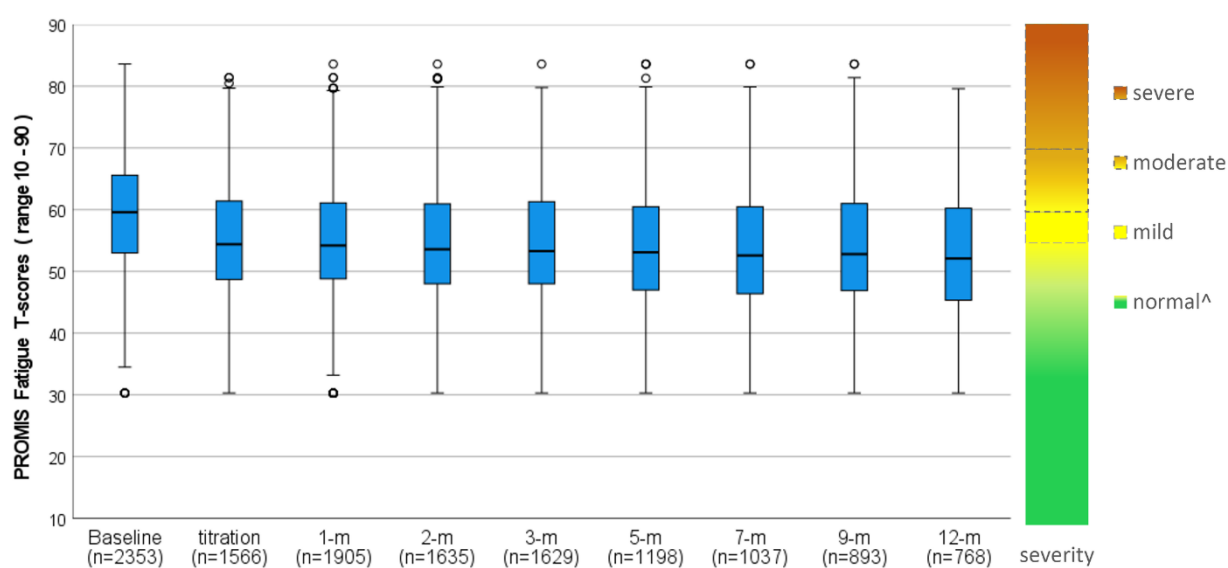


Figure 7. PROMIS sleep disturbance T-scores from baseline to 12-months following titration with severity scale **a)** score distribution box plots for whole cohort, and **b)** Comparisons of mean scores for participants with a sleep disorder vs no sleep disorder.

FATIGUE

PROMIS Fatigue T-scores (n=2353) displayed significant linear ($t_{(9430)} = 9.732$, $p < 0.001$) and quadratic ($t_{(12865)} = 9.437$, $p < 0.001$) trends of improvement over time (Figure 8). After adjustments, fatigue improved on average by 4.70 T-scores (SD=9.25; 95%CI: 4.32, 5.07; $p < 0.001$) from baseline (T=60.85; SD= 9.01) to mean follow-up (T=56.15; SD=9.71), indicating clinically meaningful improvement greater than the recommended PROMIS MCID of 3 T-scores (d= 0.51).



^50 is the mean for a sample representative of the general population

Figure 8. PROMIS fatigue T-score distribution box plots from baseline to 12-months following titration for whole cohort.

DEPRESSION

Mean DASS-Depression Scores displayed significant linear ($t_{(9826)} = 9.584$, $p < 0.001$) and quadratic ($t_{(12739)} = 7.674$, $p < 0.001$) trends of improvement for the whole cohort over time (Figure 9a). Mean difference between baseline (17.68; SD=10.91) and average follow-up (10.73; SD=10.18) was 4.53 (SD=9.85; 95%CI: 4.13, 4.92; $p < 0.001$), not satisfying the recommended 5-point threshold for clinically meaningful improvement ($d = 0.46$). When comparing those with a depressive disorder to those without, improvements from baseline to mean follow-up were greater for the depression group ($t_{(11546)} = 4.852$, $p < 0.001$) (Figure 10a). After categorizing mean depression scores at each follow-up timepoint by DASS-recommended severity ratings (Figure 11a), mean follow-up category distribution compared with baseline demonstrated significant movement from more severe categories towards the normal range ($\chi^2 = 393$; $df = 4$; $p < 0.001$).

Examining 296 participants with a depressive disorder (i.e. mixed anxiety and depression, recurrent depressive disorder, or bipolar disorder), mean improvement in depression scores from baseline (22.55; SD=11.07) to mean follow-up (14.06; SD=11.23) was 7.19 (SD=11.03; 95%CI: 5.93, 8.45; $p < 0.001$), demonstrating clinically meaningful improvement greater than 5 points and movement from severe range to moderate ($d = 0.65$). Mean difference and effect size of DASS-depression scores from baseline to each follow-up timepoint for participants with depressive conditions are reported in Table 4.

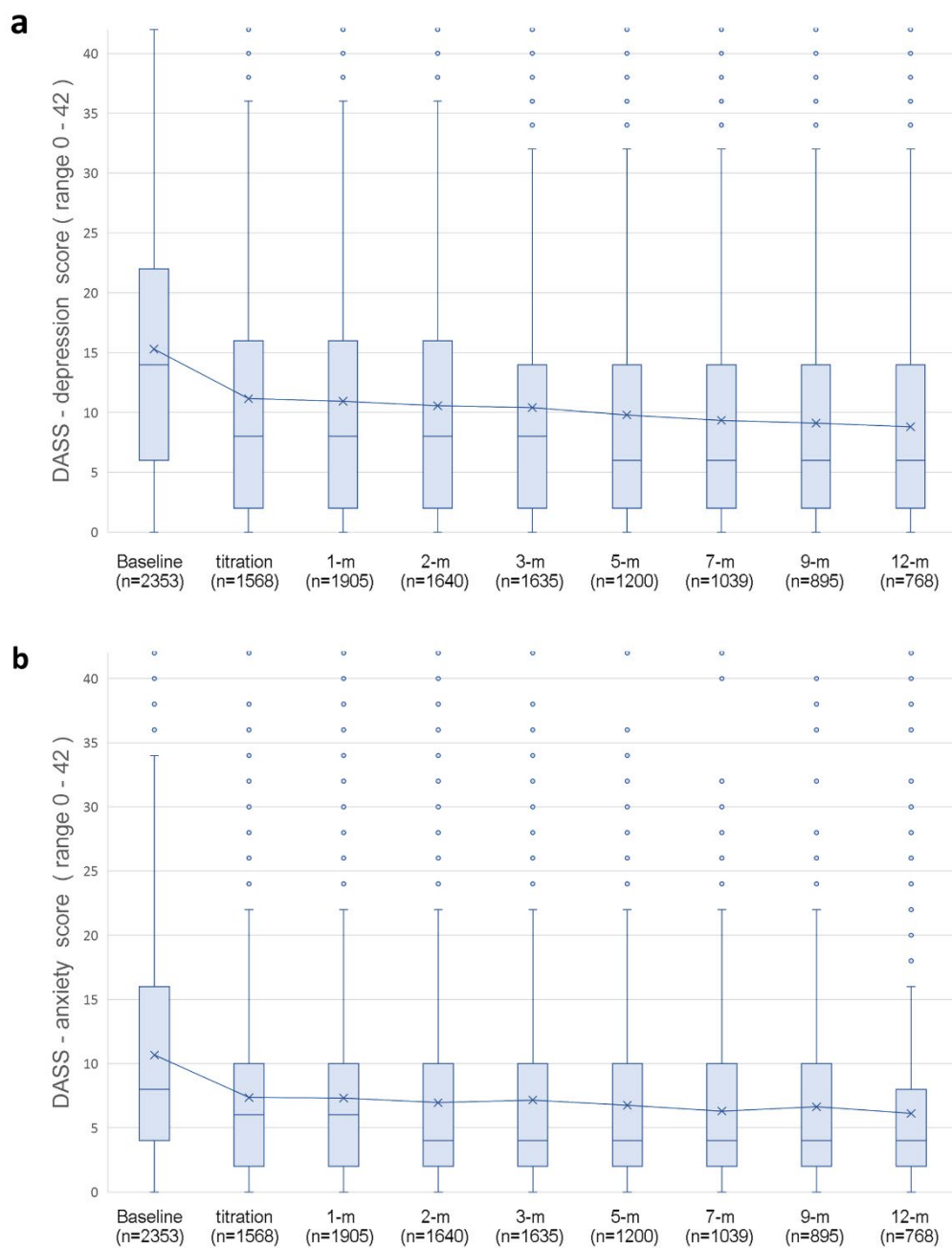


Figure 9. Mean DASS score distribution box plots with median bars and mean line from baseline to 12-months following titration across the whole cohort for **a)** depression subscale and **b)** anxiety subscale. Higher scores indicate greater symptom burden.

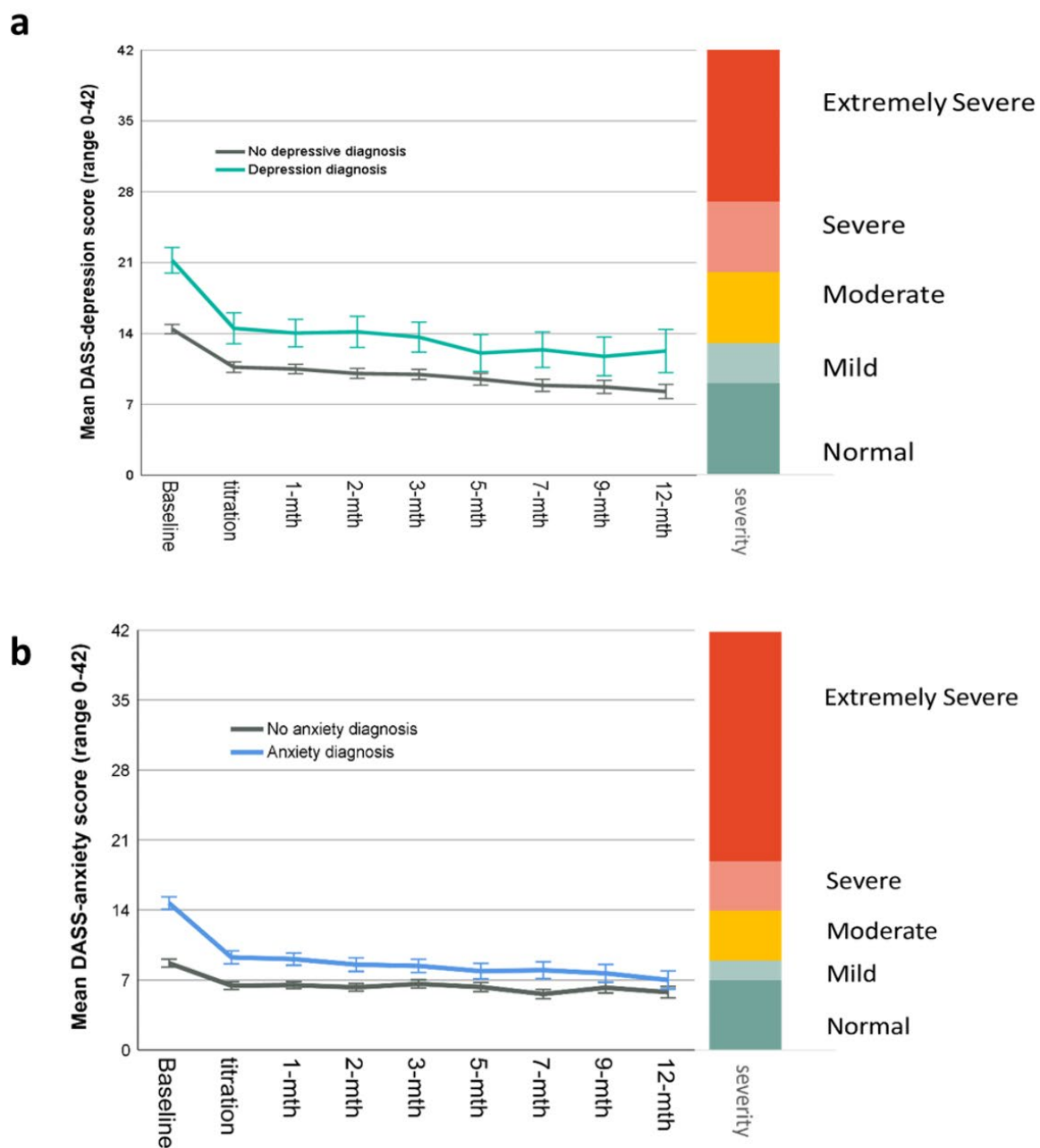


Figure 10. Mean DASS scores at each timepoint plotted with DASS condition-specific severity scales for **a)** depression subscale for participants with a diagnosed depressive condition vs those without depression and **b)** anxiety subscale showing participants with a diagnosed anxiety condition vs those without anxiety. Error bars are 95%CI.

ANXIETY

Mean DASS-Anxiety scores displayed significant linear ($t_{(9641)}=8.108$, $p<0.001$) and quadratic ($t_{(12756)}=8.360$, $p<0.001$) trends of improvement over time (Figure 9b). Mean difference between baseline (11.85; SD=8.80) and mean follow-up (8.58; SD=7.48) was 3.27 (SD=7.49; 95%CI:2.98, 3.57; $p<0.001$), not reaching the recommended 5-point MCID threshold ($d=0.44$). Comparing participants with anxiety conditions to those without anxiety, the improvement in DASS-anxiety scores from baseline to mean follow-up was greater for the anxiety group ($t_{(11383)}=10.81$, $p<0.001$) (Figure 10b). After categorizing anxiety scores at each timepoint by severity (Figure 11b), the average of follow-up distribution was compared with baseline showing significant change from more severe anxiety categories towards the normal range ($\chi^2= 372$; $df=4$; $p<0.001$).

Examining the 775 participants with anxiety health conditions (i.e. generalised anxiety or mixed depression and anxiety), the mean change from 15.44 (SD=8.93) at baseline to mean follow-up 9.79 (SD=8.17) was 5.65 (SD=8.21; 95%CI: 5.07, 6.23; $p<0.001$), indicating a clinically meaningful improvement with change larger than 5 points from severe category to moderate ($d=0.69$). Mean difference and effect size of DASS-anxiety scores from baseline to each follow-up timepoint for participants with anxiety conditions are displayed in Table 4.

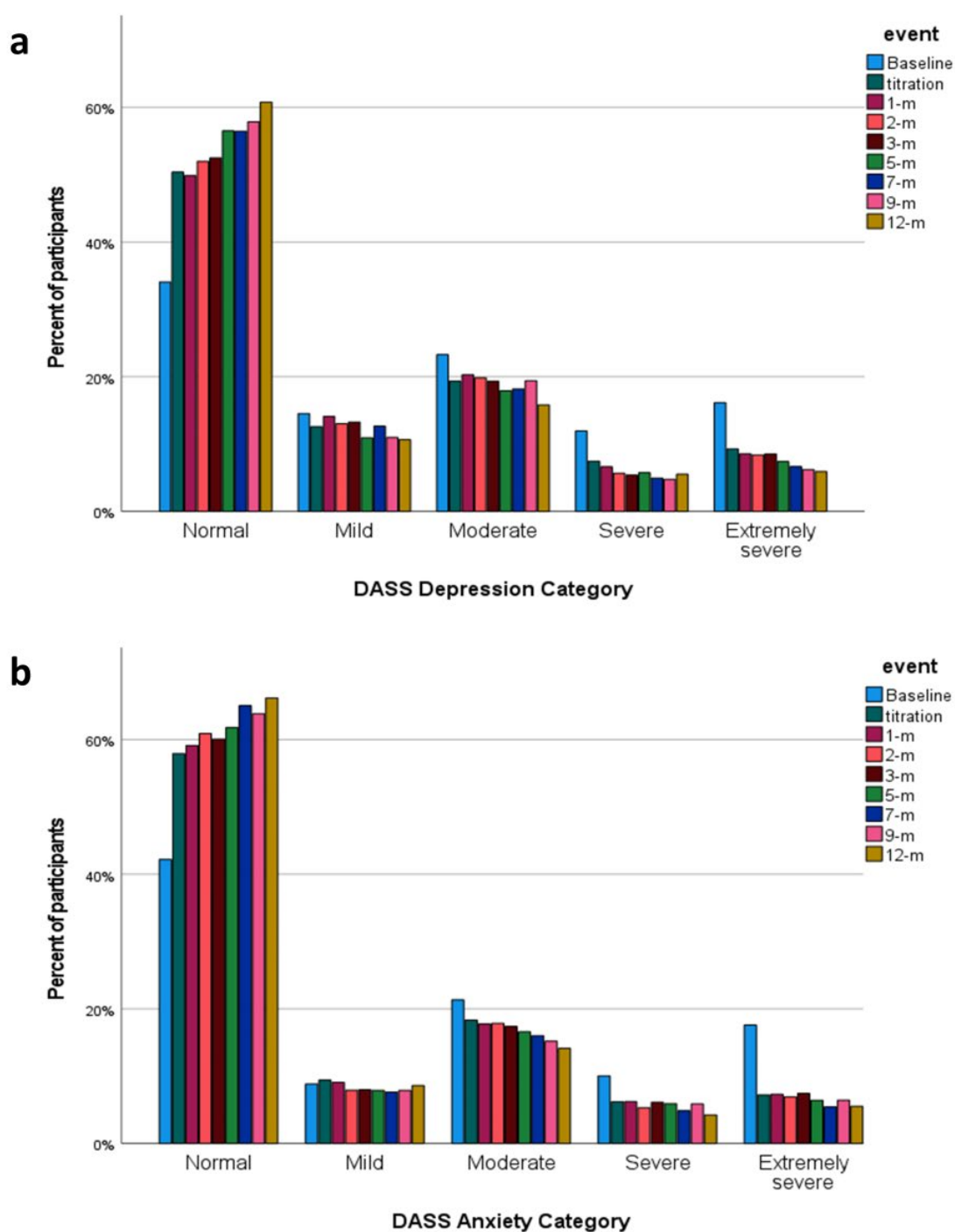


Figure 11. Percent of participants with DASS scores falling within condition-specific severity categories at each timepoint for **a)** depression subscale scores and **b)** anxiety subscale scores.

MOVEMENT DISORDER

After adjusting for age, sex, and pain duration, there were no significant linear or quadratic trends of change over time in Neuro-QoL Adult Upper Extremity Function scores (p-values 0.58 and 0.42 respectively) among participants diagnosed with movement disorder (n=49). Compared to baseline, average follow-up T-scores improved by 1.43 (SD=6.65; 95%CI: -0.44, 3.30; p=0.134), not meeting the recommended MCID of 3 T-scores (d=0.21). Mean difference and effect size of Neuro-QoL Upper Extremity Function T-scores from baseline to each follow-up timepoint for participants with movement disorders are reported in Table 4, showing no clinically meaningful changes at any follow-up timepoint.

MEDICINAL CANNABIS

When exploring the four MC composition categories, differences were observed in the degree of improvement in anxiety, depression, sleep, and fatigue across all participants. In all cases, average daily doses that were THC-dominant had greater odds of larger improvements in these outcomes compared with THC:CBD-balanced (Table 5), although CBD-dominant was also better than THC:CBD-balanced for anxiety. No differences in degree of improvement in pain intensity and interference were observed between MC compositions when looking at chronic pain patients as a group.

On further exploration of different pain types, we found that CBD-dominant daily doses were associated with a greater degree of improvement in pain intensity for: musculoskeletal pain compared with CBD-only (OR:1.57; 95%CI: 1.12, 2.2; p=0.013); headache pain compared to CBD:THC-balanced (OR:4.0; 95%CI: 1.3, 12; p=0.015); and cancer-related pain when compared to CBD:THC-balanced (OR:7.3; 95%CI: 1.0, 49; p=0.047). Pain interference improvements did not differ by cannabinoid combination.

Table 5. Mean change in PROM scores and odds of greater degree of improvement for each MC composition category.

Condition Group PROM	CBD-only M (SD)	CBD-dom. M (SD)	Balanced M (SD)	THC-dom. M (SD)	MC comparisons	OR (95%CI) ^	p [†]
All conditions, n	892	509	637	219			
DASS - Anxiety	3.17 (5.92)	3.33 (6.26)	2.6 (5.91)	3.75 (6.21)	CBD-only – CBD-dom.	0.95 (0.78, 1.16)	0.624
					CBD-only – Balanced	1.19 (0.99, 1.43)	0.069
					CBD-only – THC-dom.	0.84 (0.64, 1.1)	0.198
					CBD-dom. – Balanced	1.24 (1.01, 1.53)	0.045
					CBD-dom. – THC-dom.	0.89 (0.67, 1.18)	0.410
DASS - Depression	4.04 (7.17)	4.47 (7.28)	3.76 (7.40)	5.12 (8.21)	THC-dom. – Balanced	1.41 (1.06, 1.85)	0.015
					CBD-only – CBD-dom.	0.92 (0.76, 1.12)	0.417
					CBD-only – Balanced	1.10 (0.92, 1.33)	0.304
					CBD-only – THC-dom.	0.79 (0.60, 1.03)	0.081
					CBD-dom. – Balanced	1.19 (0.96, 1.47)	0.103
Sleep disturbance (PROMIS)	4.67 (7.11)	6.67 (8.13)	6.27 (7.90)	7.67 (7.81)	CBD-dom. – THC-dom.	0.86 (0.64, 1.14)	0.289
					THC-dom. – Balanced	1.39 (1.04, 1.82)	0.023
					CBD-dom. – CBD-only	1.61 (1.33, 1.96)	<0.001
					Balanced – CBD-only	1.47 (1.22, 1.79)	<0.001
					THC-dom. – CBD-only	2.13 (1.61, 2.78)	<0.001
Fatigue (PROMIS)	4.41 (6.61)	4.83 (6.67)	4.10 (6.48)	5.71 (6.96)	CBD-dom. – Balanced	1.09 (0.89, 1.35)	0.406
					CBD-dom. – THC-dom.	0.80 (0.60, 1.06)	0.122
					THC-dom. – Balanced	1.39 (1.04, 1.82)	0.024
					CBD-only – CBD-dom.	0.89 (0.73, 1.09)	0.257
					CBD-only – Balanced	1.09 (0.91, 1.31)	0.359
Chronic pain, n	538	362	450	167	THC-dom. – CBD-only	1.43 (1.09, 1.85)	0.010
					CBD-dom. – Balanced	1.22 (0.99, 1.51)	0.062
					CBD-dom. – THC-dom.	0.79 (0.59, 1.05)	0.107
					THC-dom. – Balanced	1.56 (1.18, 2.04)	0.002
					CBD-only – CBD-dom.	0.85 (0.67, 1.09)	0.194
Pain intensity (PROMIS)	4.48 (6.18)	5.05 (6.81)	4.35 (6.38)	4.78 (6.18)	CBD-only – Balanced	1.04 (0.83, 1.30)	0.755
					CBD-only – THC-dom.	0.92 (0.67, 1.25)	0.577
					CBD-dom. – Balanced	1.21 (0.94, 1.56)	0.136
					CBD-dom. – THC-dom.	1.08 (0.77, 1.51)	0.626
					Balanced – THC-dom.	0.88 (0.64, 1.22)	0.417
Pain interference (PROMIS)	4.59 (6.33)	5.07 (6.24)	4.23 (6.35)	4.19 (4.83)	CBD-only – CBD-dom.	0.87 (0.68, 1.11)	0.258
					CBD-only – Balanced	1.11 (0.88, 1.39)	0.377
					CBD-only – THC-dom.	1.13 (0.82, 1.55)	0.457
					CBD-dom. – Balanced	1.28 (0.99, 1.64)	0.059
					CBD-dom. – THC-dom.	1.32 (0.94, 1.83)	0.078
					Balanced – THC-dom.	1.01 (0.73, 1.40)	0.944

CBD-only contains >98% cannabidiol; CBD-dom. contains >60% to 98% cannabidiol; Balanced contains 40% to 60% of both cannabidiol and delta5-tetrahydrocannabinol; THC-dom. contains >60% to 98% delta5-tetrahydrocannabinol.

^Odds ratio effect size of mean difference in change scores.

† p values of independent samples T-tests.

Bold indicates significantly greater odds of improvement after Hochberg adjustment for multiple comparisons.

MISSED ASSESSMENTS

Analyses using linear mixed models included all available data from PROMs completed at each timepoint. No items within completed PROMs were missed. Figure 12 shows EQ-5D and QLQ-C30 results stratified by those who dropped out or failed to complete follow-up after each timepoint. Trajectories over time suggest that after titration, participants dropping out of the study at each timepoint had experienced a decline in HRQL since their previous assessments (with the only exception observed at 2-months). Participants who dropped out of the study before 3-months had better HRQL at baseline, and smaller improvements from baseline, than those who remained on the study for 3-months or more. There were no significant differences in HRQL scores observed between participants included in the study analyses and those who only completed baseline.

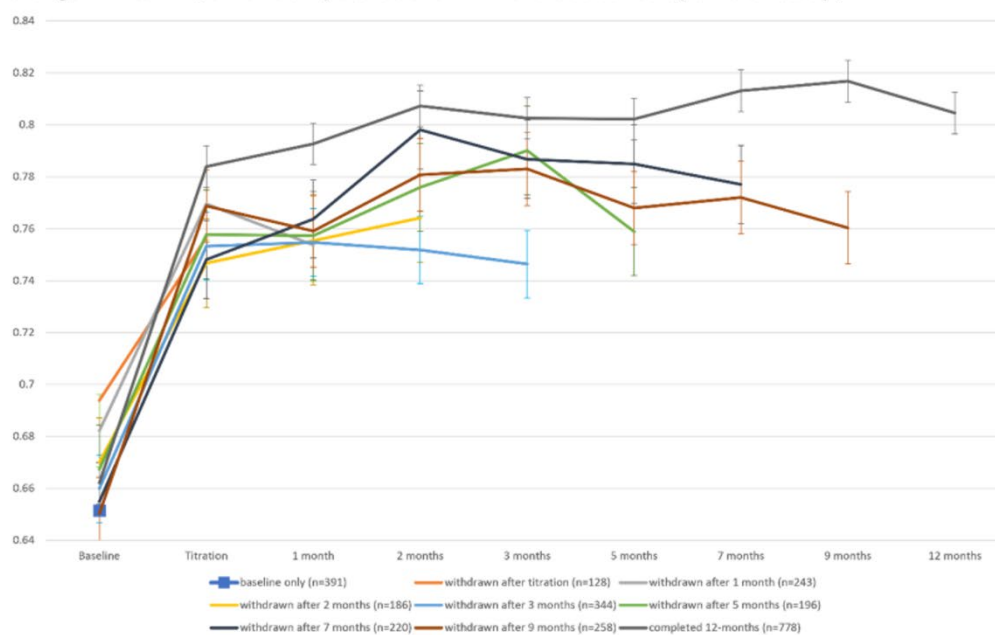
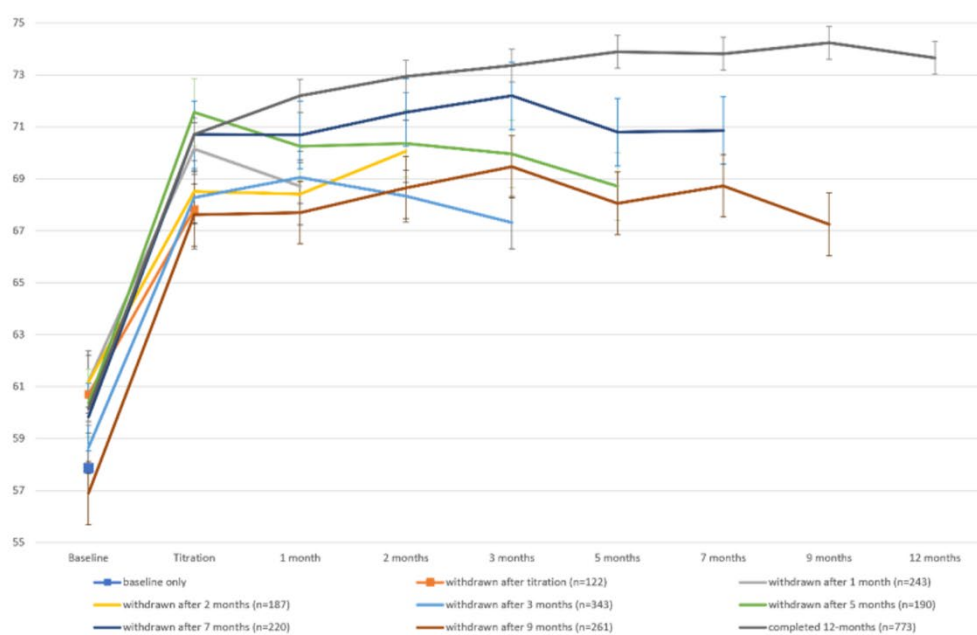
a Change in Mean EQ-5D-5L Utility Scores over 12 months stratified by time on study (with standard error bars)**b** Change in mean QLQ-C30 Summary Scores over 12-months stratified by time on study (with standard error bars)

Figure 12. Change in HRQL scores over 12-months stratified by time on study for **a)** mean EQ-5D-5L Utility Index scores and **b)** mean QLQ-C30 Summary scores.

DISCUSSION

PRINCIPAL FINDINGS

We found that short term improvements in overall HRQL reported at 3-months²⁰ were maintained over a 12-month period in patients prescribed MC in Australia. Statistically significant and clinically meaningful improvements were observed in HRQL, fatigue, pain, and sleep for people with chronic health conditions. Similar improvements were found in pain outcomes for participants with chronic pain; sleep disturbance for participants with insomnia; depression scores for patients with depression; and anxiety scores in patients with anxiety. Participants with movement disorders had improved HRQL but no significant improvements in upper extremity function scores.

COMPARISON WITH OTHER MEDICINAL CANNABIS STUDIES ASSESSING PROs

HRQL improvements observed in our study are consistent with results published in 2023 from a UK registry of 312 patients with chronic health conditions prescribed MC reporting EQ-5D-5L index score improvements over 6-months (n=63), and a 2022 Canadian registry following 2073 participants finding EQ-5D-5L health status improvements maintained up to 12-months (n=600).⁴⁴ HRQL improvements over 12-months were also observed in another cohort study of patients with chronic pain.⁴⁵ Our findings further revealed that HRQL improved in patients treated exclusively for non-pain conditions, such as insomnia, generalized anxiety, mixed depression and anxiety, and PTSD.

Similarly, Aviram et al. observed clinically meaningful improvements (greater than 30% change) in sleep disturbance, anxiety, depression, and affective pain from baseline to 12-

months in an Israeli multicentre, prospective study of 551 patients with chronic pain receiving MC.⁴⁶

Clinically significant improvements in Brief Pain Inventory pain severity and pain interference scores were observed at 1-, 3-, 6-, and 12-months follow-up compared to baseline in an observational study of chronic pain patients,⁴⁵ which were similar to our findings using PROMIS pain intensity and interference PROMs.

An observational study by Safakish et al. found chronic pain patients (n=248) experienced significant improvements in fatigue after 3-months of MC therapy,⁴⁵ and similar results have been reported for cancer patients (n=743).⁴⁷

A randomised crossover double-blind placebo-controlled trial with 29 adults with insomnia found that medicinal cannabis oil was effective in reducing insomnia severity index scores over a 2-week period,⁴⁸ and an observational study in 2021 reported Pittsburgh Sleep Quality Index score improvements after 3-months in 36 chronic pain patients prescribed MC.⁴⁹ In most previous studies examining sleep outcomes in patients treated with MC, validated PROMs were seldom used and many had small sample sizes or short treatment and follow-up periods.⁵⁰ Our results extend previous findings by indicating sleep improvements observed in insomnia patients treated with MC are maintained long-term. Similarly, results from an Australian registry of MC patients published in 2023 also showed significant improvements across the cohort in Insomnia Severity Index scores (n=1902), Brief Pain Inventory severity and interference scores (n=1651), and DASS anxiety and depression scores (n=1874), after 12-months of MC therapy, which were maintained up to 2-years.⁵¹

Sagar et al. published preliminary results of their longitudinal study in 2021, finding that participants with various health conditions treated with MC showed significant

improvements from baseline to 6-months (n=44) and 12-months (n=32) in Pittsburgh Sleep Quality Index scores, Beck Depression Inventory scores, and in State-Trait Anxiety Inventory - trait anxiety scores.⁵² Similar to our findings, an observational study by Rapin et al. reported that patients with baseline moderate to severe depression (n=115) and anxiety (n=138) showed clinically meaningful improvements in depression and anxiety scores respectively after 3-months that were maintained after 6-months of MC therapy⁵³.

When looking at opioids for pain management, most of our participants had reduced or stopped their opioid intake by the end of the study. Similar findings have also been previously reported by Pritchett et al.,⁵⁴ where 79% of participants reduced or stopped opioids after starting MC, and in a Canadian study that found the number of participants using opioids more than halved 6-months post MC therapy.⁵⁵

High quality evidence from randomized clinical trials (RCTs) suggested CBD reduces seizure frequency in epilepsy patients, however, in a real world setting there are concerns that unwanted side-effects may result from interactions with other anti-seizure medications.⁵⁶ This may explain the low numbers of participants with epilepsy recruited to this study. The small number of participants being treated for epilepsy exclusively (n=10) may have led to the inconsistent findings observed in HRQL, with significant improvement in QLQ-C30 scores but no change in EQ-5D. Cannabis use in general has previously been associated with poorer HRQL and worse outcomes in adult epilepsy patients,⁵⁷ however this may not apply to MC with controlled dosing monitored by clinicians and requires further research with larger sample sizes

We observed differences in the degree of improvement in fatigue, insomnia, anxiety, and depression depending on the ratio of CBD and THC in average daily MC doses. For these

outcomes, average daily doses of THC-dominant MC was associated with greater odds of improvement than CBD:THC-balanced MC. An Australian cross-sectional study by Trevitt et al. had similar findings regarding participants' self-rated global impression of change in anxiety when prescribed MC, however they also found improvements in pain for those prescribed THC-dominant products, and no differences regarding sleep.⁵⁸ In contrast, we observed that any daily MC doses containing THC were associated with a greater degree of improvement in sleep compared with CBD-only, and that overall, patients with chronic pain conditions did not report improvements in pain interference differently depending on CBD:THC composition. However, further exploration of the different pain types did reveal differences in musculoskeletal, headache, and cancer-related pain intensity, but this favored CBD-dominant doses. Participants on our study were taking lower daily doses averaging up to 50mg of CBD, compared with doses reported in RCTs that typically only find minimal improvements in anxiety, insomnia, and pain relief at much higher doses of CBD (300mg).⁵⁹ However, RCTs often test the immediate (within hours), or short-term (in weeks), effects of CBD on outcomes and do not account for ongoing therapy over months or years. Our findings suggest that people with chronic pain conditions experience better outcomes over time on lower doses of CBD when combined with smaller amounts of THC at a ratio of 10:1. However, we calculated average daily dose overall, whereas daily dosing regimens in practice may limit administering THC to evenings (to avoid possible intoxication during waking hours), rather than maintaining a 10:1 ratio throughout the day. Our findings suggest there are clinically important differences in outcomes for some conditions depending on the ratio of THC and CBD, however as an observational study, we cannot infer efficacy of different dosage regimens conclusively. As MC becomes increasingly used and accepted globally, further research with multicentre RCTs is needed in this area to provide

clinicians with evidence-based guidance on condition-specific MC prescribing and the efficacy of various dosing regimens for their patients.

STRENGTHS AND LIMITATIONS

Our study was large enough to assess patients across a wide range of chronic conditions and socio-demographics in a real-world setting. We recruited participants from more than 100 sites across Australia, covering most states and territories. We used validated, condition-relevant PROMs at clinically meaningful time-points allowing comparisons within groups over time, and between studies and patient groups. We reported the clinical meaningfulness of findings using predefined MCIDs, and determined MCIDs provided by PROM developers aligned with the Norman et al. MCID recommendation of half a standard deviation in patients with chronic conditions.⁴² By using a homogenous selection of MC oils (LGP products) our results were not confounded by the effects of different strains of cannabis plant or by different routes of administration. Unlike the large doses of CBD or THC typically administered in RCTs,⁶⁰ participants in our study were patients who titrated to doses used in clinical practice. The use of de-identified, automated, electronic data collection reduced the risk of response biases introduced when collecting identifiable PROM data in person.

However, as a single arm observational study, it is not possible to confidently attribute changes over time to the intervention. Within-group studies of cannabis and HRQL without control groups tend to report larger effect sizes than RCTs.⁶¹ Our observed improvements may be due in part to a placebo effect,⁶² mere-measurement effect, where PROs improve in response to completing PROMs,⁶³ or regression towards the mean, where scores fluctuate

around a true mean and our observed scores maintained at subsequent timepoints are driven by those remaining on the study.⁶⁴

Although there were no significant differences in HRQL between participants who dropped out at baseline and those who remained on the study, the loss of participants at follow-up may have led to attrition bias. Participants remaining on the study were likely to be benefitting from MC, and those dropping out may have had reduced benefit considering the small decline in HRQL observed immediately before drop-out. Participants were asked to provide reasons for study withdrawal, however only 322 volunteered this information (132 due to lack of therapeutic benefit (41%)) and many did not respond. Despite standardizing the cost of MC for participants in the study, results may have been biased due to the financial burden of purchasing MC products not Government-subsidised in Australia. It is possible participants in the study were wealthier than typical patients with chronic conditions. Although 64 participants advised that they withdrew due to unwanted side-effects (20% of those who provided reasons), adverse events were not collected in this observational study. However, there were no reports of significant adverse effects to the product manufacturer. Lastly, participants were only prescribed LGP MC oil products which limits generalizability to other MC products and forms of administration (e.g. vapourised, tincture, patches). However, we were able to determine average daily doses of CBD and THC, which can be applied to other oil products.

CLINICAL IMPLICATIONS

In clinical practice, prescribing MC to patients with chronic health conditions may improve patients' pain, fatigue, insomnia, anxiety, and depression and overall HRQL. Current clinical guidelines support prescribing MC to patients who are interested in trialling it for conditions

not responding to conventional treatments,⁶⁵ and our findings suggest any improvements would be apparent quickly and maintained long-term. Evidence on optimal CBD:THC ratios for different health conditions is emerging and will improve prescribing practices.

CONCLUSION

Long-term findings over 12-months indicate patients prescribed MC in practice have improved HRQL and reduced fatigue. Patients with anxiety, depression, insomnia, or chronic pain diagnoses also improved over 12-months in condition-specific symptoms. We did not find conclusive evidence of motor function improvement in patients with movement disorders. Patients exclusively treated for generalized anxiety, chronic pain, insomnia, and PTSD, all showed improvements in HRQL. The findings from this study contribute to the emerging evidence-base to inform decision making both in clinical practice and at policy level.

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COMPETING INTERESTS

The University of Sydney received funding from Little Green Pharma Pty Ltd. to support MT and CR to conduct the submitted work; LW is a paid employee of Little Green Pharma Pty Ltd.; no other relationships or activities that could appear to have influenced the submitted work. All authors have completed the ICMJE uniform disclosure form. This does not alter our adherence to PLOS ONE policies on sharing data and materials.

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PART C

EXPLORING PATIENT EXPERIENCE ACCESSING AND USING MEDICINAL CANNABIS

CHAPTER 6

PART C. EXPLORING PATIENT EXPERIENCE

CHAPTER 6: QUALITATIVE INTERVIEWS

CHAPTER OVERVIEW

Australia legalised medicinal MC nearly a decade ago, however little is known about the long-term lived experience of patients legally prescribed MC over this time. While PROMs provide a standardised method of measuring change in HRQL, essential for the previous chapters, the information collected is restricted to the PROM's domains and the given research context. When new treatments and processes are introduced, such as MC prescribing, it is important to explore patient experiences to identify additional benefits, concerns, or barriers specific to the new treatment and healthcare model. Optimal patient experience is associated with improved patient outcomes, patient safety, and clinical effectiveness.¹

Patient interviews can also potentially identify additional phenomena relevant to HRQL not previously captured in the domains of HRQL PROMs used. To explore this, participants from the longitudinal study reported in Chapters 4 and 5 were invited for interviews. To gain a deeper understanding of patients' lived experience, an interpretive qualitative approach was used to conduct and thematically analyse interviews. This patient-centred approach enabled participants' subjective reality to guide the interpretation of data. The qualitative study presented in the following paper provides insight into the attitudes and experiences of patients with chronic conditions accessing MC in Australia and what the outcomes of therapy mean to them over the long-term.

Supplementing the publication, Appendix 2 contains the study invitations and participant information, Appendix 3 contains the ethics approval, and the supplementary material referenced in the publication can be found in Appendix 6.

PUBLICATION DETAILS

Tait M-A, White K, Rutherford C, Costa DSJ, Campbell R, Experiences of patients prescribed medicinal cannabis in Australia long-term: A qualitative interview study. *Australian Journal of Primary Health*, 2025; UNDER REVIEW, Submitted 28 October 2025.

AUTHORSHIP ATTRIBUTION STATEMENT

The co-authors confirm the contribution of Margaret-Ann Tait as the primary author, in compliance with the international Committee of Medical Journal Editors (ICMJE) authorship criteria, for the following manuscript:

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Margaret-Ann Tait made the following contributions.

- Conception and design of the research
- Created study documents
- Submitted and obtained ethics approvals
- Conducted interviews and collected the data
- Analysis and interpretation of the data
- Created the conceptual model
- Drafted and revising the paper
- Responded to reviewer comments
- Coordinated the submission of the paper for publication

MT made substantial contributions to the study design, with critical feedback provided by RC, CR, KW and DC. MT and RC made substantial contribution to data analysis. All authors contributed towards interpretation of data and reviewed and provided critical feedback on the final manuscript.

As the primary supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

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ABSTRACT

BACKGROUND

There is limited but evidence supporting the use of medicinal cannabis (MC) to manage pain, anxiety, spasticity, insomnia, and depression. Although Australian legislation changed in 2016 to provide access to unapproved MC products, clinical guidance on prescribing MC is limited because it is still mostly an unapproved therapy accessed under strict conditions. Since this change in legislation, little is known about the patients' lived experience of long-term prescribed use of unapproved MC products in Australia. We aimed to explore, and obtain an in depth understanding of, the experiences of patients prescribed MC.

METHODS

Using an interpretive qualitative approach, participants were recruited from the QUEST Initiative, a nationwide longitudinal study of patients with any chronic health condition prescribed orally administered MC oil. Semi-structured interviews explored experiences of accessing and using MC. Thematic analysis revealed themes and subthemes from the data.

RESULTS

Fifteen participants aged 33 to 78 years (9 female) prescribed MC oil for chronic pain, insomnia, muscle spasticity, anxiety or depression were interviewed. Analysis identified four overarching themes: 'This isn't living'; 'I was looking for a solution'; 'It wasn't to get high'; and 'Everything's much better', and eight sub-themes covering concerns, barriers, patient autonomy, and benefits. Participants commonly used MC to reduce or replace conventional medications taken for their conditions and viewed MC as a low risk "natural" alternative. Barriers to accessing MC included difficulties obtaining prescriptions and the cost of MC products. Most participants demonstrated patient autonomy in seeking prescribing doctors,

engaging in shared decision-making, and self-managing their MC regimens. Symptom improvements flowed on to benefit relationships, productivity, and mental health. Although initially concerned about side-effects, participants self-managed these effectively, with benefits outweighing side-effects. Participants described roadside drug testing as an ongoing concern.

CONCLUSIONS

Patients prescribed orally administered MC oil in Australia reported many benefits of MC but faced ongoing barriers to MC access. Improved awareness and education, simplified prescribing processes, and less prohibitive driving laws could lead to wider acceptance of MC as a therapeutic option and improved patient-centred care.

INTRODUCTION

Almost half of all Australians suffer from chronic health conditions² that last a year or more and require ongoing medical attention.³ This includes 3.3 million with anxiety disorders, 1.5 million with sleep disorders,⁴ and 3.6 million people living with chronic pain, defined as pain that has persisted or recurred for longer than three months.⁵ The prevalence of these chronic conditions is similar across Western countries.^{3,6} When conventional medications fail, these patients often turn to alternative and unregulated therapies.⁷

Since discovering the endocannabinoid system in the 1990s, and its role in human physiological processes,⁸ research and evidence supporting the medical use of cannabis has grown.⁹ Internationally, the United Nations' decision to criminalise cannabis in 1961 has been questioned,¹⁰ and some countries have started revising their laws to allow medicinal cannabis (MC). Responding to user activism, calls from the community, and acknowledging the potential benefits of MC and increase in MC clinical trials, Australian legislation also changed in 2016 to facilitate further clinical research and allow doctors to prescribe MC to patients with health conditions not responding to conventional therapies.¹¹ However, identified barriers for accessing MC include a lack of clinician education on the endocannabinoid system and pharmacology of cannabinoids, clinicians' concerns regarding limited evidence for MC effectiveness and efficacy data as well as possible harms, complex prescribing pathways, state-specific regulatory hurdles, high cost of MC products, prohibitive driving laws, and competition with the illicit drug market.^{12,13} Additionally, the Australian Therapeutic Goods Administration (TGA) classifies MC mostly as an unregulated and unapproved medicine. Despite these identified barriers, since legislation changed to allow special access pathways, the TGA has recorded over a million new MC prescriptions,¹⁴

for more than 200 health conditions, predominantly pain, anxiety, depression, and sleep disorders.¹⁵

Evidence from randomised controlled trials (RCTs) and observational studies indicate MC may reduce chronic pain,^{16,17} and spasticity in Multiple Sclerosis,¹⁸ Findings from observational studies further suggest MC may alleviate depression,¹⁹ anxiety,²⁰ improve sleep,²¹ and reduce opioid prescription numbers.²² The TGA conducted a systematic review of RCTs in 2017 and found overall moderate evidence supporting the use of MC for reducing chronic pain,²³ but insufficient evidence for reducing muscle spasticity.²⁴ Similarly, a recent systematic review of RCTs evaluating MC for mental health issues found no high-quality evidence that MC effectively treats anxiety or depression.²⁵ Large observational studies in Australia have found patients prescribed MC reported improvements in health-related quality of life, pain, mood, and sleep, and reduced their use of opioids and other prescribed medications.²⁶⁻²⁸ A systematic review of MC studies globally over the past decade revealed similar patient-reported improvements across prospective observational studies,²⁹ with long-term follow-up studies showing quality of life improvements beyond 12-months.^{27,28,30,31} While collecting patient-reported outcome data using standardised quantitative measures is important for evaluating healthcare and treatment efficacy,³² qualitative data has the potential to provide richer insight into patients' lived experiences with healthcare and treatment impacts. A systematic review of qualitative research internationally found that patients with pain use MC to reduce other prescription medications or to manage medication side-effects, and were concerned by clinicians' lack of experience in prescribing MC, as well as MC side-effects, stigma, addiction, and legality.³³ However, previous studies largely focused on specific symptoms (e.g. pain) or health

conditions (e.g. cancer), did not distinguish between legal or illicit MC use, and provided only limited information about longer-term effects. After nearly 10 years of prescribing MC in Australia, this study aimed to explore whether the same barriers persist and what patients' experiences are after taking prescribed MC for more than 12 months. Specifically, we aimed to explore the subjective experiences of patients with any chronic condition legally accessing prescribed MC in Australia over the long-term (beyond 12-months), and their perceptions of how MC impacted their daily life.

METHODS

RESEARCH DESIGN

A constructivist approach using hermeneutic interpretation³⁴ focused on the lived experience of people with chronic health conditions and what being prescribed MC meant to them. Interviews began with participants describing their health condition to contextualize and recall how and why they came to be prescribed MC. Participants were then asked to describe their experiences accessing and using MC and the impact of MC therapy on daily life. This project was approved by The University of Sydney's Human Research Ethics Committee (#2020/HE000589).

RECRUITMENT OF STUDY PARTICIPANTS

Participants were purposively sampled from a broader study (QUEST)³⁵ to ensure broad representation of demographic and clinical characteristics including diagnosed health conditions, age, sex, location, education, and employment status. QUEST was a longitudinal survey study that evaluated patient-reported outcomes over 12-months in 2353 patients prescribed MC oil from clinics across Australia between December 2020 and March 2023.²⁶

After completing the QUEST study, participants who met eligibility criteria and had consented to being contacted for future research, were sent email invitations for follow-up interviews. All participants had been prescribed orally administrated pharmaceutical MC oil containing different ratios of two main phytocannabinoids: cannabidiol (CBD), a non-intoxicating compound, and Δ^9 -tetrahydrocannabinol (THC), a psychoactive compound, in combination with other naturally occurring phytocannabinoids and terpenoids in the cannabis plant. To aid recall reliability, only participants who had renewed their MC prescriptions within the previous six months were eligible. Informed consent to participate and be audio recorded was obtained before interviews.

Data Collection

Interviews were conducted in English by the lead author (MT) via Zoom videoconference or telephone between 11 August 2023 and 8 August 2024. MT, a female Clinical Research Manager and PhD student, trained in qualitative research methodology, was also the named Project Manager for the QUEST study from which participants were recruited. Apart from collecting email addresses to facilitate communication, the QUEST study did not collect identifying information, and MT had no prior relationship with interviewees. Only the interviewer and participant were present during interviews. Semi-structured interviews followed a topic guide (Supplementary File 1), developed iteratively with subsequent interviews exploring issues raised in previous interviews. Participants were asked open-ended questions about the impact on daily life of their chronic health conditions and previous treatments; motivations for accessing MC, initial expectations or concerns about using MC as a therapy; experiences with prescribing doctors; their evaluation of MC oil as a therapy; and what aspects of daily life have changed since using MC (if at all). All interviews were audio

recorded with captions via institution supported Zoom platform and transcribed verbatim by MT. Transcripts were not sent back to participants for feedback. Data was stored electronically on a secure, password-protected server at The University of Sydney.

ANALYSIS

After interviewing a representative sample, recruitment continued until no new themes were found. Using thematic analysis,³⁶ two transcripts selected at random were independently coded by two researchers (MT and RC) to identify preliminary themes. Both researchers continued to independently code an additional three transcripts, with regular meetings, to iteratively establish a coding framework until consensus was reached. All interview transcripts were then uploaded to NVivo 20 Software (QSR International) and manually coded by one researcher MT. A third researcher (KW) reviewed codes periodically for emerging themes and subthemes. All transcripts were annotated with regard to whether the participant had been prescribed a CBD only, CBD dominant, THC/CBD balanced, or THC dominant combination to enable exploration of themes and subthemes across these combinations. Reporting followed the consolidated criteria for reporting qualitative research (COREQ).³⁷

RESULTS

PARTICIPANT CHARACTERISTICS

Invitations were emailed to 137 QUEST study participants. Fifteen participants aged between 33 and 78 years participated in semi-structured interviews via Zoom videoconferencing (n=8) and telephone (n=7), with no participant withdrawing. On average, interviews lasted 26 minutes (range 16-56 minutes). Participants had been taking prescribed

MC oil for between 1 and 4-years and at the time of interview 13 participants (87%) were still taking prescribed MC daily or as needed. One participant stopped due to an unrelated health condition and the other temporarily stopped due to relocating interstate. In the 12-months prior to receiving their first MC prescription, four participants (27%) had accessed cannabis products without prescriptions (for medical and/or recreational use). Participant characteristics are presented in Table 1.

Table 1 Characteristics of 15 study participants.

Characteristics		N
Age in years	30-40	2
	41-50	2
	51-60	4
	61-70	4
	71-80	3
Gender	Female	9
	Male	6
Location	New South Wales	8
	Australian Capital Territory	1
	Queensland	1
	Western Australia	3
	Victoria	2
Marital status	Single (or divorced)	7
	Married (or de facto)	8
Education completed	High school	5
	Trade Certificate/ Diploma	4
	University degree or higher	6
Employment status	Studying	1
	Working parttime	1
	Working fulltime	4
	Home duties	1
	Retired	5
	Unemployed due to illness	3
Primary health condition	Generalized Anxiety disorder	3
	Mixed depression and anxiety	1
	Insomnia	1
	MS-related pain and spasticity	1
	Chronic Pain	
	- musculoskeletal	3
	- widespread	2
	- neuropathic	3
Secondary health condition	- visceral	1
	Insomnia	9
	Musculoskeletal pain	1
MC prescribed	None	5
	CBD only [CBD]	3
	CBD dominant [THC < CBD]	2
	THC/CBD balanced [THC=CBD]	8
	THC dominant [THC > CBD]	2

CBD cannabidiol; CBD only [less than 1% THC]; CBD dominant [5% THC]; THC/CBD balanced [50% THC]; THC dominant [80% THC]; MC medicinal cannabis; MS multiple sclerosis; THC delta-9-tetrahydrocannabinol

FINDINGS

Analysis of participants' experiences using MC revealed four main themes. Reflecting the hermeneutical interpretation, the main themes use participants' words: 'This isn't living'; 'I was looking for a solution'; 'It wasn't to get high'; and 'Everything's much better'. The thematic structure followed patient experiences chronologically with two subthemes within each theme to highlight common concerns, barriers, behaviours, and perceived benefits (table 2). Each theme and subtheme are presented below with illustrative quotes.

Table 2 Themes and sub-themes revealed through analysis.

Themes	Subthemes
1. This isn't living	Living with unmanageable chronic health conditions Conventional medication failures
2. I was looking for a solution	Willingness to try MC Access barriers
3. It wasn't to get high	Self-managing optimal MC dosage Legal barriers
4. Everything's much better	Symptom improvements Longer-term benefits

"THIS ISN'T LIVING"

The profound burden of chronic health conditions on participants was evident and worsened by duration and failure to resolve symptoms. All participants identified management of their health conditions and associated symptoms (table 1) as the primary reason for seeking MC. The burden impacted all aspects of life and was compounded by the frustration participants felt managing conditions that persisted for many years, and the failure of conventional medications to relieve these conditions without further impacting other areas of functioning.

Not having enough sleep over year after year, just gradually wears you down... I thought this isn't living ... it can just impact your life in so many ways... mental health, relationships... it's just a knock-on effect. Male, 50s; musculoskeletal pain/insomnia [THC >CBD]

The following two sub themes were identified in the analysis: Living with unmanageable chronic health conditions, and conventional medication failures.

LIVING WITH UNMANAGEABLE CHRONIC HEALTH CONDITIONS

Participants described how their chronic health conditions interfered with their daily lives and ability to function:

I've had a few injuries... damage to my lower spine, and sciatica in both legs. I had to retire from the building industry... I ended up buying a taxi, but sometimes when I stopped, I couldn't get out of the car. By the end of the day, I was so sore. Life was getting a little... down. Things weren't good. Male, 70s; neuropathic/musculoskeletal pain [CBD]

Several participants described the development of secondary health conditions, compounding the burden and further impacting their life:

I had a fractured skull; I was quite ill for a long time ... then the depression kicked in, clinical depression for nearly a decade, and lack of sleep, and pain. Female, 60s; depression/anxiety/insomnia [CBD]

CONVENTIONAL MEDICATION FAILURES

All participants had tried to manage their conditions with conventional medicines, including Schedule 8 medicines (in Australia, Schedule 8 refers to controlled prescription drugs and drugs of dependence), such as strong opioids and benzodiazepines, and described the different ways these treatments had failed. For some, these treatments were intolerable due to unwanted side-effects:

I was prescribed oxycontin and I would say, that's one of the worst drugs I've ever taken... it just wipes you right out. Female, 50s; neuropathic pain [THC > CBD]

Many felt the side-effects interfered with their ability to function and carry out their usual activities (e.g. work):

On Mersyndol [paracetamol + codeine], I wouldn't be able to go to work because I'd be very drowsy. I would be, yeah, just not really able to function throughout the day.
Female, 30s; visceral pain/insomnia [THC=CBD]

Many participants built up tolerance to the conventional medications over time, with this reduced efficacy necessitating increased dosage and concerns about becoming addicted to these medications:

Valium is okay, but I think after so long it's like taking water... it's lost its efficacy.

Female, 60s; pain/spasticity/insomnia [THC=CBD]

I really was struggling with opioid stuff. Struggling with my conscious thoughts about how I just keep taking it and taking it and one day I'm not going to be able to stop.

Male, 60s; musculoskeletal pain/insomnia [THC=CBD]

“I WAS LOOKING FOR A SOLUTION”

Typically, participants were searching for an alternative therapy to manage their conditions and reduce or replace conventional medications that were failing.

I was looking for a solution... better than all the opioids and other rubbish that the doctors prescribed that gets you addicted and affects you mentally and physically.

Male, 60s; musculoskeletal pain [CBD]

One participant, unable to effectively relieve their pain with opioids, found themselves at a crossroads between increasing their dosage and accepting further debilitating impacts, or finding an alternative therapy:

It didn't stop the pain... I was deciding whether to take the extra [Opioid tablet] and give up my driver's license and just sit around the house. Then this medicinal cannabis thing kind of came up. Male, 70s; neuropathic/musculoskeletal pain [CBD]

Two subthemes were apparent in the analysis of participants' experiences looking for a solution: Willingness to try MC, and Access barriers.

WILLINGNESS TO TRY MC

Participants often gained knowledge of MC through internet searches and online discussion groups. In most cases, participants proactively sought MC when they found information about the QUEST study:

I searched around and I saw the QUEST study getting under way. I thought, right here's my chance to try an alternative in a really structured way. Male, 60s; musculoskeletal pain/insomnia [THC=CBD]

In most cases, participants expected MC would relieve their symptoms:

I thought it would help with the depression so therefore the sleep, or help with the sleep and therefore the depression. Female, 60s; depression/anxiety/insomnia [CBD]

One participant explained they wanted to see if MC could help them manage the side-effects of other medications they were required to take:

I've been prescribed quite strong medication ... it had a massive impact on my sleep... I thought I've just got to do something because it just wasn't a nice existence to be honest with you, just chasing your tail all the time. I just thought I'd give it a go... I just pursued it and gave it a chance to see what would happen. Male, 50s; musculoskeletal pain/insomnia [THC > CBD]

Some participants considered MC to manage their condition because their doctors would no longer prescribe them Schedule 8 medicines:

I had no other option at all... we were told that there was no more [access to Schedule 8 medication] pain killers for me to take the pain away... I couldn't get a repeat prescription because it's all about doctors not prescribing S8 medications. Female, 70s; widespread pain [THC=CBD]

Many participants viewed MC as a safer option without the unwanted side-effects from conventional medications they had taken, and regarded it as safe because it was a “natural” product:

I knew it wasn't dangerous, cannabis - it's not chemical, it's all natural. Male, 50s; musculoskeletal pain/insomnia [THC > CBD]

While others believed the risks associated with MC would be outweighed by the potential benefits:

I thought that any negative impact that [MC] could have would be far outweighed by positive impact if it actually helped me sleep. Male, 30s; insomnia [THC=CBD]

Some participants believed the stigma of cannabis stemmed from misinformation and that public perception has largely changed and become more positive:

Cannabis has been tied to the same sort of thing as, like date rape drugs and people being off their head all the time, and the criminal aspect of it. They're just misinformed. Male, 60s; musculoskeletal pain [CBD]

"It's not the stigmatized thing that it was 30, 40 years ago." Female, 50s; neuropathic pain [THC<CBD]

ACCESS BARRIERS

When consulting their regular doctors (GPs) about accessing MC, participants found that most doctors were unwilling to prescribe it due to the burdensome application process:

I spoke to my local doctor about it, about doing the research. And he was going to support me on that. There wasn't an issue with that until he found out how much paperwork you had to do. Female, 70s; widespread pain/insomnia [THC=CBD]

Some participants expressed concerns their doctors would react negatively to their MC enquiries possibly jeopardising their relationship:

Normal doctors... you mention the words cannabis, and they don't want to know you. Female, 70s; widespread pain [THC=CBD]

Due to GP reluctance to prescribe MC, in most cases participants had to seek out another GP for their MC prescription:

My GP was adamant that they didn't want to get involved in it, they didn't want to take this on as part of their service, so I had to seek out another GP that was doing it.

Male, 50s; musculoskeletal pain/insomnia [THC > CBD]

After obtaining prescriptions, some participants mentioned the financial burden due to the high cost of prescribed MC products as unapproved medicines:

It's so expensive. It'd be great if it came down in price so it would be a product that could be prescribed or obtained just like paracetamol... Being the age I am and in the financial state I'm in, \$165 a bottle is quite expensive. Male, 60s; musculoskeletal pain [CBD]

One participant was frustrated by the short use by date on MC oil products, with others echoing this, and further commenting on the expense and wastage for patients only taking small doses:

If you're on disability [payments], the cost is still high if you're not going to use very much. Most of my bottles ended up going back to the pharmacy to be disposed of.

Female, 50s: neuropathic pain [THC > CBD]

“IT WASN'T TO GET HIGH”

Participants described the impact of policies not distinguishing MC from illicit cannabis use and how they actively self-managed MC dosing to avoid unwanted intoxication.

'It wasn't to get high, it was to help me sleep.' Female, 60s;

depression/anxiety/insomnia [CBD]

Under this theme, two subthemes were identified in the analysis: Self-managing optimal MC dosage, and Legal barriers.

SELF-MANAGING OPTIMAL MC DOSAGE

Participants described efforts made to maximise the therapeutic benefits of MC oil without experiencing unwanted intoxicating side-effects. In the absence of clear clinical guidance to achieve this, participants described the challenges of self-managing their doses and monitoring their body's response over time:

I guess I probably didn't expect to have to pay a lot of attention to the dosing - particular levels... and when I would consume it... could make a difference. I had to pay a lot of attention to that in order to maximize the benefits. Male, 40s;
anxiety/insomnia [THC<CBD]

Most participants were initially vigilant to avoid unwanted intoxicating effects.

Nevertheless, some participants reported feeling intoxicated or 'stoned' if they had mistakenly taken too much MC or awoke soon after a night-time dose:

I don't take it during the day because I don't like feeling stoned. I take it at night... if I wake up sometimes at night, I'll think, oh my god, I'm stoned. But, no, it's really been good because usually I sleep through it, and then when I wake up in the morning, I wake up refreshed. Female, 60s; pain/spasticity/insomnia [THC=CBD]

Some participants reported experiencing other side-effects of MC oil, such as increased appetite, but typically found them minimal and manageable:

It can make you very hungry ... that's something to be mindful of - that you have to be quite sort of disciplined about food because I did put some weight on. Male, 50s; musculoskeletal pain/insomnia [THC > CBD]

A few participants needed to take more MC oil over time, suggesting they had built-up tolerance. To counteract this, one participant would take breaks from taking MC oil, and then start again to increase effectiveness:

I did notice though that after using it continually for, say, a month, the benefits seem to wear off. So, what I found the best thing to do was to use it for 3 or 4 weeks, then stop for a couple of weeks, and then get back on it again. [That] seemed to work like a charm. Male, 60s; musculoskeletal pain [CBD]

Others found ways to lower their risk of building tolerance by reducing the frequency of dosing:

I try not to take it every single night. I'm happy the nights where I don't take so I won't build up a tolerance to it. Male, 30s; insomnia [THC=CBD]

Whereas some participants found that over time they could manage without being dependent on MC or other medications, and only accessed it occasionally as needed:

I can kind of not take [MC] if I don't feel I need it. So, I'll just take a couple of Panadol. Whereas before, I couldn't wait for 4 h to go so that I could have more medication for my pain. Female, 70s; widespread pain/insomnia [THC=CBD]

One participant described a concerning occasion where MC oil interacted with another medication they had started, highlighting the need to disclose their MC use to any doctor or specialist they see:

Whenever I go to a doctor or a specialist ... I tell them I'm on medical cannabis... [I previously] had one tablet that's gone against it [contraindication]... I was thinking, hang on, the room is spinning, why's that?! So, I went off them straight away and within about 3 or 4 days I was back to normal. Female, 70s; widespread pain
[THC=CBD]

LEGAL BARRIERS

For context, cannabis use is illegal in most Australian states and territories and police routinely conduct roadside drug testing for THC which cannot distinguish between illicit and medicinal use. After commencing MC, participants were concerned about the possibility of being arrested or losing their driver's license after a roadside drug test:

The only concern or side-effect I'm worried about is the driving side of things... losing of my license or being, you know, taken up [arrested]. Female, 50s; neuropathic pain
[THC<CBD]

One participant was more concerned about the consequences of being arrested for driving on MC on their reputation or employment:

I was petrified of being pulled over by the police. I didn't want to break the law. I don't want to lose my job; I don't want to have to face a judge. That part freaks me out. I don't want my name tainted. Female, 40s; anxiety/insomnia [THC=CBD]

Some participants reported the MC product options available to them were limited to only CBD because of driving laws:

If you're caught with any THC in your system you lose your license. So, I've kept away from that. Male, 60s; musculoskeletal pain [CBD]

One participant pointed out they did not receive any formal documentation to show to law officials to prove their MC use was legal:

I don't actually know if I'm approved. I would guess I am, but I've never seen any documentation. Female, 30s; visceral pain/insomnia [THC=CBD]

“EVERYTHING'S MUCH BETTER”

Most participants described improvements in their health condition, their ability to reduce other medications that were causing concerns, and the overall positive impact of MC on other areas of life.

Certainly, helping with those three big things, the sleep, anxiety and pain, enabled me to live a better life generally. I just found myself feeling better once those things were reduced. Male, 40s; anxiety/insomnia [THC<CBD]

Our analysis revealed the following two subthemes: Symptom improvements, and Longer-term benefits.

SYMPTOM IMPROVEMENTS

Participants reported sleep improvements including ‘*sleeping deeper and staying asleep without a disruption*’ and waking more refreshed compared with previous medications:

More restorative sleep, rather than the fake sleep you get with other medications and where you really do have a hangover. Female, 60s; depression/anxiety/insomnia [CBD]

Participants also described having improved mood due to less pain with MC without side-effects of conventional medicines:

I was a lot happier. I think that's purely because of the lack of pain plus lack of discomfort, and I wasn't foggy in the head like I am with opioids and other prescribed things. Male, 60s; musculoskeletal pain [CBD]

Participants reported their reduced anxiety and improved mental health with MC:

Just a reduction in sort of general anxiety was a big one. An ability to... just shifting into a relaxed sort of frame of mind, reducing some of the symptoms around hyper vigilance and just, yeah, being sort of on edge. Male, 40s; anxiety/insomnia [THC<CBD]

One participant described how MC relieved their muscle spasticity, improving bladder function:

Before... I might go to the toilet once every 2 hours... just pass a small amount. Now I can go, and I can actually empty my bladder, and that's pretty good. Female, 60s; pain/spasticity/insomnia [THC=CBD]

One participant who previously self-medicated with illicit cannabis said '*it's been great to be able to get it legally*', and further described the benefits of MC oil compared to illicitly sourced cannabis:

It's been more surprising to me how beneficial it's been, as opposed to the other stuff that I would normally either grow or buy from somebody else. So yeah, I have been really surprised with the results. Female, 50s; anxiety/insomnia [THC=CBD]

In most cases, the perceived benefits of MC matched participants expectations. However, some indicated MC did not reduce their symptom burden as much as they had anticipated:

I got exactly what I was expecting, which was pain relief and the mental relief of it as well. Male, 60s; musculoskeletal pain [CBD]

It did ease the pins and needles and numbness and the needle effect in the neck. I was hoping more from it, I know we all do, but it took the edge off, you know, it's a pain managed. Female, 60s; depression/anxiety/insomnia [CBD]

LONGER-TERM BENEFITS

Participants reported being able to reduce their use of problematic medicines they were previously dependent on and caused unwanted side-effects:

My intake of Mersyndol [paracetamol + codeine] has dropped a lot. I will only take it every now and again if it's a really terrible migraine or, I've sort of shifted towards like a Naprogesic [naproxen] type medication to manage because I am actively using the cannabis now and it helps. Female, 30s; visceral pain/insomnia [THC=CBD]

While other participants were able to completely stop using other prescribed medications:

I ended up giving away the Lyrica. It took about 3 months... but it's gone... Male, 70s; neuropathic/musculoskeletal pain [CBD]

As a result of managing their health condition without the use of problematic medications causing unwanted side-effects, many participants reported flow-on improvements in other areas of their lives, including their social life and relationships:

I have this clarity of mind because I'm very relaxed... And, you know, that's improved our relationship too because I am more able to just, you know, be happy. Female, 30s; visceral pain/insomnia [THC=CBD]

As a flow-on effect of symptom control and feeling clear-headed, participants reported they were able to focus on improving other areas of their lives to promote a healthy lifestyle, such as drinking more water.

Because I'm getting better sleep, I'm more able to focus on the extra things that I need to do to cope, like drinking more water, doing those positive behaviours that, now I have more clarity of mind, I will be cognizant of, I guess. Female, 30s; visceral pain/insomnia [THC=CBD]

Having an overall feeling of general wellness was also described by participants.

It really has made a difference to my life. It's made an amazing difference to my whole outlook. Female, 60s; pain/spasticity/insomnia [THC=CBD]

Table 3 contains additional illustrative quotes for each of the themes and subthemes described.

Table 3 Illustrative quotes for themes and subthemes.

Theme	Subtheme	Quotes
"This isn't living"	Living with unmanageable chronic health conditions	<i>I've got an immune deficiency health condition for which I've been prescribed quite strong medication. Since I've been taking it, it's had a massive impact on my sleep which obviously over the years has had an impact on my mental health.</i> Male, 50s; musculoskeletal pain/insomnia [THC > CBD] <i>I had a back injury... it was very painful and disrupted life quite considerably... I'll become almost immobilized some days.</i> Male, 60s; musculoskeletal pain [CBD] <i>I was just so tired all the time, and just strung out ... It was like I was my mind was racing all the time.</i> Male, 50s; musculoskeletal pain/insomnia [THC > CBD]
	Conventional medication failures	<i>I wanted to get off the heavy drugs that I was using. [Opioids] made me feel so drowsy and actually quite terrible. I didn't have any pain, but I did still feel bad.</i> Male, 60s; musculoskeletal pain/insomnia [THC = CBD] <i>After being prescribed all sorts of chemicals... I found that they impaired my ability to do things.</i> Male, 60s; musculoskeletal pain [CBD] <i>I was taking a codeine tablet, Lyrica... it helped... but after a little while you had to have another... And it just kept growing and growing.</i> Male, 70s; neuropathic/musculoskeletal pain [CBD] <i>Other treatments [Benzodiazepines] that I've tried had some varying degrees of success ... but often meant that I would have to use more, and it just didn't feel like a path that I wanted to be on for too long... I always felt like I was dancing with the devil.</i> Male, 40s; anxiety/insomnia [THC < CBD] <i>Since I did my back in 1997, I was on pretty heavy S8 medications and trying to work as well. Schedule 8 medications like Oxycontin, I was on Fentanyl patches at that stage as well. So, basically my goal was to try and get off all of that. [I wanted to be] pain free as well and be able to do things.</i> Female, 70s; widespread pain/insomnia [THC = CBD] <i>I really didn't want to take sleeping tablets. I'd had the odd diazepam and even Melatonin... didn't I feel really groggy the next day!</i> Female, 50s; anxiety/insomnia [THC = CBD]
Theme	Subtheme	Quotes
"I was looking for a solution"	Willingness to try MC	<i>I don't believe anyone has ever died from [MC] and it's far less detrimental than tobacco, alcohol, sugar, social media, driving, all sorts of things that we do.</i> Male, 30s; insomnia [THC = CBD] <i>It's better for you like in terms of stomach linings and all of those things - I prefer a natural remedy... I just don't like to take too many pharmaceuticals, so I prefer most things natural.</i> Female, 50s; neuropathic pain [THC < CBD] <i>Opioids ... do more damage I think than the cannabis does. There's certainly no addictive properties.</i> Male, 60s; musculoskeletal pain [CBD] <i>I've long believed that weed is extremely safe... It'd be far, far less unpleasant than being sleep deprived. Sleep deprivation is very unhealthy. So overall I was, you know, anything to help my sleep would be a positive.</i> Male, 30s; insomnia [THC = CBD] <i>I have used marijuana since I was young... but not in an abusive way. I just wanted to pursue that in a legal method rather than having to grow it or find it.</i> Female, 50s; anxiety/insomnia [THC = CBD] <i>I do have to push back against some assumptions around it... people saying, 'Oh, this is, you know, it's a gateway drug, you know. Next week you'll be, you know, injecting heroin in a car park somewhere.' When I give them some of the details around the</i>

benefits, the lack of negative effects compared to other similar products, people seem to be quite open to it. Male, 40s; anxiety/insomnia [THC<CBD]

- Access barriers**
- My GP is pretty conservative, so he wouldn't be interested in doing that.* Female, 50s; anxiety/insomnia [THC=CBD]
- I had asked to be prescribed marijuana years ago [by] a psychiatrist... and she immediately dismissed that, basically. She prescribed me SSRIs instead, which didn't help at all.* Male, 30s; insomnia [THC=CBD]
- My doctor just wouldn't prescribe it at all... most of them didn't have any training in it, and also the possible chance of litigation.* Male, 60s; musculoskeletal pain [CBD]
- My doctor really had no idea about medicinal cannabis. He did quite a bit of background, it took for him probably 3 months before he was kind of satisfied... he would see it through as a way to get off the opioids, and it was so helpful. Really, really, helpful. He just did everything he possibly could to get it all happening.* Male, 60s; musculoskeletal pain/insomnia [THC=CBD]
- [GP] said 'I'll do whatever I can to help...[but] don't tell anyone'... She was really concerned that if I shared it with people... she'd be inundated with patients.* Female, 50s; neuropathic pain [THC > CBD]
- It's quite expensive. But I just decided that it didn't matter. I was just going to pay anyway to see how it went.* Female, 70s; widespread pain/insomnia [THC=CBD]
- [MC bottle expiry date] says it runs out by October. That's a lot of money down the drain! Does that mean it's not going to be effective... or is it going to be dangerous?* Female, 40s; anxiety/insomnia [THC=CBD]
- I do think over the summer, when it gets very hot, I think it loses potency.* Male, 50s; musculoskeletal pain/insomnia [THC > CBD]
- Wish it was cheaper. But I'm still buying it and I'm still using it.* Female, 60s; pain/spasticity/insomnia [THC=CBD]

Theme	Subtheme	Quotes
"It wasn't to get high"	Self-managing optimal dosage MC	<i>The guidelines were always start low and go up in small increments if required. So, I kind of stuck with that and haven't had any significant issues.</i> Male, 40s; anxiety/insomnia [THC<CBD]
		<i>I think you need to get it into your system - you can't just take it once.</i> Male, 50s; musculoskeletal pain/insomnia [THC > CBD]
		<i>You know, you've got to allow at least 2 to about 3 to 4 weeks for it all to get right into your system. So, it just doesn't work instantly.</i> Female, 70s; widespread pain [THC=CBD]
		<i>First time I took it I do remember nothing happened for hours. I thought this is not going to be any good. It doesn't kick in straight away, it can take sometimes 3 hours, sometimes it will be an hour.</i> Male, 50s; musculoskeletal pain/insomnia [THC > CBD]
		<i>I find that if I've had more food that day, that could certainly impact as well.</i> Female, 30s; visceral pain/insomnia [THC=CBD]
		<i>I went from half strength the first few days ... to the full prescribed amount from then on, and I found that was really good. I think the first bit was just making sure that I had no reactions.</i> Male, 60s; musculoskeletal pain [CBD]
		<i>I've settled into a pretty consistent dosing schedule now. And it seems to work very well.</i> Male, 40s; anxiety/insomnia [THC<CBD]
		<i>I mainly stick to the recommended dosage. If I find that it's not enough, I'll adjust it... up by the point of a ml. And I never really went above that, because I didn't really need to.</i> Female, 50s; neuropathic pain [THC<CBD]

I've got my daily dosages and I stay on that, I don't go over it. I'll ask [nurse practitioner] if anything's playing up, can I have a little more? And she'll say yes or no. Female, 70s; widespread pain [THC=CBD]

[My current dose] would have made me feel like I was, you know, feel like I was stoned or something at the outset because I wasn't used to it. Female, 40s; anxiety/insomnia [THC=CBD]

I definitely have tried too much, to see what happens... too much makes you feel doughy. If it makes you feel tired, it's not worth doing. Male, 60s; musculoskeletal pain/insomnia [THC=CBD]

I was kinda anxious about it because I didn't really want to be stoned. Female, 50s; neuropathic pain [THC > CBD]

You get very hungry sometimes. So, I gotta be mindful of having healthy snacks around. Female, 30s; visceral pain/insomnia [THC=CBD]

The only side effect would be that if I took quite a bit extra dose... I would be a little bit stoned in the morning, but that was fine. It would wear off quickly... far less unpleasant than being sleep deprived. Male, 30s; insomnia [THC=CBD]

Early on when I was dialling in the dosages... maybe I had a little bit too much, but nothing at a point that I feel like in danger, or that I'd damaged myself. Male, 40s; anxiety/insomnia [THC < CBD]

I smoked cannabis before so I sort of knew the effect, but I did say to the doctor, is it going to be the same because that can be quite intense and you know I don't want to be like that all the time... I just didn't want to be a stone head really. But this is like less, it's not as intense... you don't really get stoned. It just sort of just relaxes everything. Male, 50s; musculoskeletal pain/insomnia [THC > CBD]

I was over-thinking 'cause I'd taken too much... Now I know how to moderate it and it's not too intense. Female, 40s; anxiety/insomnia [THC=CBD]

I guess you get paranoid if you've had a little bit too much, but I know that feeling now so it doesn't bother me at all. Female, 30s; visceral pain/insomnia [THC=CBD]

For me, it actually works better not to take any [before bed] and to only take [MC] when I woke up in the middle of the night, and that was very effective. Male, 30s; insomnia [THC=CBD]

I was taking half a ml which I was getting an effect from. But obviously over time I'm having to do more. Male, 50s; musculoskeletal pain/insomnia [THC > CBD]

Now, because my body is used to it, I'm needing a little bit higher dose. Female, 30s; visceral pain/insomnia [THC=CBD]

I try not to take it every single night. I'm happy the nights where I don't take so I won't build up a tolerance to it. Male, 30s; insomnia [THC=CBD]

If I haven't had it in a while, I'll reduced my dose a little bit... being mindful that it is a little bit stronger when I have not had it for a while. Female, 30s; visceral pain/insomnia [THC=CBD]

There were a lot of times, and still now, that having that extra tool in my toolkit has been really helpful. Particularly if I've had a really hard day. Female, 30s; visceral pain/insomnia [THC=CBD]

I've kept the last supply [of MC] as an emergency kind of thing ... I find it very good as a cupboard support mechanism. Male, 60s; musculoskeletal pain [CBD]

It's like any drug, you could mistreat it if you wanted to. Male, 60s; musculoskeletal pain/insomnia [THC=CBD]

Legal barriers

[THC] can show up in a roadside test, despite the fact that you may or may not be under the influence of it. Male, 40s; anxiety/insomnia [THC < CBD]

I was petrified of being pulled over by the police. Literally. Like even if you're not on it, the next day it'll come up as positive. So, I did get a letter [from the doctor]. I was proactive and I got a letter. Female, 40s; anxiety/insomnia [THC=CBD]

I can't afford to lose my license, and I know that [having a prescription] doesn't [mean I can] keep my license... but it depends on the policeman on the day, and it can assist from what I've understood. Female, 50s; anxiety/insomnia [THC=CBD]

Although [MC] is legal... if the police pulled you over and you had a test it would come up positive. It's a bit of a grey area; would you be charged? I don't drive if I've taken it. I'll hold off if I need to go out and do stuff... It's not worth risking. Male, 50s; musculoskeletal pain/insomnia [THC > CBD]

The only concern I have is if I get drug tested... I don't drive or anything on it. If I know that I have taken a THC dose, like that's it, I stay home. I'm not silly around that type of thing. It's not worth it. Female, 30s; visceral pain/insomnia [THC=CBD]

Where I live is a really remote location and there's no backup for me if I lose my license. I hung on to just cannabidiol for as long [as I could] before I incorporated THC... I was waiting for them to change legislation in regard to being able to drive. Female, 50s; neuropathic pain [THC > CBD]

For driving reasons... I was happy that [my prescribed MC] didn't have any THC. I'm on the CBD... that has, like, hardly any THC - just what you can't get out really. Female, 60s; depression/anxiety/insomnia [CBD]

I came up with this pain management with CBD, which doesn't have THC, so you don't fail a roadside test. Male, 70s; neuropathic/musculoskeletal pain [CBD]

Theme	Subtheme	Quotes
"Everything's much better"	Symptom improvements	<i>Being able to actually get into bed and not be uncomfortable all night, and being able to sleep, was a real blessing. Getting 6 or 7 hrs sleep, unbroken sleep, compared with 1.5 to 2 hr windows of sleep was a real plus.</i> Male, 60s; musculoskeletal pain [CBD]
		<i>On the nights that I do take it, I will be able to sleep right through, instead of tossing and turning and just generally feeling frustrated at the lack of sleep.</i> Female, 30s; visceral pain/insomnia [THC=CBD]
		<i>I sleep deeper. I wake more refreshed, and you know before I would wake up in the morning and I would still be tired.</i> Female, 60s; pain/spasticity/insomnia [THC=CBD]
		<i>I can fall back to sleep a lot easier if I have a dose. And then yeah, waking up, the big thing is like I feel more refreshed in the morning... I have more energy to go and do the things that made me happy.</i> Female, 30s; visceral pain/insomnia [THC=CBD]
		<i>Once you're sleeping better, everything's much better, generally.</i> Male, 40s; anxiety/insomnia [THC < CBD]
		<i>You know, just getting the sleep, I think, was a major thing for me. I don't think it really makes a massive difference with pain to be honest. If I get pain in my leg from my injury, that is there regardless... the best part I think is the fact that I get a much better rest.</i> Male, 50s; musculoskeletal pain/insomnia [THC > CBD]
		<i>I feel no pain ...and generally I just feel great. I'm walking around like you wouldn't think I was on anything.</i> Female, 70s; widespread pain [THC=CBD]
		<i>It actually did reduce the swelling in areas where I had inflammation, and I wasn't feeling the pain.</i> Male, 60s; musculoskeletal pain [CBD]
		<i>It actually helps me reduce that anxiety. I think that's a big part of you know... your body is a bit kind of loser; you're not always tense.</i> Male, 60s; musculoskeletal pain/insomnia [THC=CBD]
		<i>It just sort of enabled me to just get into a more natural rhythm of being alert and focused, and then to be able to down regulate and relax and chill out.</i> Male, 40s; anxiety/insomnia [THC < CBD]

I will let things go a bit easier... and... just let it go. Female, 50s; neuropathic pain [THC<CBD]

I guess I was just really surprised in how such a small amount can be effective, and I didn't feel impaired in any way, just kind of motivated and kind of happy, and not stuck in my head with, you know, negativity and stuff like that. Female, 50s; anxiety/insomnia [THC=CBD]

You can think clearly. It just gives me that ability to have clarity and make sensible decisions I suppose and just be logical. Male, 50s; musculoskeletal pain/insomnia [THC >CBD]

**Longer-term
benefits**

I was taking Temaze if I'm unable to sleep, like on a daily or nightly basis, or 2 nightly, and eventually I've come off those as well. Female, 70s; widespread pain/insomnia [THC=CBD]

[MC] is the only thing I take now. It's been a massive change. I've gone from weekly scripts of all different kinds of things. I think now I feel better in myself. Male, 60s; musculoskeletal pain/insomnia [THC=CBD]

I've been prescribed various [Benzodiazepines] in the past. I haven't taken those for a long time now. I've also had a prescription for amitriptyline that I no longer take. Male, 40s; anxiety/insomnia [THC<CBD]

So then, you know, having more restful sleep, not having that inherent stress, I was able to put exercise back into my routine. Female, 30s; visceral pain/insomnia [THC=CBD]

I can do a lot more now than I used to before I went on [MC]. I used to do my housework, and then I'd have to sit down for at least, you know the rest of the day, because I was in too much pain. But now, I can do my housework... do whatever I want. Female, 70s; widespread pain [THC=CBD]

I've put in a new kitchen... I've always been gonna do it, but it's been too difficult. This year, I've done it... And like I said, I've only taken one Panadeine Forte this year. Male, 70s; neuropathic/musculoskeletal pain [CBD]

It has certainly worked for me and helps me live a productive good life... I got on with life and found my way. Female, 50s; neuropathic pain [THC<CBD]

My life is definitely better. Generally, I feel more like my social life is better, relationships, generally better, just because I'm feeling better. Male, 40s; anxiety/insomnia [THC<CBD]

I feel like I am probably coping better. I'm calmer and I'm a bit more open to people. Female, 50s; anxiety/insomnia [THC=CBD]

It was so profoundly life changing in that it helped me in a range of areas, and it still does. Female, 30s; visceral pain/insomnia [THC=CBD]

CBD cannabidiol; CBD only [less than 1% THC]; THC<CBD: CBD dominant [5% THC]; THC=CBD: THC and CBD balanced [50% THC]; THC >CBD: THC dominant [80% THC]; MC medicinal cannabis; MS multiple sclerosis; THC delta-9-tetrahydrocannabinol

To further illustrate the experiences of patients prescribed MC, study themes and subthemes were synthesised into a conceptual model (Figure 1). The conceptual model follows the journey of patients with chronic health conditions not responding favourably to conventional medicines. Initially patients face barriers accessing MC, then further challenges managing their MC use to maximise benefits and avoid side-effects or legal punishment. Eventually, the benefits of MC flow beyond symptom relief to improve life in general.

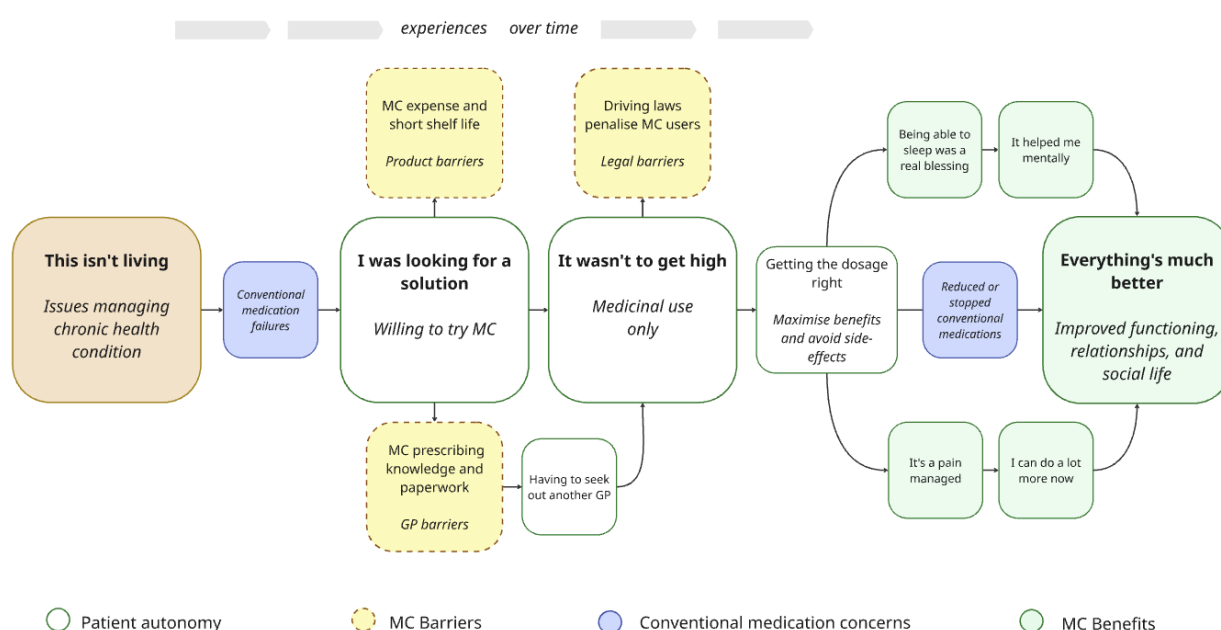


Figure 1 Conceptual model of patient experiences over the course of accessing and using medicinal cannabis (MC) long-term for chronic health conditions.

DISCUSSION

To our knowledge, this study is the first to provide insight into the experiences of patients prescribed MC in Australia long-term. Qualitative interviews used a patient-centred approach to reveal richer insight into patients' lived experiences with healthcare and treatment impacts.³⁸ Reasons for seeking MC to manage their health conditions were most

often due to concerns with conventional medicines and wanting a safer alternative.

Participants reported improvements in distressing symptoms without the side-effects of conventional medicines, and additional long-term flow-on benefits of improved relationships, general functioning, and wellbeing.

The improvements participants reported in pain, sleep, and anxiety, support the quantitative findings from the QUEST Initiative.²⁶ and qualitative findings from other studies overseas.^{33,39} Our findings support previous qualitative research with cancer patients using MC showing that participants reported improved sleep without unwanted side-effects, and decreased use of benzodiazepines and other sleep medications.⁴⁰ Similar to previous findings,^{26,41,42} we also found participants were able to reduce the use of other medications for sleep, anxiety, opioids for pain, and antidepressants due to MC therapy. However, a recent randomised controlled trial of 84 patients in the USA accessing MC for insomnia, pain, anxiety and depression, found that after 2 years 14% met criteria for Cannabis Use Disorder.⁴³ A novel finding from our study was that some participants reported their conditions became more manageable with MC in the long-term, accessing MC only as needed, reducing their overall dependence on medications generally.

Experiences reported by participants in this study confirmed the persistence of barriers previously described in a 2021 qualitative study of attitudes of cancer patients in Australia,⁴⁴ and those identified in 2020 during a Senate inquiry into MC access in Australia.¹² These included a lack of general awareness about MC products,⁴⁵ the complex prescription process,⁴⁴ high cost of MC products,⁴⁴ and restrictive driving laws.¹² In this study, many participants were concerned about driving laws in Australia where drivers can be charged with a criminal offense and lose their licence if any trace amount of THC is detected. Stigma,

an issue raised in other qualitative studies internationally,^{33,39,46} was also identified by study participants as a potential barrier due to the perceived association of illicit cannabis use with being intoxicated and committing crimes. The latter being perpetuated, at least in part, by Australia's driving laws that don't distinguish medicinal use from illicit. Previous research indicates stigma can lead to patients not disclosing their MC use with clinicians.³⁹ Many participants in the current study reported seeking another doctor for their MC prescription due to their usual doctors either being unreceptive to MC or unwilling to engage with the prescribing process. However, most participants described being open about their MC use both with their clinicians (usual and new) and in the wider community. This may be due to their participation in the QUEST study; as a research participant, they may have felt more protected from criticism and more justified in their choices, which may limit generalisability of findings. It is likely that patients who feel the need to consult a separate doctor for their MC prescription, may feel reluctant to disclose this to their usual doctor. However, patient-centred practice is improved through shared decision-making, respecting patient autonomy and self-determination.⁴⁷ After years living with chronic health conditions and trialling different treatments, patients become active agents in managing their healthcare and demonstrate self-efficacy through information-seeking and by selecting and educating their healthcare providers.⁴⁸

MC PATIENT'S SELF-DETERMINATION

Participants experienced wide ranging benefits of being prescribed MC which may be explained through self-determination theory (SDT). According to SDT, well-being and motivation are optimised when the basic psychological needs for autonomy, competence, and relatedness are satisfied.⁴⁹ Numerous studies have shown that the satisfaction of these

needs is positively related to well-being and negatively related to depression and anxiety.⁵⁰

Findings from this study suggest that being an active agent in their health management satisfied participants' need for autonomy. MC was usually their choice, many had initiated conversations about MC with their doctors, conducted their own research, overcame barriers, and took control of their own dosing regimen. Participants felt competent when successfully obtaining MC and receiving the desired improvements in health and functioning. Finally, participants found doctors who would listen and consider their choice of therapy, or legitimize their MC use, satisfying their need to feel close and understood by others. This was further reinforced when their relationships and social functioning improved after taking MC. Future research could further explore the benefits of prescribing MC through the lens of SDT.

RECOMMENDATIONS TO ADDRESS MC CONCERNS

Participants reported some initial concerns regarding MC side-effects and whether they would experience the same intoxicating effects caused by illicit cannabis. These concerns could be addressed through evidence-based educational resources, specifically on how MC differs from illicit cannabis in administration, dosage, and intoxicating effects. There were some side-effects of MC, which participants were generally able to self-manage by adjusting their MC dose regimen through a process of trial and error. Insights from participants in this research about self-managing optimal MC dosage (Table 3) could be useful for future patients considering MC therapy. Similarly, access to educational resources regarding the endocannabinoid system and pharmacology of cannabinoids would benefit clinicians.

Many participants in this study received MC prescriptions from clinicians other than their usual GP, often because their usual GP was reluctant to navigate the special access scheme

or doubted the potential benefits of MC therapy. Indeed, the number of clinicians specialising in MC has increased, contributing to the recent sharp rise in MC prescribing.⁵¹ The growing number of cannabis clinics in Australia is a point of concern for the Australian Health Practitioner Regulation Agency (AHPRA), because a conflict of interest is introduced when clinicians work in a facility that only prescribes one medication,⁵¹ and unlike their regular GP, may fail to properly account for a patient's unique medical history and health care needs.⁴⁸ Whether prescribing MC or not, GPs need to understand the impact of MC therapy on their patients and be aware of possible contraindications with other prescribed medications. Better access to information and streamlined prescribing processes would improve clinicians' ability and capability to facilitate shared decision-making and patient-centred care.

Policing of driving laws in Australia include random road-side drug-testing for the presence of THC in a driver's bodily fluids, resulting in criminal offence charges and loss of licence irrespective of actual impairment. While THC may impair driving ability,⁵² evidence from previous studies suggest driving impairment is largely associated with occasional recreational cannabis use, rather than regular MC use at therapeutic levels.⁵³ Participants in our study actively managed their MC dosing and timing to avoid intoxication and reported MC reduced impairments caused by their chronic conditions and previous conventional medications. Further research is needed to establish safe guidance on THC levels associated with impairment using standard THC units, form of consumption (e.g., sublingual oil, inhaled, etc.), and time since administration, similar to alcohol guidelines.⁵⁴ This would provide patients with formal guidance for monitoring their risk of impairment and inform the development of tests that detect when guidelines are exceeded, rather than penalise legitimate MC users based on THC presence.

STRENGTHS AND LIMITATIONS

Study strengths include representation across conditions and symptoms commonly treated with MC, and all participants were legally prescribed MC and continually monitored by their prescribing practitioner for 12-months or longer. Interviewing patients accessing MC for up to 4-years allowed us to evaluate whether concerns and barriers persist long-term and gain insights into patient self-management and the long-term outcomes of MC therapy. A limitation of this study was that all participants had accessed MC while participating in the QUEST study, which would understate the barriers to accessing MC generally faced by patients in Australia. Furthermore, all participants were accessing MC oil from the same manufacturer, limiting generalisability across types of MC products. Four participants had accessed illicit cannabis within 12-months prior to receiving their MC oil prescriptions, and two indicated that following the QUEST study they received prescriptions for other MC products administered via medical vapouriser. It is possible that prior cannabis use and different modes of MC administration may have differentially impacted MC effectiveness. Although participants stated they replaced their previous illicit cannabis use with prescribed MC, it is possible some may still have been using illicit cannabis while also using prescribed MC, potentially affecting study findings. Unfortunately, findings were not sent back to participants for feedback or further clarification. Finally, our requirement to have renewed their MC prescription within 6 months of being interviewed (to aid recall) meant that participants in this study were all benefitting from MC and had continued their prescriptions after the QUEST study ended. The experiences of patients who discontinued MC therapy due to either lack of therapeutic benefit or significant barriers to access are unknown.

CONCLUSION

To our knowledge, this is the first qualitative interview study looking at the experiences of patients across different health conditions prescribed MC long-term (up to 4 years) in Australia. This study provides unique in-depth insight into the experiences of these patients since national legislation and access pathways to MC changed. Despite the many benefits patients report in terms of symptom control with minimal side effects, there are still ongoing barriers to use and access, particularly via patient's regular GP, warranting further attention. Although doctors in Australia have been prescribing MC for nearly a decade, there appears to be a general lack of clinician guidance prescribing MC products, with many patients reporting difficulties accessing MC through their usual doctor. Although this study only included 15 participants, our findings suggest there is a group of patients with chronic conditions wanting to reduce their use of conventional medications who may benefit from MC oil through symptom relief and improved quality of life in the long-term.

FUNDING

No funding was received for conducting this study.

CONFLICTS OF INTEREST

The University of Sydney received funding from Little Green Pharma Pty Ltd. to support MT and CR to conduct research outside of the submitted work (The QUEST Initiative). The current study recruited patients who had previously participated in the QUEST study. The authors declare no other conflicts of interests.

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PART D

DISCUSSION AND FUTURE DIRECTIONS

CHAPTER 7

PART D. DISCUSSION AND FUTURE DIRECTIONS

CHAPTER 7: DISCUSSION AND CONCLUSIONS

CHAPTER OVERVIEW

In this final thesis chapter, the research aims described in **chapter 1** are revisited and key findings from this program of research discussed. This chapter highlights the contributions this thesis makes to the current evidence-base for the benefits MC therapy, with a focus on HRQL outcomes in people with chronic health conditions. The implications of findings for clinical practice are considered, and the strengths and limitations of this research discussed. Finally, key findings from the systematic review and three observational studies using diverse quantitative and qualitative designs within this thesis are synthesised to provide recommendations for future research, policy, and clinical practice.

REVIEW OF RESEARCH OBJECTIVES

The overarching aim of this thesis was to describe and evaluate HRQL in patients prescribed MC for chronic health conditions and explore their experiences accessing MC in Australia. This thesis constitutes a mixed methods program of research, resulting in five peer-reviewed publications (three published; two under review) addressing the following aims:

1. Determine how HRQL was defined in studies of patients prescribed MC, assess the quality and completeness of HRQL reporting in MC research, and whether rationales were provided for selecting HRQL PROMs.

2. Through meta-analyses of evidence from primary research spanning the last decade, determine whether the HRQL of patients receiving MC improved over the short, medium, or long-term.
3. In a pre- and post-therapy study, assess HRQL and other PROs in a large sample of patients with chronic health conditions prescribed MC in Australia over the short-term (up to 3-months) and long-term (up to 12-months). Determine whether patients with specific health conditions have improvements in symptoms related to those conditions.
4. Using short- and long-term follow up HRQL/PRO data, explore differences across health conditions and MC cannabinoid compositions.
5. Through interviews, explore the subjective experiences of patients prescribed MC in Australia over the long-term, including their perceptions of how MC impacted their daily life, and any barriers they encountered accessing MC prescriptions.

SUMMARY OF FINDINGS

PART A. HOW AND WHY IS HRQL ASSESSED IN PATIENTS USING MC

Chapter 1 discussed the complexity of chronic health conditions, their prevalence in Australia and globally, and the high burden associated with these conditions at the individual and societal level (e.g. economic burden). MC is increasingly being considered a treatment option for these conditions in many countries; however, historical and on-going legal restrictions have inhibited research, limiting the availability of high-quality evidence supporting MC efficacy. PRO data (and an understanding of the endocannabinoid system) is needed to provide clinicians with knowledge and evidence-based guidance on prescribing

MC for different health conditions. HRQL is universally valued as an important PRO across all health conditions, making it an important endpoint in clinical research. **Chapter 1** considered the various ways of conceptualising and assessing HRQL, highlighting the importance for researchers to be explicit about the meaning and context of HRQL assessment in their studies to inform their choice of HRQL measure, reduce ambiguity in interpretation, and improve scientific rigor.¹

Chapter 2 reviewed studies published over the past decade that reported HRQL outcomes in patients before and after MC treatment. Of the 64 included studies, only five (8%) were rated as meeting all PRO reporting requirements (either fully or partially). Most studies (81%) used generic HRQL questionnaires (e.g., EuroQol Group: EQ-5D), while some used condition-specific questionnaires (e.g. Multiple Sclerosis Quality of Life: MSQoL-52). HRQL was rarely defined and more than a third of studies did not provide a reason for assessing HRQL. There is an expectation from professional and clinical organisations, health agencies, and regulatory bodies to include PROs in clinical studies to evaluate treatment benefits and harms.²⁻⁴ However, if researchers do not include a HRQL-specific research question, it is unclear whether their chosen HRQL PROMs are fit-for purpose, which can lead to misleading findings. This is particularly important considering HRQL results can differ for patients within the same study depending on the HRQL PROM used.¹ This was exemplified in **chapter 2** revealing the eight studies assessing patients with multiple sclerosis (6 observational and 2 RCTs) reported vastly different short-term HRQL results: arguably, this may be due to the use of four different HRQL PROMS across these eight studies. Further, this diversity in the measures used likely arose due to none of the studies providing HRQL definitions and more than half failing to report their rationale for assessing HRQL; both best practice

requirements for HRQL assessment and selecting appropriate measures. Although studying the same patient population and therapy, these issues limited comparability across the studies.

Overall, HRQL improvements were observed in these studies across patients with multiple health conditions using MC over short-, medium- and long-term follow-up. Meta-analyses found small to moderate main effect improvements in HRQL across both RCTs and observational studies. RCTs only assessed HRQL after short-term MC use (2 weeks to 3-months), and indications traditionally considered appropriate for MC, such as symptom relief for persons with cancer and epilepsy, did not show meaningful improvements in HRQL. However, in medium- (5 to 9-months) and long-term (12 to 24-months) prospective studies, all but one (97%) reported statistically significant HRQL improvements across all chronic health conditions assessed.

PART B. ASSESSING HRQL AND PROs IN PATIENTS PRESCRIBED MC IN AUSTRALIA

Chapter 3 introduced the quantitative component of this program of research by presenting a published study protocol for longitudinally assessing a range of PROs in a large real-world cohort of patients in Australia newly prescribed MC across a wide range of chronic health conditions. Arrangements were made to ensure all participants were charged the same amount for their prescribed MC oil products to eliminate variability in out-of-pocket costs and enable future health economic evaluation (beyond the scope of this thesis). Rigorously developed and validated PROMs were carefully selected to comprehensively evaluate all domains under our definition of HRQL and condition-specific PROs. PROMs were administered at clinically meaningful time-points, determined from clinical guidelines on appropriate follow-up across multiple chronic health conditions.⁵⁻⁷ The protocol included a

statistical analysis plan for reporting not only the statistical significance, but also the clinical meaningfulness of findings referencing predefined minimal clinically important differences (MCIDs). This was important because studies with large sample sizes can identify statistically significant changes that are barely noticeable to patients and considered too small to be clinically meaningful. The potential impact of missing PRO data was reduced through electronic data collection methods and linear mixed models analysis using all available data and maximum likelihood estimation. The complete detailed statistical analysis plan in **Appendix 2** was developed to ensure study results were as transparent and robust as possible and minimised risks of outcome reporting bias and data-driven results.

Chapter 4 contains the publication of primary findings from this longitudinal cohort study focusing on HRQL outcomes up to 3 months post-baseline. Half of participants in the study were prescribed MC for more than one chronic health condition. As discussed in **chapter 1**, chronic conditions are complex and often co-occur, with one chronic condition often developing due to the presence of another.⁸ Overall, HRQL improved over 3-months in patients accessing prescribed MC in Australia. Results showed both statistically significant and clinically meaningful improvements in overall HRQL and fatigue across a diversity of people with chronic health conditions. Similar improvements were found in pain scores for participants with chronic pain, depression scores for patients with depression, and anxiety scores in patients with anxiety. HRQL was assessed using two different PROMs: the QLQ-C30, which produced a summary score covering 15 HRQL domains over 1-week; and the EQ-5D-5L, which captures only five HRQL domains over 1-day. The QLQ-C30 was chosen because its domains covered all aspects of our definition of HRQL, whereas the EQ-5D-5L was chosen primarily due to its wide use across MC studies and enabled more direct

comparison of study results. While both PROMs revealed similar HRQL improvements over the 3-month period, EQ-5D-5L index scores decreased slightly over time for older participants, whereas QLQ-C30 summary scores were not affected by age. When assessing HRQL again at 12 months follow-up, the published results presented in **chapter 5** showed HRQL improvements on QLQ-C30 summary scores were nearly double the improvements captured by EQ-5D-5L. This difference may be due to the PROMs' domain coverage and recall period, suggesting EQ-5D-5L may be less stable and more sensitive to daily fluctuations in symptom burden, while the QLQ-C30 is more reflective of lasting changes over longer time periods. Similarly, significant HRQL improvements were observed in patients with epilepsy assessed with QLQ-C30, however EQ-5D-5L did not change. This further reinforces the message from **chapter 1** and **chapter 2** of this thesis, that careful consideration of the context and meaning of HRQL is required when choosing PROMs for assessment purposes. Although developed for use with cancer patients, the QLQ-C30 is a core measure assessing HRQL domains relevant across all cancer types -- domains that are also relevant to most chronic health conditions. These novel findings from **chapter 5** suggest that when assessing patients using MC for chronic health conditions, the QLQ-C30 may be more appropriate than the generic EQ-5D-5L due to its ability to detect HRQL change in this cohort.

The study covered in **chapter 5** found that short term improvements in overall HRQL reported at 3-months in **chapter 4** were maintained over a 12-month period. Across the cohort, improvements were observed in HRQL, fatigue, pain, and sleep, and condition-specific symptoms improved for patients with anxiety, depression, insomnia, or chronic pain. HRQL improvements were also observed in patients exclusively treated for generalized

anxiety, chronic pain, insomnia, and post-traumatic stress disorder. Due to taking MC, nearly half of participants reduced their use of other prescribed medications to manage their symptoms, and by 12-months, 1 in 4 had completely stopped one or more medications.

Chapter 5 also reported findings related to the different cannabinoid combinations (i.e. CBD:THC ratios) associated with HRQL improvements for each chronic health condition. Daily MC doses containing THC were associated with a greater degree of improvement in sleep compared with CBD-only. Exploration of the different pain types also revealed different cannabinoid combinations were associated with greater improvements in musculoskeletal, headache, and cancer-related pain intensity, but this favored CBD-dominant doses. Our findings suggest that people with chronic pain conditions experience better outcomes over time on relatively low doses of CBD when combined with small amounts of THC at a ratio of 10:1. However, we calculated average daily dose overall, whereas daily dosing regimens in practice may limit administering THC to evenings (to avoid possible intoxication during waking hours), rather than maintaining a 10:1 ratio throughout the day. Recent evidence suggests high concentrations of THC (above 10%, or 5mg per dose) are associated with greater risks of poor mental health outcomes.⁹

PART C. EXPLORING THE PATIENT EXPERIENCE OF USING MC

The qualitative study presented in **chapter 6** provides deeper insight into the experiences of patients prescribed MC in Australia. Nearly a decade after Australia legalised MC, little was known about the lived experience of patients legally prescribed MC over the long-term. Participants from the longitudinal cohort study described in **chapters 4 and 5** were interviewed 1-4 years after commencing MC therapy. Thematic analysis confirmed the

quantitative findings of symptom improvements associated with MC therapy (particularly pain, sleep, and anxiety) being maintained long-term. Reasons for seeking MC to manage their health conditions were most often due to concerns with conventional medicines and wanting a safer alternative. In **chapter 6**, participants described long-term improvements in their condition without the side-effects of conventional medicines. Furthermore, these improvements flowed on to benefit relationships, productivity, mental health, and wellbeing, and reduced medicinal drug dependence (e.g., opioids, antidepressants, and benzodiazepines). A novel finding was that some participants reported their conditions became more manageable with MC in the long-term, accessing MC only as needed, and reducing their overall dependence on medications generally. This suggested that reducing opioid use improved pain management, supporting findings from animal studies showing that opioid use prolonged neuropathic pain,¹⁰ potentially contributing to the development and maintenance of chronic pain conditions.

Chapter 6 also revealed the barriers to accessing MC, as previously identified in a 2021 Australian Parliamentary Review,¹¹ persist: many GPs were reluctant to prescribe MC, forcing patients to seek new GPs for MC specifically; and MC products were expensive with a short shelf-life. Participants were also concerned about driving laws that penalise drivers if roadside testing detects the presence of THC, even at trace amounts, regardless of actual impairment. As described in **chapter 6**, participants actively managed MC dosing and timing to avoid intoxication. A review of the evidence regarding driving laws found that although THC can impair driving ability,¹² MC users monitor impairment and wait an appropriate period before driving,¹³ with some patients finding MC reduced impairments caused by their chronic conditions and side effects of conventional medications.¹⁴ Further research is

needed to establish guidance on THC levels associated with impairment using standard THC units, form of consumption (e.g., sublingual oil, inhaled, etc.), and time since administration, similar to alcohol guidelines.¹⁵ Considering THC doses above 5mg are also associated with poorer mental health outcomes,⁹ bringing therapeutic benefit into question, testing for this threshold is recommended. This would provide consumers with formal guidance for monitoring their risk of impairment and inform the development of tests that detect when guidelines are exceeded, rather than penalise legitimate MC users based on THC presence.

CLINICAL IMPLICATIONS OF FINDINGS

Current clinical guidelines recommend clinicians consider trialing MC with patients who have chronic pain conditions not responding to first line treatments,¹⁶ but acknowledge more evidence and education is needed for clinicians to put this into practice. Findings across this program of research contribute to the emerging evidence-base to inform decision making both in clinical practice and at the policy level. **Chapter 2** presented a systematic review of 64 MC studies published in the last decade and revealed overall HRQL improvements across patients prescribed non-synthetic MC. In all but one (97%) of prospective studies, statistically significant HRQL improvements were observed from 5 months up to 24 months across all chronic health conditions assessed. Overall, effect sizes of these improvements were considered clinically meaningful.

Findings from the studies presented in **chapters 4 and 5** suggested that prescribing MC in clinical practice may improve overall HRQL and alleviate symptoms of pain, fatigue, insomnia, anxiety, and depression in patients with chronic health conditions. These improvements (defined by MCIDs) were regarded large enough to be clinically meaningful in

practice, were apparent quickly, and, similar to studies with high-quality PRO reporting reviewed in **chapter 2**,¹⁷⁻²⁴ maintained long-term. As noted by Arkell et al, HRQL improvements were still observed in some studies where patients' underlying conditions remained unchanged (e.g. pain severity or anxiety).²⁵ HRQL improvement was also supported through analysis of patient interviews in **chapter 6**, showing long-term improvements in mental and social functioning beyond symptom reduction.

Considering 24.5% of participants in the study presented in **chapters 4 and 5** had used cannabis without a prescription prior to joining the study, prescribing MC may avoid potential risks of cannabis abuse by self-medicating while enabling clinicians to monitor possible adverse effects. As discussed in **chapter 6**, this patient-centred approach supports patient autonomy, self-determination, and improved long-term outcomes.²⁶ Patients should be provided relevant and timely information regarding all treatment options to make informed decisions about how to manage their health conditions. Ideally, this would include trialling MC at an earlier stage of treatment, rather than going through the process of trying conventional medications that could potentially introduce unwanted side-effects and prolong the burden of their health conditions.

Evidence on optimal CBD:THC ratios for different health conditions is emerging and will improve prescribing practices. The longitudinal study reported in **chapter 4 and 5** observed many patients changing MC products during the study period. After a titration period on the first product, some participants did not find benefits and were subsequently prescribed alternative MC products with different cannabinoid combinations. This variation of product types and cannabinoid content over time was also observed in other Australian studies.^{25,27} It is possible that a large proportion of participants who dropped out of the study and

discontinued MC following titration was due to MC product indications (optimal condition-specific cannabinoid combinations) not matching conditions treated. This possibly reflects a lack of clinician knowledge and evidence-based guidance in Australia concerning optimal cannabinoid combinations for different health conditions. Results from the meta-analyses of RCTs in **Chapter 2** suggest patients with fibromyalgia and Inflammatory Bowel Disease had HRQL improvements receiving THC. High quality evidence from RCTs suggested CBD-only reduces seizure frequency in epilepsy patients. However, in a real world setting there are concerns that unwanted side-effects may result from interactions with other anti-seizure medications.²⁸ Findings in **Chapter 5** suggest that THC-dominant daily dosages of MC oil were superior to THC:CBD balanced dosages for improving patient-reported depression and fatigue. Also, CBD-only dosages were not as effective as daily MC oil dosages containing THC for improving sleep disturbance. Furthermore, different cannabinoid combinations were associated with greater reduction in pain intensity depending on the pain type. For example, patients with musculoskeletal pain reported greater improvements with CBD-dominant daily dosages compared with CBD-only, and patients with headaches or cancer-related pain reported greater improvements with CBD-dominant dosages compared with balanced dosages of CBD and THC. These findings highlight the nuances of MC therapy and the need for individualised patient care. This may partly explain the real-world practice described by the Australian Health Practitioner Regulation Agency (AHPRA) that some clinicians were prescribing more than one product and leaving the patient to try each and discover what works.²⁹ Although discouraged by AHPRA, with careful medical oversight and incorporating the harm-reducing titration regimen, this may be a more patient-centred approach that empowers patients and reduces the burden placed on patients and clinicians from repeat appointments and delays identifying the optimal cannabinoid combination. However, the

high cost of MC products, as pointed out in **chapter 6**, would further burden patients having to purchase multiple items, particularly considering the short expiry date on many products. As evidence grows, clinicians will need to be provided with access to educational resources regarding MC; the cannabinoid combinations and products most likely to be beneficial for the more commonly treated chronic health conditions.

Chapter 6 revealed patients perceived many GPs as reluctant to prescribe MC, forcing patients to seek new GPs for MC specifically. The growing number of cannabis clinics in Australia is a point of concern for AHPRA, because a conflict of interest is introduced when clinicians work in a facility that only prescribes one medication.³⁰ This is not unique to Australia – findings from a US study suggested providers who were unwilling to partner with patients when seeking information about MC may be replaced by MC dispensaries, which may fail to properly account for a patient’s unique medical history and health care needs.³¹ Ideally, all GPs should be provided with the educational resources required to engage in shared decision making with patients and open conversations regarding MC. The WHO Comprehensive Mental Health Action Plan 2013-2030 outlines a patient-centred approach of listening and responding to individuals’ understanding of their condition and what helps them to recover, working with people as equal partners in their care, and offering choice of treatment and therapies.³²

STRENGTHS AND LIMITATIONS OF THE PROGRAM OF RESEARCH

A strength of this thesis is that all studies conducted across the program of research, and those reviewed in **chapter 2**, used non-synthetic cannabinoids (phytocannabinoids) derived from the cannabis plant, reflective of current MC products available in countries where MC

prescribing is legal. Plant-based MC, including full-spectrum MC oil, is considered therapeutically superior due to the ‘entourage effect’, where the combination of the many naturally occurring phytocannabinoids and terpenoids in the cannabis plant have been found to improve and broaden therapeutic benefits while ameliorating THC intoxication.³³ Furthermore, the studies covered in **chapters 4-6** followed participants across short-, medium-, and long-term follow-up with meta-analyses in **chapter 2** comparing studies with similar follow-up assessment periods. Another strength is the wide coverage of health conditions treated with MC evaluated across this program of research.

The studies in **chapters 4 and 5** were large enough to assess patients across a wide range of chronic conditions and socio-demographics in a real-world setting. Participants were recruited from more than 100 sites across Australia, covering most states and territories. As described in **chapter 3**, assessments involved validated, condition-relevant PROMs at clinically meaningful time-points allowing comparisons within groups over time, and between studies and patient groups. Clinical meaningfulness of findings was reported using predefined MCIDs, and findings confirmed MCIDs provided by PROM developers were aligned with Norman et al.’s MCID recommendation of half a standard deviation in patients with chronic conditions.³⁴ By using a homogenous selection of MC oils (LGP products) results were not confounded by the effects of different strains of cannabis plant or by different routes of administration. Unlike the large doses of CBD or THC often administered in RCTs,³⁵ participants were real-world patients who titrated to doses used in clinical practice. The differences observed between the two HRQL PROMs used throughout **chapters 4 and 5** supported and strengthened the message from **chapter 1** that researchers need clear

definitions of HRQL in the context of research objectives and patient population when selecting PROMs.

Generally, meta-analysis of observational studies should be interpreted cautiously, particularly over medium- and long-term assessment periods, due to possible attrition bias.³⁶ This was a limitation of findings in **chapters 4 and 5**, and the review in **chapter 2**, because participants remaining in observational studies are more likely those who are benefitting from therapy, inflating positive findings. While observational studies do more accurately reflect patient outcomes in practice, another limitation of findings across these chapters was that observational studies cannot associate their findings with MC efficacy, due to a lack of blinding or randomisation to control groups to mitigate bias and placebo effects. As reported in **chapter 2**, most of the observational studies reviewed (36/52) made no attempts to reduce the biasness of their results.

Finally, this program of research was limited to English language across the reviewed studies, PROMs used, and participants recruited. Although gender identity and ethnicity of included participants was diverse (Appendix 4 and 5), this limitation reduced generalisability to non-English speaking patients. Similarly, patients with lower socio-demographic status may have found the cost of MC products prohibitive, reducing their representation across MC studies more broadly.

CONSIDERATIONS FOR FUTURE RESEARCH

The program of research presented in this thesis has uncovered areas of research requiring further investigation. More research, ideally with RCTs, is needed to identify optimal MC cannabinoid combinations and methods of administration for improving condition-specific

symptoms for different chronic health conditions, including the different types of pain. Additionally, research into optimal THC levels for achieving therapeutic benefit without impairment-inducing intoxication based on age, weight, and sex, is required to establish standardised guidelines for consumers.¹⁵

Future research could explore whether there is an association between PROs and clinicians' training on the endocannabinoid system and their MC prescribing experience. This may be expanded for further studies evaluating the acceptability and implementation of different types of clinician educational resources (knowledge levels and delivery methods) on the endocannabinoid system. Currently, there are several specialized cannabis education providers accessible to clinicians in Australia, either industry-operated or through The Australian and New Zealand College of Cannabinoid Practitioners.

To ensure HRQL is measured and interpreted appropriately in future studies, researchers should provide definitions of HRQL in the context of their research and explain why it is being measured. Their choice of PROM should be justified following International Society for Quality of Life Research recommendations for minimum standards, which include: documented conceptual and measurement model; evidence for reliability and validity; interpretability of scores; quality translation, and acceptable patient and investigator burden.³⁷ Currently available cannabis-specific PROMs focus heavily on cannabis use side-effects and outcomes related to treating cannabis use disorders, rather than HRQL. More research is needed to determine the important side-effects and desired outcomes of MC therapy with the aim to inform the development of a core set of MC-specific HRQL PROMs. Following COSMIN guidelines, this would involve: conceptual considerations; finding existing PROMs through a systematic review or literature search; quality assessment of

measurement properties and feasibility; and generic recommendations on the selection of PROMs for each core outcome.^{38,39} While there may be a wide range of health conditions being treated, this thesis has revealed HRQL outcomes common across conditions that may be suitable for inclusion in such a core set of measures including key symptoms (e.g. pain, sleep, and anxiety); aspects of functioning, including social functioning; productivity; and reduced dependence on medications. A validated MC-specific HRQL PROM set would improve outcome comparisons across studies, and subsequent development of a health state classification system for MC-specific PROMs would facilitate health economic evaluations.

A critical look at Australia's policies concerning MC is warranted. Considering the current legislative position and regulatory framework, Australia is well-placed to establish a patient-centred MC policy and health-care model informed by the successes and failures of other nations globally. To achieve this, a systematic review of national MC policies and health care models comparing benefits, harms, and health economic outcomes internationally is needed.

CONCLUSIONS

HRQL encompasses multiple aspects of health status and functioning and is an important outcome for patients with chronic health conditions. This program of research found HRQL improvements in people with diverse chronic health conditions using MC. These benefits were clinically meaningful, apparent soon after commencing therapy, and maintained over the long-term. Patient-centred care involves working with patients to find treatments that align with their values and needs for treatment. Overall, the evidence supporting MC has

grown in recent years requiring a re-evaluation of clinical guidelines and policies to better inform communities and clinicians and facilitate a responsible integration of MC therapy into Australia's health-care model.

RECOMMENDATIONS FOR FUTURE RESEARCH, POLICY, AND CLINICAL PRACTICE

Taking the findings from this thesis into consideration, the following recommendations are proposed:

- MC researchers should report how HRQL is defined and assessed in the context of their studies and provide justifications for PROM selection. Reason: disparate HRQL findings between studies evaluating people with the same health condition can be reduced or qualified by adequately considering and addressing these aspects—
Chapters 1 - 5.
- Patients experiencing unwanted side-effects from conventional medications should be given the option of MC therapy. Reason: evidence suggests MC is an effective method for reducing patients' use of conventional medications for sleep, anxiety, depression, and opioids for pain. Over the long-term, chronic conditions may become more manageable, reducing overall dependence on medications generally. Offering choice of treatment and therapies, and discussing the costs, benefits and potential harms of each option, is a patient-centred approach that supports patient autonomy – **Chapters 5 and 6.**
- Clinicians should be able to offer MC as a first line treatment option for patients at risk of developing chronic pain. Reason: patients may be able to avoid the unwanted side-effects of opioids and their potential to prolong chronic pain. Patient-centred care involves shared decision-making where patients are given relevant and timely information to make informed decisions about how to manage their conditions –
Chapters 1 and 6.

- Make evidence-based educational resources more accessible to raise awareness of MC. Reason: patients and clinicians lack knowledge of MC efficacy, side-effects, and access pathways – **Chapter 6.**
- Implement formal medical school training on the endocannabinoid system and cannabinoid pharmacology. Reason: improved clinician knowledge of MC would improve clinician ability to effectively facilitate shared decision-making. Patients will be less likely to search for alternative doctors who may not fully understand the patient's health care needs. Whether prescribing MC or not, GPs need to understand the impact of MC therapy on their patients and be aware of possible contraindications with other prescribed medications - **Chapter 6.**
- Australian driving laws should be reviewed and revised to excuse drivers with MC prescriptions from facing criminal charges due to detection of trace levels of THC. Guidelines are needed using standard THC units and driving impairment tests designed accordingly. Reason: MC is a legitimate prescribed therapy, and evidence suggests driving impairment is less likely with regular MC use at therapeutically beneficial levels, and functioning is often improved for patients using MC. Patients with prescriptions should be treated equally and not face criminal charges based on their choice of medication – **Chapter 6.**
- A review of best-practice international MC policies and health care models is needed to inform practice in Australia. Reason: Australia is well-placed to establish a patient-centred MC policy and health-care model informed by the successes and failures of other nations globally – **Chapter 7.**

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Appendix

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APPENDIX 1: SUPPLEMENTARY MATERIAL

- CHAPTER 2

Referenced in the publication:

Online Resource 1: Medline (OVID) Search Strategy

Online Resource 2: PRO reporting criteria adapted from STROBE and CONSORT-PRO tools

Online Resource 3: Overview of 64 included studies

Online Resource 4: Health conditions of included studies participants

Online Resource 5: Completeness of PRO reporting for each study

Online Resource 6: Risk of Bias for each RCT included in the meta-analysis

Additional material:

PRISMA checklist

Online Resource 1: MEDLINE (Ovid) search strategy

-
1. Cannabis/
 2. Medical Marijuana/
 3. exp Cannabinoids/
 4. cannabi*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]
 5. marijuana.mp.
 6. CBD.mp.
 7. Tetrahydrocannabinol.mp.
 8. THC.mp.
 9. sativ*.mp.
 10. Phytotherapy/
 11. nabiximol.mp.
 12. hemp.mp.
 13. epidiolex.mp.
 14. phytocannabinoid.mp.
 15. 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14
 16. "Quality of Life"/
 17. "Surveys AND Questionnaires"/ OR patient reported outcome measures.mp. OR Patient Reported Outcome Measures/
 18. Symptom Assessment/ OR symptom*.mp.
 19. questionnaire.mp.
 20. HRQL.mp.
 21. HRQOL.mp.
 22. (health-related adj 'quality of life').mp.
 23. (patient* adj2 interview*).mp.
 24. 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23
 25. 15 AND 24
 26. limit 25 to (english language AND yr="2015 -Current")
 27. limit 26 to (humans AND "all adult (19 plus years)")
 28. 27 NOT (address OR autobiography OR bibliography OR biography OR clinical conference.pt OR clinical trial, veterinary OR clinical trials, veterinary as topic OR clinical trial protocol OR clinical trial protocols as topic OR comment OR congress OR consensus development conference OR consensus development conference, nih OR dictionary OR directory OR editorial OR english abstract OR "expression of concern" OR historical article OR interactive tutorial OR lecture OR legal case OR legislation OR letter OR news OR newspaper article OR observational study, veterinary OR patient education handout OR periodical index OR portrait OR randomized controlled trial, veterinary OR technical report OR video-audio media OR webcast).pt.
 29. 27 not 28
 30. limit 29 to (abstracts AND pharmacologic actions)
 31. 29 NOT 30
-

Online Resource 2: PRO reporting criteria adapted from STROBE and CONSORT-PRO tools.

1. Title and Abstract identifies study design and PROs

Study design indicated with a commonly used term in the title or the abstract (e.g. RCT or observational/prospective) AND the abstract summarises design, methods, results, and conclusions AND PROs are clearly identified in the abstract as a primary or secondary outcome.

2. Rationale for PRO assessment

Did the authors provide a background and rationale for PRO assessment?

Yes: The paper provided the background and rationale for the PRO assessment.

Partial: The paper cited some relevant PRO literature but did not provide a rationale for PRO assessment for this study.

No: The paper did NOT provide the background or rationale for the PRO assessment.

3. Hypotheses regarding PROs

Did the authors state the a priori objectives and /or hypotheses about PROs?

Yes: The PRO hypotheses/objective regarding relevant PRO domain(s) are explicitly stated.

Partial: PRO hypotheses/objective are implied but not explicitly stated.

No: PRO hypotheses/objective are neither implied nor stated.

4. Did the authors adequately justify and describe the PRO measures (PROM(s))?

Yes: Choice of PROM(s) is justified by their coverage of the relevant PRO domains. Evidence of reliability/validity of PROM(s) should be referenced. Scoring of items/questions into domains/scales should be described, along with direction of scores (e.g. higher scores equal better QOL).

Partial: Choice of PROM(s) is not justified; authors simply state which PROM(s) they used with a relevant reference (may or may not explicitly mention reliability/validity). Scoring not mentioned.

No: Choice of PROM(s) is not justified; authors simply state which PROM(s) they used with any references. Scoring not mentioned.

5. PRO Assessment - data collection methods

Did the authors adequately describe PRO data collection methods?

Yes: Authors describe how the PROM was administered, and when completed, e.g. “PROs assessed before treatment, 6-wks post, and 6-mths post. Trained nurse administered all questionnaires in clinic”; “patients completed PROs in clinic before treatment and then 6-wks after at home via online data collection platform”.

Partial: Some but not complete description of data collection methods.

No: Data collection methods not reported (i.e. it is not clear how the PRO was administered, by whom, and where or when it was completed).

6. Methods - Participant selection

Are the eligibility criteria, and the sources and methods of selection of participants and their groupings (e.g. random allocations, exposed/unexposed, criteria for matched controls) provided?

7. Sample size

Was sample size/power appropriate to detect PRO differences?

Yes: PRO sample size was justified in terms of a priori effect size (e.g. 0.5 SD) or mean difference, type I error rate (alpha), or power – or sample size calculation given in these terms.

Partial: Power justified post hoc [e.g. only mentioned “we had the power to detect differences”].

No: No sample size or power calculations mentioned or <10 participants in each treatment group.

8. Statistical methods

Were all statistical methods, including those used to control for confounding described?

(including adjustments for assessment of multiple PRO domains, e.g. Bonferroni)

9. Statistical considerations - missing data

Were statistical approaches for dealing with missing data explicitly stated?

Yes: The extent of missing data and statistical methods for dealing with missing data were both clearly stated.

Partial: The extent of missing data and statistical methods for dealing with it were vague or only one stated.

No: The study did not mention the extent of missing data or how missing data was handled.

10. PRO reporting - time points

Was a description (e.g. flow diagram) of participants through the study reported in relation to PROs, including information on the reason for missing PRO data?

Yes: PRO completion rates were reported for each time point, and reasons for missed assessments reported

Partial: PRO completion reported for some but not all time points AND/OR reasons missing NOT reported for each time point or are unclear.

No: no description of sample size for each timepoint.

11. PRO reporting - baseline characteristics

Did the authors adequately describe baseline sample characteristics for the PRO sample?

Yes: an informative set of baseline PRO demographic and clinical characteristics is reported for each health indication and medical therapy received (either in table or text).

Partial: Some baseline PRO demographic and clinical characteristics are reported, or an informative set but not at the level of indications and therapy.

No: No baseline/demographic information provided.

12. PRO reporting - domains

Were PRO results reported adequately for all domains? (e.g. mean and SD, median and IQR, or proportion cases above a cut-point. The estimated effect size and its precision such as 95% confidence interval should be presented for multidimensional PROs from each domain and time point.)

Yes: PRO results were reported for all PRO domains measured including effect size and 95%CI.

Partial: PRO results reported for some but not all domains measured (i.e. selective reporting, e.g. may report only statistically significant domains – prone to reporting bias).

13. Other analyses

Did they report other PRO analyses done—eg analyses of subgroups and interactions, and sensitivity analyses?

14. Limitations

Were PRO specific limitations and implications for generalizability addressed? For example, if PRO assessments are limited to a subgroup of the main study population, reasons why patients were excluded from the PRO study should be provided (such as where appropriate translations were unavailable). If PRO data are missing, it is particularly important to discuss the potential reasons in relation to the clinical context and implications for interpretation, e.g. "Non-completers at one year might have had a different symptom profile and overall quality of life than completers, and therefore some degree [of] selection bias is possible"

Yes: Identified sources of potential bias or imprecision when discussing PRO-specific limitations and implications, including both direction and magnitude of any potential bias.

Partial: Identified some PRO limitations and their implications.

No: Did not address PRO-specific limitations

15. Interpretation

Was PRO data interpreted in relation to clinical outcomes? Did they give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence?

Yes: Interpretation of PRO results include discussion of a minimal important change or a responder definition (e.g. >30% improvement on validated Pain scale) and clinical significance of PRO results were linked to the other trial outcomes such as adverse events, and comparisons made with other similar studies.

Partial: Partial interpretations and comparisons of PRO results.

No: Findings not supported by results; or findings clearly due to low power are reported as definitive evidence against the alternate hypothesis or interpreted favourably using statistical significance when findings may not be clinically important.

16. Bias

Did they describe any efforts to address potential sources of bias?

17. Discussion - Generalisability

Did they discuss the generalisability (external validity) of the study results?

18. Other information - Funding

Did they give the source of funding (or state no funding) and the role of the funders for the present study and, if applicable, for the original study on which the present article is based?

Online Resource 3. Overview of 64 included studies (ordered by year of publication)

1 st Author, year	Country	Title	Study Aims	Journal
Dickinson et al., et al., 2025	United Kingdom	UK Medical Cannabis Registry: An Analysis of Outcomes of Medical Cannabis Therapy for Hypermobility-Associated Chronic Pain	To evaluate clinical outcomes in patients with hypermobility spectrum disorder and hypermobile Ehlers-Danlos syndrome with chronic pain following MC treatment.	ACR Open Rheumatology
Varadpande et al., et al., 2025	United Kingdom	UK Medical Cannabis Registry: An Analysis of Clinical Outcomes of Medicinal Cannabis Therapy for Cancer Pain	To evaluate the change in PROMs of patients enrolled in the UKMCR prescribed MC for chronic pain management.	Journal of Pain and Palliative Care Pharmacotherapy
Datta et al., et al., 2025	United Kingdom	UK medical cannabis registry: A clinical outcome analysis of medical cannabis therapy in chronic pain patients with and without co-morbid sleep impairment	To assess PROMs following MC treatment in Chronic Pain patients with and without co-morbid sleep impairment.	Pain Practice
Tait M, et al., 2025	Australia	Improvements in health-related quality of life are maintained long-term in patients prescribed medicinal cannabis in Australia: The QUEST Initiative 12-month follow-up observational study.	To assess 12-month follow-up data to determine if our previously reported improvements at 3-months were maintained long-term and to explore differences across health conditions and MC compositions.	PloS one
Francis et al., 2024	United Kingdom	Assessment of Clinical Outcomes in Patients With Osteoarthritis: Analysis from the UK Medical Cannabis Registry	To evaluate pain-specific and general HRQL changes in patients with osteoarthritis using patient-reported outcome measures.	Journal of Pain and Palliative Care Pharmacotherapy
Gupta et al., 2024	United Kingdom	UK medical cannabis registry: an updated analysis of clinical outcomes of cannabis-based medicinal products for inflammatory bowel disease	To evaluate differences in PROMs for patients prescribed MC for IBD over an 18-month period using data collected from the UKMCR.	Expert Review of Gastroenterology and Hepatology
Sultan et al., 2024	United Kingdom	Controlled Inhalation of Tetrahydrocannabinol-Predominant Cannabis Flos Mitigates Severity of Post-Traumatic Stress Disorder Symptoms and Improves Quality of Sleep and General Mood in Cannabis-Experienced UK Civilians: A Real-World, Observational Study	To investigate the safety and effectiveness of THC-predominant cannabis flowers for inhalation to manage PTSD symptoms in a real-world setting.	Medical Cannabis and Cannabinoids
Stienrut et al., 2024	Thailand	Medical Cannabis Prescription Practices and Quality of Life in Thai Patients: A Nationwide Prospective Observational Cohort Study	To explore the prescribing patterns of traditional practitioners and assess the impact of cannabis oil on patients' quality of life, with a specific focus on comparing outcomes between cancer and non-cancer patients.	Medical Cannabis and Cannabinoids
Warner-Levy et al., 2024	United Kingdom	UK Medical Cannabis Registry: a cohort study of patients prescribed cannabis-based oils and dried flower for generalised anxiety disorder	To investigate real-world outcomes and safety of different MC formulations in GAD patients.	Expert Review of Neurotherapeutics
Lamonarca et al., 2024	Argentina	Psychiatric comorbidities before and after cannabidiol treatment in adult patients with drug resistant focal epilepsy	To evaluate, in the same patient population that was part of a previous observational study, depression, quality of life, anxious symptoms and daytime sleepiness before and after CBD treatment.	Epilepsy and Behavior

1 st Author, year	Country	Title	Study Aims	Journal
Li et al., 2024	United Kingdom	UK Medical Cannabis Registry: a case series analyzing clinical outcomes of medical cannabis therapy for generalized anxiety disorder patients	To analyze key changes in anxiety-specific and general HRQL outcomes and safety in patients with GAD prescribed a homogenous selection of MCs, to reduce the associated biases that otherwise affect UK Medical Cannabis Registry data.	International Clinical Psychopharmacology
Barre et al., 2024	France	Limited Impact of Cannabidiol on Health-related Quality of Life of People with Long-term Controlled HIV: A Double-blind, Randomized, Controlled Trial	To test whether oral CBD-rich medication could significantly improve people with HIV's HRQL.	Open Forum Infectious Diseases
Lent et al., 2024	United States	Changes in health-related quality of life over the first three months of medical marijuana use	To evaluate changes in eight domains of HRQL over the first three months of medical marijuana treatment.	Journal of Cannabis Research
Dujic et al., 2024	Croatia	Chronic Cannabidiol Administration Mitigates Excessive Daytime Sleepiness and Fatigue in Patients with Primary Hypertension: Insights from a Randomized Crossover Trial	To establish whether chronic CBD supplementation will improve self-reported outcomes related to quality of life.	Cannabis and Cannabinoid Research
Sridharan et al., 2024	United Kingdom	Comparison of Cannabis-Based Medicinal Product Formulations for Fibromyalgia: A Cohort Study	To analyze changes in general health-related quality of life (HRQoL) and fibromyalgia symptom severity assessed by PROMs.	Journal of Pain and Palliative Care Pharmacotherapy
Haupts et al., 2024	Germany	Patient-reported benefits from nabiximols treatment in multiple sclerosis-related spasticity exceed conventional measures	To investigate the effectiveness of nabiximols in a real-world setting for the treatment of MS spasticity using GAS as a primary measure of treatment success.	Neurodegenerative Disease Management
Lynskey et al., 2024	United Kingdom	Prescribed Medical Cannabis Use Among Older Individuals: Patient Characteristics and Improvements in Well-Being: Findings from T21	To describe the characteristics of older individuals (aged 65 years or older) seeking MCs in the UK, examine 3-month changes in measures of well-being (general health, quality of life, mood/depression and sleep) in this group and compare their characteristics and treatment outcomes with those in younger individuals.	Drugs and Aging
Brett et al., 2024	United States	An observational time-series study on the behavioral effects of adjunctive artisanal cannabidiol use by adults with treatment resistant epilepsies	To determine if independent adjunctive use of artisanal CBD was beneficial for adults with treatment resistant epilepsies.	BMC Neurology
Murphy et al., 2024	United Kingdom	Clinical outcome analysis of patients with multiple sclerosis - Analysis from the UK Medical Cannabis Registry	To assess changes in MS-specific and general HRQL outcomes alongside adverse event incidence in patients prescribed MCs for MS from the UK.	Multiple Sclerosis and Related Disorders
Vivek et al., 2024	United Kingdom	UK Medical Cannabis Registry: Assessment of clinical outcomes in patients with insomnia	To assess changes in sleep-specific HRQL for those prescribed cannabis-based medicinal products for insomnia.	Brain and Behavior
Murphy et al., 2024	United Kingdom	A cohort study comparing the effects of medical cannabis for anxiety patients with and without comorbid sleep disturbance	To compare the PROMs of patients prescribed MCs for GAD, with and without impaired sleep	Neuropsychopharmacology Reports

1 st Author, year	Country	Title	Study Aims	Journal
Aiewtrakoon et al., 2024	Thailand	Efficacy and Safety of Cannabidiol Oil on Chronic Insomnia: The First Randomized, Double-Blind, Placebo-Controlled, Crossover, Pilot Study in Thailand	To investigate the impact of a continuous four-week sublingual CBD intake on sleep indicators.	Journal of the Medical Association of Thailand
Kelley et al., 2024	United States	Observational Analysis of the Influence of Medical Marijuana Use on Quality of Life in Patients	To identify a potential relationship between cannabis use and quality of life measures including physical and emotional limitations, energy and fatigue, pain, and physical and social functioning.	Medical Cannabis and Cannabinoids
Francis et al., 2024	United Kingdom	Assessment of clinical outcomes in patients with inflammatory arthritis: Analysis from the UK Medical Cannabis Registry	To assess changes in validated PROMs after initiation of cannabis-based medicinal products and the safety of MC in patients with inflammatory arthritis.	International Clinical Psychopharmacology
Hershkovich et al., 2023	Israel	The role of cannabis in treatment-resistant fibromyalgia women.	To use the World Health Organization Quality of Life Bref questionnaire to characterize the impact of Cannabis Treatment initiation on the quality of life in women suffering from treatment-resistant fibromyalgia.	Pain practice
Vigano et al., 2023	Canada	The Quebec Cannabis Registry: Investigating the Safety and Effectiveness of Medical Cannabis.	To investigate the safety and effectiveness of medical cannabis in the real-world clinical practice setting.	Cannabis and cannabinoid research
Tait M, et al., 2023	Australia	Health-related quality of life in patients accessing medicinal cannabis in Australia: The QUEST initiative results of a 3-month follow-up observational study.	To assess overall HRQL, pain, fatigue, sleep, anxiety, and depression in a large real-world sample of patients accessing prescribed medicinal cannabis.	PloS one
Ergisi et al., 2023	United Kingdom	An Updated Analysis of Clinical Outcome Measures Across Patients From the UK Medical Cannabis Registry.	To analyze safety and the change in HRQL outcomes for all patients enrolled in the UKMCR who were prescribed MCs. Supplementary aims included evaluation of dosage regimens.	Cannabis and cannabinoid research
Arkell et al., 2023	Australia	Assessment of Medical Cannabis and Health-Related Quality of Life.	To assess whether patients using medical cannabis report improvements in health-related quality of life over time.	JAMA network open
Nathan et al., 2023	United States	Assessing Efficacy and Use Patterns of Medical Cannabis for Symptom Management in Elderly Cancer Patients.	To evaluate the effect of MC on the symptoms of this patient population. Secondary outcome measures include summary data on medical cannabis formulations and ratios used.	The American journal of hospice & palliative care
Hardy et al., 2023	Australia	Phase IIb Randomized, Placebo-Controlled, Dose-Escalating, Double-Blind Study of Cannabidiol Oil for the Relief of Symptoms in Advanced Cancer (MedCan1-CBD).	To assess whether CBD oil, when used in conjunction with standard palliative care, reduced symptom burden in patients with advanced cancer.	Journal of clinical oncology
Rifkin-Zybutz et al., 2023	United Kingdom	Clinical outcome data of anxiety patients treated with cannabis-based medicinal products in the United Kingdom: A cohort study from the UK medical cannabis registry.	To assess changes in anxiety symptoms as measured by the GAD-7 and the incidence of adverse events as collected by self-report form. The effect of type of MC product or previous cannabis experience influenced GAD-7 scores or the reporting of an adverse event was also analysed. The secondary aim was to investigate sleep quality and health-related quality of life outcomes.	Psychopharmacology

1 st Author, year	Country	Title	Study Aims	Journal
Tait J, et al., 2023	United Kingdom	Clinical outcome data of chronic pain patients treated with cannabis-based oils and dried flower from the UK Medical Cannabis Registry.	To evaluate changes in general HRQL, chronic pain-specific outcomes, and adverse events in patients treated exclusively with Cannabis-based medicinal products.	Expert Review of Neurotherapeutics
Bapir et al., 2023	United Kingdom	Comparing the effects of medical cannabis for chronic pain patients with and without co-morbid anxiety: A cohort study.	To compare the outcomes of chronic pain patients with and without co-morbid anxiety following MC treatment.	Expert Review of Neurotherapeutics
Nicholas et al., 2023	United Kingdom	UK medical cannabis registry: Assessment of clinical outcomes in patients with headache disorders.	To assess changes in validated PROMs.	Expert Review of Neurotherapeutics
Vickery et al., 2022	Australia	A large Australian longitudinal cohort registry demonstrates sustained safety and efficacy of oral medicinal cannabis for at least two years.	To analyse collected Patient MC dose, safety and validated outcome data.	PloS one
Aungsumart et al., 2021	Thailand	A pilot study of the government pharmaceutical organization (GPO) cannabis extract for multiple sclerosis (MS) spasticity treatment in Thailand	To evaluate the efficacy and safety of Government Pharmaceutical Organization cannabis extract in the treatment of spasticity in MS patients in Thailand.	Journal of the Medical Association of Thailand
Eibach et al., 2021	Germany	Cannabidivarin for HIV-Associated Neuropathic Pain: A Randomized, Blinded, Controlled Clinical Trial	To investigate cannabidivarin (CBDV) a novel phytocannabinoid derived from the Cannabis sativa L. plant, in patients with HIV-associated neuropathic pain.	Clinical Pharmacology & Therapeutics
Erridge et al., 2021	United Kingdom	An initial analysis of the UK Medical Cannabis Registry: Outcomes analysis of first 129 patients	To analyze the early outcomes of the first series of patients prescribed MCs in the UK with respect to effects on HRQL and clinical safety.	Neuropsychopharmacology Reports
Gruber et al., 2021	United States	No pain, all gain? Interim analyses from a longitudinal, observational study examining the impact of medical cannabis treatment on chronic pain and related symptoms	To examine patients using MC to treat chronic pain pre versus post MC treatment.	Experimental and Clinical Psychopharmacology
Kawka et al., 2021	United Kingdom	Clinical Outcome Data of First Cohort of Chronic Pain Patients Treated With Cannabis-Based Sublingual Oils in the United Kingdom: Analysis From the UK Medical Cannabis Registry	To investigate the HRQL outcomes of patients with chronic pain who were prescribed MC oil preparations.	Journal of Clinical Pharmacology
Lucas et al., 2021	Canada	Cannabis Significantly Reduces the Use of Prescription Opioids and Improves Quality of Life in Authorized Patients: Results of a Large Prospective Study	To identify the primary characteristics of a large national cohort of medical cannabis patients in Canada, including detailed patterns of cannabis use; to assess the impacts of regulated, physician-supervised MC access on prescription substance use and quality of life; and to analyze key variables potentially associated with changes in prescription drug use and quality of life over 6 months.	Pain Medicine

1 st Author, year	Country	Title	Study Aims	Journal
Meng et al., 2021	Canada	Patient-reported outcomes in those consuming medical cannabis: a prospective longitudinal observational study in chronic pain patients	To assess the impact of cannabis on pain intensity and pain-related interference for patients consuming cannabis for up to 12 months. Secondary aims were to identify associated changes in opioid consumption, mental health, quality of life, and general health symptoms.	Canadian Journal of Anesthesia
Naftali et al., 2021	Israel	Cannabis is associated with clinical but not endoscopic remission in ulcerative colitis: A randomized controlled trial	To assess the effect of cannabis in improving clinical and inflammatory outcomes in ulcerative colitis patients.	PLoS ONE
Peterson et al., 2021	United States	Measuring the Change in Health-Related Quality of Life in Patients Using Marijuana for Pain Relief	To determine if there is a relationship between HRQL and MC use in patients using it to relieve pain.	Medical Cannabis and Cannabinoids
Schloss et al., 2021	Australia	A Phase et al., 2 Randomised Clinical Trial Assessing the Tolerability of Two Different Ratios of Medicinal Cannabis in Patients With High Grade Gliomas	To investigate the tolerability of two different ratios of oral medicinal cannabis oil in patients who have been diagnosed with high grade gliomas as an adjunct to standard treatment.	Frontiers in Oncology
Naftali et al., 2021	Israel	Oral CBD-rich Cannabis Induces Clinical but Not Endoscopic Response in Patients with Crohn's Disease, a Randomised Controlled Trial	To evaluate efficacy of oral use of cannabis oil rich in CBD for induction of clinical, laboratory, and endoscopic remission in mild-to-moderate Crohn's disease.	Journal of Crohn's & colitis
Capano et al., 2020	United States	Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in chronic pain patients: a prospective cohort study	To investigate the impact of full hemp extract cannabidiol (CBD) on opioid use and quality of life indicators among chronic pain patients.	Postgraduate Medicine
Chaves et al., 2020	Brazil	Ingestion of a THC-Rich Cannabis Oil in People with Fibromyalgia: A Randomized, Double-Blind, Placebo-Controlled Clinical Trial	To determine the benefit of a tetrahydrocannabinol (THC)-rich cannabis oil on symptoms and quality of life of fibromyalgia patients.	Pain Medicine
Gulbransen et al., 2020	New Zealand	Cannabidiol prescription in clinical practice: An audit on the first 400 patients in New Zealand	To review the changes in self-reported quality of life measurements, drug tolerability, and dose-dependent relationships in patients prescribed CBD oil for various conditions at a single institution.	BJGP Open
Safakish et al., 2020	Canada	Medical cannabis for the management of pain and quality of life in chronic pain patients: A prospective observational study	To evaluate the short-, and long-term effects of plant-based MC on outcomes of interest related to pain, quality of life, tolerability, and opioid medication use in a large cohort of chronic pain patients using medical cannabis over the course of one year.	Pain Medicine
Bar-Sela et al., 2019	Israel	Cannabis-related cognitive impairment: a prospective evaluation of possible influences on patients with cancer during chemotherapy treatment as a pilot study	To evaluate the effect of cannabis consumption on cognitive abilities as well as on symptom relief in patients with cancer during chemotherapy treatment.	Anti-Cancer Drugs
Gaston et al., 2019	United States	Quality of life in adults enrolled in an open-label study of cannabidiol (CBD) for treatment-resistant epilepsy	To compare QOL at baseline and after 1 year of treatment with CBD.	Epilepsy and Behavior

1 st Author, year	Country	Title	Study Aims	Journal
Palmieri et al., 2019	Italy	Spontaneous, anecdotal, retrospective, open-label study on the efficacy, safety and tolerability of cannabis galenical preparation (Bedrocan)	To investigate the short-term therapeutic effects, safety/tolerability and potential side effects of the cannabis galenical preparation (Bedrocan) in patients with a range of chronic conditions unresponsive to other treatments.	International Journal of Pharmacy Practice
Ueberall et al., 2019	Germany	Effectiveness and tolerability of THC:CBD oromucosal spray as add-on measure in patients with severe chronic pain: Analysis of 12-week open-label real-world data provided by the German pain e-registry	To assess 1)analgesic effects by using a composite responder definition that incorporates response- and relief-rates of a combination of nine different patient-reported/relevant parameters (such as pain intensity, pain-related disabilities with respect to daily life activities, sleep, overall well-being, physical and mental quality-of-life, depression, anxiety and stress),and 2) to evaluate prevalence and spectrum of treatment-emergent adverse events in response to MC as add-on treatment to pre-existing analgesic medications.	Journal of Pain Research
Markova et al., 2019	Czech Republic	Sativex as add-on therapy vs. further optimized first-line ANTispastics (SAVANT) in resistant multiple sclerosis spasticity: a double-blind, placebo-controlled randomised clinical trial	To evaluate the efficacy of MC oromucosal spray (Sativex) as add-on therapy to optimised standard antispasticity treatment in patients with moderate to severe MS spasticity.	International Journal of Neuroscience
Irving et al., 2018	United Kingdom	A Randomized, Double-blind, Placebo-controlled, Parallel-group, Pilot Study of Cannabidiol-rich Botanical Extract in the Symptomatic Treatment of Ulcerative Colitis	To investigate the efficacy and safety of MC, CBD-rich botanical extract treatment, in patients with mild to moderate Ulcerative Colitis which had proved refractory to 5-ASA therapy.	Inflammatory Bowel Diseases
Gruber et al., 2016	United States	Splendor in the grass? A pilot study assessing the impact of medical marijuana on executive function	To assess the impact of 3 months of MC treatment on executive function, exploring whether MC patients would experience improvement in cognitive functioning, perhaps related to primary symptom alleviation.	Frontiers in Pharmacology
Haroutounian et al., 2016	Israel	The Effect of Medicinal Cannabis on Pain and Quality-of-Life Outcomes in Chronic Pain: A Prospective Open-label Study	To determine the long-term effect of MC treatment on pain and functional outcomes in participants with treatment-resistant chronic pain.	Clinical Journal of Pain
Haupts et al., 2016	Germany	Influence of Previous Failed Antispasticity Therapy on the Efficacy and Tolerability of THC:CBD Oromucosal Spray for Multiple Sclerosis Spasticity	To determine whether antispasticity treatment history influenced the efficacy and safety of add-on MC oromucosal spray in MS spasticity patients.	European Neurology
Russo et al., 2016	Italy	Should we care about sativex-induced neurobehavioral effects? A 6-month follow-up study	To characterize effects of 1- and 6-month Sativex administration in cannabis-naïve MS patients including neurobehavioral function, tolerability, possible abuse, and effects on QoL and motor functions.	European Review for Medical and Pharmacological Sciences
Russo et al., 2016	Italy	Evaluating Sativex R in Neuropathic Pain Management: A Clinical and Neurophysiological Assessment in Multiple Sclerosis	To investigate the role of Sativex in improving pain in MSs patients.	Pain Medicine

1 st Author, year	Country	Title	Study Aims	Journal
Vermersch et al., 2016	Italy	Tetrahydrocannabinol: Cannabidiol oromucosal spray for multiple sclerosis-related resistant spasticity in daily practice	To collect data from everyday clinical practice concerning the effectiveness and tolerability of MC.	European Neurology
Ware et al., 2015	Canada	Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS)	To evaluate safety issues in patients with chronic pain using cannabis as part of their pain management regimen.	Journal of Pain

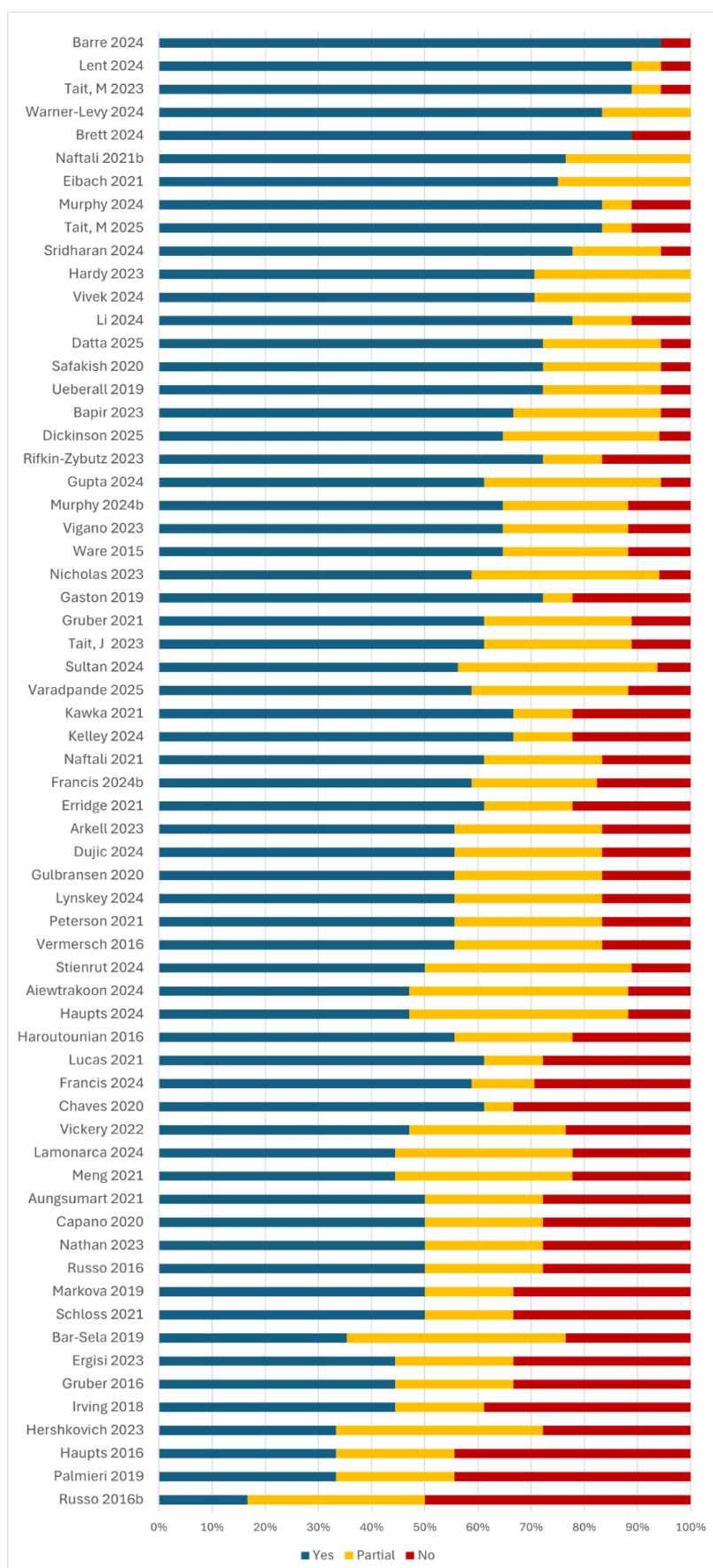
CBD, cannabidiol; GAD, generalised anxiety disorder; HRQL, Health-related quality of life; IBD, inflammatory bowel disease; MC, Medicinal Cannabis; MS, Multiple Sclerosis; PROM, patient reported outcome measure; PTSD, Post-Traumatic Stress Disorder; QOL, Quality of Life; RCT randomised controlled trial; THC, tetrahydrocannabinol; UKMCR, UK Medical Cannabis Registry

Online Resource 4: Health conditions of participants treated with Medicinal Cannabis (MC) in included studies.

	Health conditions of participants treated with MC	Number of studies recruiting participants with health condition
1	Agoraphobia	3
2	Alcohol use disorder	1
3	Alzheimer syndrome	3
4	Amyotrophic lateral sclerosis	1
5	Anorexia and wasting	6
6	Anxiety disorder	16
7	Arthritis / Osteoarthritis	7
8	Attention deficit / hyperactivity disorder	6
9	Autism	6
10	Back pain	4
11	Behavioral disorder	2
12	Benzodiazepine dependence	2
13	Bipolar disorder	2
14	Brain injury	2
15	Cancer symptoms	16
16	Cardiovascular disease	1
17	Chemotherapy-induced nausea and vomiting	5
18	Chronic fatigue	2
19	Chronic gum disease	1
20	Chronic kidney disease	2
21	Chronic neuropathic pain	9
22	Chronic pain	24
23	Complex regional pain syndrome	6
24	Congenital Adrenal Hyperplasia	1
25	Dementia	2
26	Depression	11
27	Diabetes	2
28	Dyslipidemia	1
29	Dysmenorrhea	1
30	Dystonia	2
31	Eating disorder	3
32	Ehlers-Danlos	3
33	Endometriosis	2
34	Epilepsy	13
35	Fibromyalgia	8
36	Gastrointestinal disorder	3
37	Glaucoma / intraocular eye pressure	4
38	Hashimoto's thyroiditis	1
39	Hereditary spastic paraplegia	2
40	HIV	2
41	Hypertension	2
42	Inflammatory Bowel Disease (ulcerative colitis and Crohn's disease)	14
43	Irritable bladder syndrome	1
44	Irritable bowel syndrome	3
45	Memory loss	1
46	Migraine/headache	11
47	Motor neuron disease	2
48	Movement disorder	1

49	Multiple Sclerosis	15
50	Multiple system atrophy	1
51	Narcolepsy	1
52	Nystagmus	1
53	Obsessive compulsive disorder	5
54	Opioid use disorder	2
55	Osteomyelitis	1
56	Palliative Care	3
57	Panic disorder	3
58	Parkinson disease	7
59	Perimenopause	1
60	Polymyalgia rheumatica	1
61	Posttraumatic stress disorder	12
62	Premenstrual dysphoric disorder	1
63	Psychiatric disorders	1
64	Refractory nausea and vomiting	6
65	Restless legs syndrome	1
66	Severe eczema	1
67	Sleep disorder / insomnia	12
68	Spasticity	4
69	Stress	1
70	Stroke	2
71	Substance use disorder	1
72	Tic disorder	2
73	Tinnitus	2
74	Topical steroid withdrawal syndrome	1
75	Tourette syndrome	3
76	Tremors	6
77	Vaginismus	1

Online Resource 5: Completeness of PRO reporting for included studies assessed with the revised PRO checklist (combining STROBE/CONSORT-PRO checklists). Ratings displayed as % of total criteria met.



Online Resource 6: Judgement on risk of bias (RoB 2) items for each randomised controlled trial included in meta-analysis (n=8).

	Randomisation process	Deviations from intended interventions	Missing outcome data	Outcome measurement	Selection of reported result	Overall risk-of-bias judgement
Barre 2024	-	-	+	+	-	-
Chaves 2020	+	+	+	+	-	-
Dujic 2024	-	-	-	+	+	-
Hardy 2023	+	+	+	+	+	+
Haupts 2016	-	+	+	+	+	-
Irving 2018	+	+	+	+	+	+
Naftali 2021	+	-	+	+	-	-
Naftali 2021b	+	+	+	+	-	-

+	Low
-	Some concerns
X	High



PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	4-6
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	6
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	7
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	6-7
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	suppl. 1
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	7
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	8-9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	7-9
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	8
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	9
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	9
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	9-10
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	9-10
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	9
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	9-10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	10
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	10
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	29-30
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	9



PRISMA 2020 Checklist

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Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	11
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	22-25
Study characteristics	17	Cite each included study and present its characteristics.	table 1, supp 3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	21, fig 4, supp 6
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	fig 5-8
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	21-22
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	fig 5-8
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	22-26
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	23-26
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	29-30
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	22-26
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	27-29
	23b	Discuss any limitations of the evidence included in the review.	29
	23c	Discuss any limitations of the review processes used.	28
	23d	Discuss implications of the results for practice, policy, and future research.	29-30
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	6
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	6/PROSPERO
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	6/PROSPERO
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	30
Competing interests	26	Declare any competing interests of review authors.	31
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Suppl 2

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: <http://www.prisma-statement.org/>

APPENDIX 2: INVITATIONS, PARTICIPANT INFORMATION, AND SAP - CHAPTERS 3-6

Subject: Research Invitation: Quality of Life and Medicinal Cannabis

We invite you to participate in our research study to understand how symptoms and quality of life change over time in people accessing medicinal cannabis.

The study will be conducted by researchers at the University of Sydney. We are looking for people who have received a prescription for medicinal cannabis to complete a series of online questionnaires about quality of life issues. Participants complete questionnaires before starting medicinal cannabis treatment, 2 weeks after starting treatment, then every 1 – 2 months for up to 1 year. It can take about 30 minutes to complete questionnaires on each occasion. **Please read the information sheet attached to this email.** This provides detailed information about the study and what is involved to help you decide whether you would like to take part.

After reading the attached form, use the link below to go to the consent form where you can either agree to take part in the study and begin the first questionnaire, or you can choose 'opt out' if you do not wish to take part.

Your participation is completely voluntary and if you do not wish to take part this will not affect the care that you are currently receiving.

Thank you for considering participating in this important study.

You may open the consent form by clicking the link below:

[Online Consent Form \(or opt-out\)](#)

If the link above does not work, try copying the link below into your web browser:

https://redcap.sydney.edu.au/surveys/?s=SAMPLE_LINK

This link is unique to you and should not be forwarded to others.

Subject: Research Invitation: QUEST follow-up interviews

I am writing to invite you to participate in a follow-up interview to explore your experiences of being prescribed medicinal cannabis.

You are receiving this invitation because you participated in the QUEST Initiative study and indicated on your consent form that you agreed to be contacted by email about future medicinal cannabis studies.

This study will be conducted by researchers at the University of Sydney. We are looking for QUEST study participants who have received a prescription for medicinal cannabis within the last 6 months to be interviewed about their experiences and quality of life issues. Interviews will take about 30-45 minutes and will be conducted via Zoom teleconferencing or by telephone, depending on your preference. **Please read the information sheet attached to this email.** This provides detailed information about the study and what is involved to help you decide whether you would like to take part.

After reading the enclosed information sheet, please contact me on (02) 8627 1558 or by email: margaret-ann.tait@sydney.edu.au if you would like to participate in the study, or if you have any questions.

Your participation is completely voluntary and if you do not wish to take part this will not affect the care that you are currently receiving.

Thank you for considering participating in this important study.

Kind regards,

Margaret-Ann Tait
Project Manager, The QUEST Initiative
Research Manager, Quality of Life Office, University of Sydney



Quality of Life Office
School of Psychology
Faculty of Science

ABN 15 211 513 464

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Web: <http://www.sydney.edu.au/>

The QUEST initiative: QUality of life Evaluation Study
Assessing Health Related Quality of Life in patients receiving medicinal cannabis

PARTICIPANT INFORMATION STATEMENT

(1) What is this study about?

People accessing medicinal cannabis may have a range of conditions and symptoms that impact their quality of life. We would like to know how these conditions and symptoms impact quality of life and if this changes over time. The results from this study will help future patients with these conditions make decisions about their treatment.

You are invited to participate in this study because you are being prescribed medical cannabis. This Participant Information Statement tells you about the research study to help you decide if you want to take part. Please read this sheet carefully and ask questions about anything that you don't understand or want to know more about.

Participation in this research study is voluntary.

By giving your consent to take part in this study you are telling us that you:

- ✓ Understand what you have read.
- ✓ Agree to take part in the research study as outlined below.
- ✓ Agree to the use of your personal information as described.

(2) Who is running the study?

The study is being carried out by the following researchers:

- Dr Claudia Rutherford, Senior Research Fellow, School of Psychology, University of Sydney
- Ms Margaret-Ann Tait, Senior Research and Administration Officer, School of Psychology, University of Sydney

Margaret-Ann Tait is conducting this study for the degree of Doctor of Philosophy at The University of Sydney. This will take place under the supervision of Dr Claudia Rutherford.

This study is being funded by Little Green Pharma Ltd.

(3) What will the study involve for me?

Your doctor will identify if the study is suitable for you and enter some basic information about you into the study register. This includes your age, sex, health condition, and which medicinal cannabis product you are receiving. We will not collect any information that can identify you such as your name, physical address, or birth date.

You will be sent a link via email to join the study. When you open the link you will be asked if you consent to taking part.

If you decide you **do not** want to take part, select 'opt-out'. Your email address will be removed from the study. If you do not open the link, two reminders will be sent to you, after which you will automatically 'opt-out' and your email address will be removed from the study.

If you **do** wish to take part in the study, select 'yes'. After selecting 'yes' you can proceed to the first questionnaire. You will then receive emails to complete follow-up questionnaires when they are due.

The online questionnaire pack starts with some general information about you. For example, this information includes your living arrangements, whether you are employed, and what other medications you may be taking. This information is for research purposes only and will not be shared with your doctor.

You will then be asked about your quality of life and symptoms. Completing questionnaires involves choosing an answer to a set of questions. An example of a question that you might be asked is:

During the <u>past week</u> : (select the number response that best applies to you)	Not at all	A little	Quite a bit	Very much
	1	2	3	4
Have you had trouble sleeping?	1	2	3	4

Your completed questionnaire will be used only by researchers involved in the project and will be stored securely in Australia on the University of Sydney's servers.

You will complete the questionnaires on your own in English without interpretation from others.

(4) How much of my time will the study take?

You will complete questionnaires at the time you join the study, and then again at 2 weeks after starting medicinal cannabis therapy, monthly for 3 months, then every two months (i.e. 5, 7, and 9 months after starting medicinal cannabis therapy), and once again at 12 months. Questionnaires will take approximately 30 minutes to complete.

(5) Who can take part in the study?

You CAN take part in the study if:

- you are an adult (aged ≥ 18 years)
- you are able to read and understand English
- you are able to provide informed consent
- you have a life-expectancy of more than 3 months

- you have been identified as eligible to receive medicinal cannabis by a TGA approved Authorised Prescriber, or doctor using the special access scheme (SAS-B) (or equivalent in other countries and jurisdictions) and your prescribing doctor has TGA approval to prescribe Little Green Pharma products.
- you have:
 - not received any prescribed medicinal cannabis therapy in the previous 4 weeks, **or**
 - you have started prescribed medicinal cannabis therapy (Little Green Pharma product), within the previous 2 days and not received any prescribed medicinal cannabis therapy in the previous 4 weeks

You CANNOT take part in the study if you:

- are unconscious, confused or cognitively impaired
- are pregnant or breastfeeding
- are unable to speak, read and/or write in English
- are denied access to medicinal cannabis under the relevant Special Access Scheme in your country
- are unable to provide informed consent
- are currently receiving prescribed medicinal cannabis treatment for more than 2 days
- have received prescription medicinal cannabis within the last 4 weeks (excluding previous 2 days)

(6) Do I have to be in the study? Can I withdraw from the study once I've started?

Being in this study is completely voluntary and you do not have to take part. Your decision whether to participate will not affect your current or future relationship with the researchers or anyone else at the University of Sydney, and it will not affect your current or future treatment at the clinic you are having treatment or relationships with your doctor or treating team.

If you decide to take part in the study and then change your mind later, you can withdraw at any time by contacting the doctor who prescribed medicinal cannabis. If you withdraw from the study, you will no longer receive the study participant discount on the cost of your medicinal cannabis prescription.

Submitting your completed questionnaire is an indication of your consent to participate in the study. You can withdraw your responses from the study before the data has been analysed. After that point your data cannot be removed and will be included in the study.

(7) Are there any risks or costs associated with being in the study?

Aside from giving up your time, we do not expect that there will be any risks or costs associated with taking part in this study.

(8) Are there any benefits associated with being in the study?

Little Green Pharma have agreed to standardise the cost of their products across Australia and UK so that all patients taking part in this study will be charged the same discounted rate. The cost of medicinal cannabis products for participants will be set at **AUD150.00 per unit (bottle)**, plus delivery fee of \$15.00. If you withdraw from the study, you may not receive the study participant discount on the cost of your medicinal cannabis prescription.

(9) What will happen to information about me that is collected during the study?

By providing your consent, you agree to us collecting personal information about you for the purposes of this research study. Personal and health information may include your age, health conditions, and the treatments that you have received. Your information will only be used for the purposes outlined in this Participant Information Statement, unless you consent otherwise.

All study information will be collected via the University of Sydney research data capture system, REDCap, a secure web application that runs on The University of Sydney's servers, ensuring data stays within the Sydney University data centre. Information will be stored electronically on the Research Data Store (RDS), a secure, password-protected server at the University of Sydney for at least 5 years, only accessible by the researchers, Dr Rutherford and Ms Tait. Any information that may identify you (such as email addresses) will be kept strictly confidential, except as required by law. Study findings may be published, but no individual participant will be identified in these publications.

We intend to give the information from this project to other researchers so that they can use it in their projects. Before we do so, we will take out all the identifying information so that the people we give it to won't know whose information it is. They won't know that you participated in the project and they won't be able to link you to any of the information you provided.

(10) Can I tell other people about the study?

Yes, you are welcome to tell other people about the study.

(11) What if I would like further information about the study?

If you would like more information about the study, please contact Margaret-Ann Tait at margaret-ann.tait@sydney.edu.au or phone +61 2 8627 1558.

(12) Will I be told the results of the study?

You can tell us that you wish to receive feedback by ticking the relevant box on the consent form. After the study is finished, you will be emailed a one page summary of the overall results.

(13) What if I have a complaint or any concerns about the study?

Research involving humans in Australia is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this study have been approved by the HREC of the University of Sydney [Project number: 2020/589]. As part of this process, we have agreed to carry out the study according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect people who agree to take part in research studies.

If you are concerned about the way this study is being conducted or you wish to make a complaint to someone independent from the study, please contact the university using the details below. Please quote the study title and protocol number.

The Manager, Ethics Administration, University of Sydney:

- **Telephone:** +61 2 8627 8176
- **Email:** human.ethics@sydney.edu.au
- **Fax:** +61 2 8627 8177 (Facsimile)

This information sheet is for you to keep



Interview Participant Information Sheet

The QUEST Initiative: Follow-up Interview Study

A/Prof Claudia Rutherford

Sydney Nursing School, Faculty of Medicine and Health

Email: claudia.rutherford@sydney.edu.au

Ms Margaret-Ann Tait (PhD Student)

Phone: +61 2 86271558 | Email: margaret-ann.tait@sydney.edu.au

1. What is this study about?

You are invited to take part in an interview for a research study exploring the experiences of patients being prescribed medicinal cannabis. The aim of the study is to gain a deeper understanding of the impacts of being prescribed medicinal cannabis from the perspective of patients and to identify the issues they consider important when managing their health condition. The findings will be used to enhance scientific evidence and inform future patients about the impact of treatment, which may assist them to make better informed treatment decisions.

2. Who is running the study?

The study is being conducted by the following researchers:

- Claudia Rutherford, Associate Professor, University of Sydney
- Margaret-Ann Tait, Doctor of Philosophy student, University of Sydney
- Kate White, Professor of Cancer Nursing, University of Sydney and SLHD

The study is being conducted by Margaret-Ann Tait as part of the requirements for a Doctor of Philosophy degree under the supervision of A/Professor Claudia Rutherford and Professor Kate White.

This Participant Information Sheet will tell you what is involved in the study and help you decide whether or not you wish to take part. Please read this information carefully.

If there is anything you do not understand or if you feel you need more information, please contact Margaret-Ann Tait, phone +61 2 8627 1558 or email: margaret-ann.tait@sydney.edu.au

3. What will happen to information that is collected?

If you agree to participate, you will be required to provide your name and email address or phone number so that we can contact you for the interview. Your personal information will only be used to contact you for this purpose. Your contact details will be stored securely in a database

that will be password protected. Only the researchers will have access to this information.

The interview will be audio recorded and transcribed (typed out). When we transcribe your interview, any information that could identify you (such as your name) is removed. The recordings and transcripts will be labelled with a study ID and stored on a secure, password-protected server, accessible by only the research team.

We may use some direct quotes from the interview transcripts in our study reports, publications, and presentations of the results. Nothing that could identify you will ever be included in any of the outputs from this study.

Once the study is completed, interview recordings and transcripts will be securely stored electronically for a minimum of five years on a password protected server at University of Sydney. After five years, all study materials will be permanently deleted from the server.

4. Who can take part in the study?

You are eligible to participate if you participated in the QUEST Initiative study and received a prescription for medicinal cannabis within the last 6 months.

5. What will the study involve for me?

Participation will involve being interviewed about your experience of being prescribed medicinal cannabis. You will be asked about how you felt before starting therapy, your experience of medicinal cannabis therapy, and how you manage your health condition.

If you are interested in participating in an interview, please contact Margaret-Ann Tait directly by email: margaret-ann.tait@sydney.edu.au or phone: +61 2 8627 1558. If you agree to participate, you will be asked to arrange a suitable time to be interviewed by Zoom videoconferencing or telephone.

An online consent form will be emailed to you before your scheduled interview. If you agree to participate, you will be asked to read and sign the online consent form. By giving consent to take part in this study you are telling us that you:

- Understand what you have read
- Agree to take part in the research as outlined in this document
- Agree to the use of your personal information as described in this document

The interview will be conducted by Margaret-Ann Tait and will take approximately 30-45 minutes.

6. Can I withdraw once I've started?

Participation in this study is completely voluntary and you do not have to take part. Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your relationship with any members of the research team.

If you take part in an interview you may refuse to answer any questions that you do not wish to answer. If you decide to stop the interview early, the interviewer will ask you whether you wish to discard existing interview data up to that point. You can either choose to withdraw your

participation but allow the study team to retain the data already collected or choose to discard all information collected to that point. There are no consequences to your decision. The interviewer will securely delete your details, and any interview recordings will be erased if you choose the latter.

Please note that after your interview has been transcribed and analysed, it cannot be withdrawn. This is because the analysed data does not contain any identifying information, and we will not be able to tell which one yours is.

7. Are there any risks or costs?

Aside from giving up your time there are no costs associated with taking part in this study.

Discussing your experiences may cause you to feel some distress. If you feel distressed at any point during the interview you can ask to take a break or to stop the interview. If you feel you need to talk to someone about your feelings, you can contact Lifeline (13 11 14) or Beyond Blue (1300 22 4636).

www.beyondblue.org.au/about-us/contact-us

<https://www.lifeline.org.au/about-lifeline/contact-us>

8. Are there any benefits?

There are no direct benefits to you from your participation in the study. However, the information collected through this study will help improve future patients make better informed treatment decisions.

9. Will I be told the results of the study?

You have a right to receive feedback about the overall results of this study. You can indicate if you are interested in receiving feedback by providing your email address on the consent form. This feedback will be in the form of a brief lay summary.

10. What if I have a complaint or any concerns?

The ethical aspects of this study have been approved by the Human Research Ethics Committee (HREC) of The University of Sydney [HREC Approval No. 2020/589] according to the *National Statement on Ethical Conduct in Human Research (2007)*.

If you are concerned about the way this study is being conducted or you wish to make a complaint to someone independent from the study, please contact the University:

Human Ethics Manager

human.ethics@sydney.edu.au

+61 2 8627 8176

This information sheet is for you to keep



Detailed Statistical Analysis Plan (SAP)

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1. Administrative Information

1.1. Title, registration, versions, and revisions

Full study title	The QUEST initiative – QQuality of life Evaluation Study Assessing Health Related Quality of Life in patients receiving Medicinal Cannabis
Acronym	The QUEST Initiative
Australian New Zealand Clinical Trials Registry (ANZCTR) number	12621000063819
Study Protocol Version	3.0 (02 February 2021)
SAP version	1 (30 August 2022)
SAP revision history	2 (8 August 2023)
SAP revision justification	This revision includes detailed SAP for secondary objectives at 12-month follow-up.
SAP revision timing	1. Revision will be conducted after publishing the 3-month follow-up manuscript. This revision includes detailed SAP for secondary objectives at 12-month follow-up. 2. Further revision will be conducted after publishing the 12-month follow-up manuscript. This revision will concern detailed SAP for exploratory objectives at 12-month follow-up for future papers.

1.2. Roles and Responsibility

Author	Margaret-Ann Tait ^{1,2}
Statistician	Margaret-Ann Tait ^{1,2}
Supervising Statistician	Daniel Costa ¹
Principal investigator	Claudia Rutherford ²
Contributors and roles	Daniel Costa ¹ , contributed to design and revised the SAP. Rachel Campbell ¹ , revised the SAP.

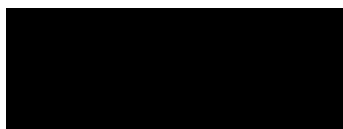
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1.3. Signatures

We the undersigned, certify that we read this SAP and approve it as adequate in scope of the main analyses of The QUEST Initiative.

1.3.1. Author

Name: Margaret-Ann Tait



.....

Date: 08 August 2023

1.3.2. Statistician

Name:

.....

Date:

1.3.3. Principal Investigator

Name:

.....

Date:

2. Introduction

2.1. Background

Although cannabis was used as a medicine as far back as 2600 BC¹, the scientific identification of cannabinoids, cannabidiol (CBD) and Δ^9 -tetrahydrocannabinol (THC), as analgesics in 1940 reignited interest in cannabis-based medicine as adjunctive treatment for the symptomatic relief of chronic pain.¹ The past two decades have seen a resurgence in cannabis research particularly in response to growing concerns around the misuse and adverse events associated with opioids.² Consequently, a number of countries have introduced legislation to allow the use of cannabis for medicinal purposes, despite previously criminalizing its consumption.

The Australian Therapeutic Goods Administration (TGA) currently approves Special Access Scheme (SAS) applications from health care providers who provide a clinical justification for prescribing medicinal cannabis where conventional therapies have failed.[8] There are no TGA-imposed restrictions on the types of health conditions; however, prescriptions are more commonly sought for chronic pain and spasticity from neurological conditions.

2.1.2. Patient-reported outcomes and health-related quality of life

Quality of life is a key consideration for patient-centred care. The term *health-related quality of life* (HRQL) is used in health settings where definitions of quality of life relate to the impact of disease or treatment.

In clinical studies, a widely accepted definition of HRQL is:

“a multidimensional construct encompassing perceptions of the impacts – positive and negative - of a disease or its treatment on physical, emotional, social, and cognitive functions, as well as somatic discomfort and other symptoms.”³

Another key term is patient-reported outcome (PRO), defined as:

“a measurement of any aspect of a patient’s health status that comes directly from the patient, without interpretation of the patient’s responses by a clinician or research associate”.⁴

PROs are regarded as the gold standard for assessing pain⁵, and are particularly important endpoints to include when assessing patients with chronic conditions where the primary aim is to palliate symptoms.⁶ PROs encompass symptoms of disease, side-effects of treatment, psychological symptoms and various aspects of functioning (e.g. physical, role, social, sexual). HRQL can constitute a specific PRO or a set of PROs in any given clinical context.

PROs are captured and quantified by PRO measures using validated and reliable standardised questionnaires that allow comparisons between treatment groups, and within groups over time.

2.1.3. Impact of medicinal cannabis on HRQL

Two systematic reviews in 2015 assessed HRQL in patients across all health conditions being treated with medicinal cannabis.^{7,8} They found only small improvements were reported for patients with pain, multiple sclerosis, and inflammatory bowel disorders⁷, with moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity, and only low-quality evidence showing cannabinoids improve nausea and vomiting due to chemotherapy, weight gain in HIV infection, sleep disorders, and Tourette syndrome.⁸ However, as medicinal cannabis use increases, the formulations and methods of administration have also been refined and adapted to each health condition being treated. Furthermore, access to medicinal cannabis often relies on the judgement and clinical justification of a prescribing doctor, which may cover a wider range of health conditions than previously explored in systematic reviews.

Our protocol for this longitudinal observational study⁹ was prospectively registered and published to prevent outcome reporting bias.¹⁰ Likewise, prospective registration of a detailed statistical analysis plan (SAP) is encouraged to prevent data-driven analyses.¹⁰

2.2. PRO Objectives

The following objectives and hypotheses are based on those stated in the QUEST protocol, published in 2021.⁹

We established the QUEST Initiative with the objective to evaluate HRQL in patients accessing prescribed medicinal cannabis by authorized prescribers and under the SAS across clinics within Australia using a comprehensive suite of validated PRO measures. The findings from this study have the potential to be integral to future treatment assessment and recommendations for patients with a range of health indicators for accessing medicinal cannabis.

2.2.1. Primary Objective

The primary objective of this study is to examine changes in PROs (overall HRQL, pain, fatigue, sleep, anxiety, and depression) from baseline to 3 months for a large cohort receiving medicinal cannabis. These are the domains that are expected to reflect the change in HRQL in those receiving medicinal cannabis therapy. Research questions and key outcomes to address the primary objective in this study are summarised in **table 1**.

2.2.2. Secondary Objective

The secondary objective of this study is to examine changes in PROs (overall HRQL, pain, fatigue, sleep, anxiety, depression) from baseline to 12 months and explore differences between patients accessing medicinal cannabis with different chronic health conditions: chronic pain, movement disorders,

insomnia, and mood disorders. The specific research questions and key outcomes to address the secondary objectives in this study are summarised in **table 2**.

2.2.3. Exploratory Objectives

The exploratory objectives of this study are to explore:

- (1) which health conditions are more likely to have lower symptom burden (e.g., pain, anxiety, motor function, etc.) as assessed with questionnaires specific to their condition (e.g., chronic pain, movement disorders, insomnia, and mood disorders), with the hypothesis that all health conditions will experience lower symptom burden at 3 months compared with baseline and this will be maintained over a 12-month period; and
- (2) associations among PROs, with the hypothesis that a high symptom burden (e.g., poorer scores on functioning domains, or higher scores on pain scales) is associated with poorer overall HRQL at all timepoints; and
- (3) associations between PROs and resource and medication use over time, with the hypothesis that lower symptom burden assessed with scores on questionnaires specific to health conditions is associated with reduced health care–resource use and reduced use of opioids and other prescribed medications for managing symptoms at 3 months compared with baseline and this will be maintained over a 12-month period.

The specific research questions and key outcomes to address the exploratory objectives in this study will be summarised in **table 3** (to be included in future SAP revisions after 12 months).

2.3. Hypotheses

The study includes 3 hypotheses:

- (1) PROs (overall HRQL, pain, anxiety, depression, sleep, fatigue) will improve from baseline to 3 months in patients accessing medicinal cannabis; and
- (2) improvements in PROs (overall HRQL, pain, anxiety, depression, sleep, fatigue) at 3 months will be maintained over a 12-month period; and
- (3) no differences in PROs (overall HRQL, pain, anxiety, depression, sleep, fatigue) will be observed between patients being treated for different conditions (e.g., chronic pain, movement disorders, insomnia, and mood disorders). Specifically, improvements in PROs will be observed across all health conditions, particularly for PROs related to their health condition (e.g., depression will improve for those being treated for depression).

2.4. Scope

This SAP will be the guiding document for the analyses that will be conducted to address the primary objective of the QUEST study (3-month follow-up). We intend to present the results of the primary and secondary objectives in separate manuscripts. All the aims and research questions of the secondary objectives are included in this SAP (12-month follow-up), and we aim to update the SAP for exploratory objectives as an addendum in the future.

3. Study methods

3.1. Study design

This is a multi-centre prospective longitudinal cohort study of patients newly prescribed medicinal cannabis oil formulations in Australia by Authorised Prescribers and under the Special Access Scheme. The prescriber is responsible for identifying eligible patients and completing screening forms. Little Green Pharma Ltd. (LGP) is responsible for the manufacture and quality of the medicinal cannabis oil products following TGA guidelines. The four LGP medicinal cannabis oil formulations accessed in this study are: CBD dominant 1:20; Balanced 10:10; THC dominant 20:5; and CBD 50 (containing less than 0.2mg/ml of THC). Patients must provide consent and complete baseline questionnaires via an online platform before beginning medicinal cannabis therapy. Follow-up questionnaires are completed online at specified assessment timepoints.

3.2. Power considerations

Following guidelines¹¹ for the EORTC QLQ-C30 questionnaire, and allowing for 20% loss to follow-up, a sample size of 2142 was required with a minimum follow-up of 3 months. This sample size provides 95% power to detect the smallest effect size threshold of 0.1 for the insomnia domain, using a two-sided significance level of 1%.¹²

Our aim is to recruit a large broad and representative sample of medicinal cannabis users. Feasibility data shows approximately 400 patients are seen across participating centres each month. Using a conservative recruitment rate of 50% (low end of PRO non-intervention studies), we anticipate recruiting 200 patients per month. As such, we will include every eligible patient treated at each participating centre during a 12-month recruitment period (an estimated 2400 participants). As the study is powered to detect the smallest effect (i.e., the 0.1 for insomnia), it is likely to also detect small effects for the other domains. This large real-world cohort will provide sufficient power and enable several important analyses exploring differences in PROs between disease groups commonly treated with medicinal cannabis.

3.3. Timing of final analysis

Analyses will be conducted at two time-points: 3-month follow-up, and 12-month follow-up. These follow-up time-points permit the assessment of immediate and mid- to long-term changes in HRQL.

3.4. Timing of outcome assessments

As noted in Section 6.4.6, and Table 1, of the protocol, patients completed the baseline questionnaire after consenting to the study and prior to starting medicinal cannabis therapy. Patients typically titrate to therapeutic dosage regimen over a two-week period and complete a follow-up titration questionnaire 14-21 days after starting therapy. Patients then completed follow-up questionnaires at 1, 2, 3, 5, 7, 9, and 12-months post titration. Participants are sent two reminder emails every two days if questionnaires have not been completed. This allows an assessment time window of 1 week after the questionnaire is due.

Questionnaires were administered at each of the following timepoints:

T0	T1	T2	T3	T4	T5	T6	T7	T8
Baseline	Titration	1-month follow-up	2-month follow-up	3-month follow-up	5-month follow-up	7-month follow-up	9-month follow-up	12-month follow-up
Before starting treatment	Assessed 14 days after starting treatment	Assessed 4 weeks after titration	Assessed 8 weeks after titration	Assessed 13 weeks after titration	Assessed 21 weeks after titration	Assessed 30 weeks after titration	Assessed 39 weeks after titration	Assessed 52 weeks after titration

4. Statistical principles

4.1. Confidence intervals and P-values

We will encounter multiplicity issues because multiple primary outcomes will be tested for significance in the same cohort. The QUEST cohort addresses six different primary outcomes (see **table 1**), and seven additional secondary outcomes in the 12-month follow-up study (**table 2**). Exploratory objectives at 12 months will also cover an additional 10 PRO domains and subscales.

Because there are 23 PROs and three main time points (baseline, 3-months, 12-months), and because we anticipate correlation among them, statistical significance levels will be adjusted using the Hochberg method (step-up modifications of the Bonferroni method).¹³ The relevant PROs, identified as key outcomes *a priori* as the focus of hypothesis testing, may be subject to p-value adjustment.

Analyses will be performed in SPSS and assume equal variances between groups.

Continuous variables will be summarized descriptively by number of patients (n), mean, standard deviation (SD), 95% confidence interval (CI) of the mean. For categorical and ordinal variables, data were summarized by number (n) and percentage (%).

4.1.1. Interpreting clinical importance

It is important to have a large enough sample size to detect a meaningful difference, and to interpret the results with reference to both statistical significance and detection of clinically meaningful difference. The minimally clinically important difference (MCID) is:

“The smallest difference which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient’s management.”¹⁴

Studies with very large sample sizes may detect a statistically significant change which is not actually large enough to be regarded as clinically meaningful or important in practice (example c in figure 1). Conversely, a small sample size may detect clinically meaningful differences but dismiss it as not statistically significant (example d in figure 1).

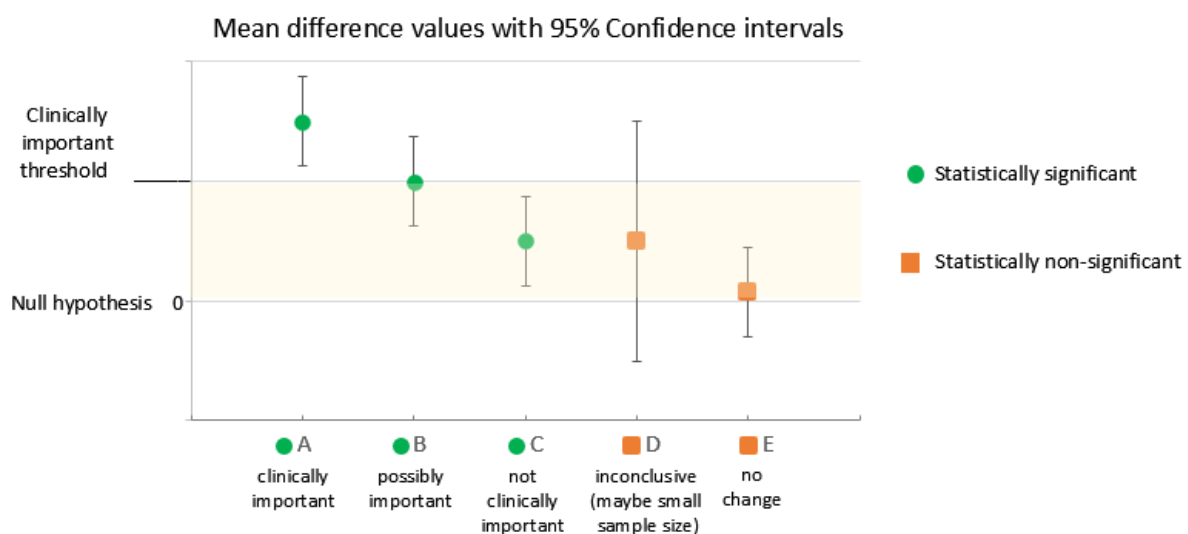


Figure 1. Confidence intervals* showing five possible conclusions in terms of statistical significance and practical importance. [Adapted from Armitage, Berry & Matthews, 2008; Figure 4.2].¹⁵

The MCID for the EQ-5D-5L index score in general populations fall between 0.037 and 0.069.¹⁶

Interpretation guidelines are also available for the EORTC QLQ-C30, differences between groups¹¹ and change over time¹⁷. These will be used to interpret the clinical importance of results for each of the 15 HRQL domains assessed by the QLQ-C30 questionnaire. However, MCIDs also depend on the health condition, context, and the baseline from which it starts. For this reason, it is more appropriate to assess change scores in relation to the sample being assessed.

Where interpretation guidelines are not available for the other questionnaires, 0.5 standard deviation will be used as a threshold for discrimination for clinically important changes in HRQL for chronic

diseases.¹⁸ Cohen's guidelines for effect sizes will be used to interpret the observed mean differences and changes in the other key PROs.¹⁹

Reporting a standardized mean difference also allows us to compare results between studies that use different measures for the same outcome.

Statistical significance considers the confidence interval. The 95% confidence interval is the range within which we are 95% confident contains the true mean of the population from which our sample was taken. That is, if we were to run the experiment again with similar patients, we are 95% confident that their mean will fall within this range.

4.2. Analysis populations

For each PRO, we will include all participants with a score for that PRO at baseline and at least one time point (up to 3-months for primary analysis, and up to 12-months for secondary and exploratory analyses) while taking medicinal cannabis therapy after titration.

5. Study Population

5.1. Screening data

The following patient screening details will be collected at recruitment sites:

- Age
- Sex
- Up to two health conditions treated with medicinal cannabis
- S-DN4 Neuropathic pain screening short form²⁰ (if pain is selected as a health condition)
- Duration of pain – if pain recorded as a health condition
- Comorbidities
- Medicinal cannabis type and dosage
- Date of any previously prescribed medicinal cannabis
- Reasons for declining study participation, if applicable

5.2. Eligibility

Patients are eligible for participating in the study if all of the following criteria are satisfied:

- adult patients (aged ≥ 18 years)
- patient has been identified as eligible to receive medicinal cannabis by a TGA approved Authorised Prescriber or via the special access scheme (SAS-B) (or equivalent in other countries and jurisdictions) and the doctor has sought and obtained TGA approval for LGP product for their patient
- patient is able to read and understand English
- patient is able to provide informed consent
- patient has not started any prescribed medicinal cannabis therapy in the previous 4 weeks; or started therapy less than 2 days prior to completing baseline questionnaires (we expect no therapeutic benefit within 2 days)
- patient has a life-expectancy > 3 months

- patient **does not** have cognitive impairment (e.g. advanced Alzheimer's)
- patient **is not** pregnant or breastfeeding

5.3. Recruitment

A STROBE flow diagram will be generated showing numbers of eligible patients screened; patients recruited and completing baseline questionnaires, patients completing follow-up questionnaires.

5.4. Withdrawal/follow-up

Information including numbers and reasons at each timepoint for patients withdrawn, excluded, missing, or lost to follow-up will be displayed on the STROBE flow diagram.

5.5. Baseline patient characteristics

A table listing baseline characteristics of all eligible patients screened for the study will be grouped by those screened - not joined, recruited - baseline only, and participants analysed - baseline and follow-up completed. Characteristics to be descriptively summarised include age, sex, cancer status, palliative care status, and primary health condition. Additional baseline characteristics including living arrangements, marital status, work status, and level of education will be summarised for all participants, grouped by recruited-baseline only, and participants analysed-baseline and follow-up completed.

5.6. Potential confounding covariates

Potential confounding covariates include age, gender, and history/duration of pain. For example the impact of cancer on specific HRQL domains varies by age whereby some HRQL domains improve with age while others deteriorate.²¹ Differences in these characteristics will be explored at baseline and where significant, they will be adjusted for in the longitudinal analyses.

Primary and secondary outcomes will be analysed using linear mixed models, with time included as a repeated measures variable, and age, gender, history/duration of pain, and baseline PRO values included as respondent-level variables.

6. Statistical Analyses

6.1. Outcome definitions

Tables 1 and 2 include full descriptions of outcomes.

6.2. Analysis methods

Linear mixed models will be used to examine change over time in PRO scores (i.e., time will be included as a random factor), adjusted for potential confounders and PRO levels at baseline, and with duration of pain, and previous cannabis use, will be modelled as fixed factor covariates.

Using the EQ-5D-5L, a health profile will be generated by assessment timepoints. A health index (ranging from 0 to 1) will be calculated from individual health state profiles using Australian population

utility weights,²² and mean, SD, and 95% confidence intervals provided for the cohort by assessment timepoint.

Using the QLQ-C30, scores will be generated for each of the 15 subscales by assessment timepoint. An overall HRQL summary score (ranging from 0-100) will be calculated using 13 of the 15 subscales. Means, standard deviations, and 95% confidence intervals will be summarised for the cohort by assessment timepoint.

PROMIS measures generate T-scores. T-scores are standard scores with a mean of 50 and standard deviation of 10 in a reference population.

Where scores are highly skewed, a suitable transformation will be sought to achieve normality.

DASS-21 scores will be generated to a score of 0-42 using the instrument developer's manual and described according to the manual's predefined categories. Change will be analysed using Chi-squared and Cochran's Q test.

6.3. Missing data

Missing items within questionnaires are not expected. This is due to the online administration platform alerting participants of missed items and the requirement to complete those items before progressing to the next page. Only participants who complete at least two questionnaires (baseline and one other) will be included in the analysis. At each assessment time-point, two email reminders will be sent automatically to participants who have not completed questionnaires.

Common reasons for incompleteness are likely to be a consequence of a premature treatment discontinuation due to drug-related adverse events or lack of efficacy (likely missing not at random), or patient not responding to emails (could be missing completely at random or missing not at random, depending on reason). Common reasons for intermittent missing data are technical/ logistical issues (likely to be missing completely at random).

The compliance of completing questionnaires is a critical issue in the evaluation of PROs. Linear mixed models will use all available data, so missing data will be explicitly imputed. Where possible reasons for non-compliance will be recorded by the investigator at each assessment. Graphs will be prepared to show PRO trajectories over time, including compliance rates at each timepoint to assess whether missing data is likely to be missing completely at random or not. For overall HRQL, 3-month trajectories will be stratified to show those who drop out at each timepoint. Reasons and patterns of missing PRO data will be assessed and described.

6.4. Additional analyses

6.4.1 *Economic evaluation*

The economic evaluation will use the collected data around pharmaceutical and other medical costs, including healthcare seeking behaviour, to explore the drivers of patient-level cost. As this project is not proposing a comparative randomised study, we are not proposing to conduct formal economic evaluation resulting in a cost per quality-adjusted life year (QALY). We will use baseline resource use as an indicator of typical care, and contrast resource use through the study with baseline data. We will explore the relationship between quality of life and resource use across the cohort, which is potentially important information in future economic evaluation of medicinal cannabis.

6.4.2 *Subgroup analyses*

If sample size permits, we will conduct an analysis in different subpopulations. Examples of subpopulations that may be eligible for further analysis are those with different types of health conditions treated with medicinal cannabis (pain types, movement disorder, anxiety, depression, PTSD, etc). These groups are determined by doctors and recorded at participant registration.

Between group comparisons of continuous variables will be applied using linear mixed models with group variables as fixed effects, with time by group interactions to assess differences in PRO scores over time differ by group, adjusting for covariates.

Additional variables to explore include:

- Type of product (four different THC:CBD ratios);
- Daily dosage (<1mg, 1-2mg, >2mg);
- Duration of pain (in months)
- History of cannabis use within previous 12 months (none, recreational use, medicinal use);
- Patient Global Impression of Change

6.5. Statistical software

All analyses will be carried out using SPSS v28.0.

7. Conclusion

This SAP presents the principles of analysis of the QUEST Initiative cohort and discusses its major methodologic and statistical concerns. We hope that the results of the QUEST Initiative will be as transparent and robust as possible, so that we minimised the risk of outcome reporting bias and data-driven results.

Acknowledgement

This SAP was adapted from the SAP prepared by Madeleine King, et al. for the Quality of life after breast-conserving therapy and adjuvant radiotherapy for non-low-risk ductal carcinoma in situ (BIG 3-07/TROG 07.01) trial.

List of Tables

Table 1. Research questions, key PROs, measures and scoring guidance to address the primary objectives in the QUEST study.

Table 2. Research questions, key PROs, measures and scoring guidance to address the secondary objectives in the QUEST study.

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TABLE 1. Research questions, key PROs, measures, scoring and reporting to address the primary objectives in the QUEST study.

Outcome	Research question	Measure(s)	Scoring guidance	Reporting
HRQL	Is there a change from baseline to 3 months in HRQL, for a large cohort receiving medicinal cannabis?	EQ-5D (index score) EORTC QLQ-C30 (summary score)	The EQ-5D contains 5 items covering the dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In addition to the 5 items there is a visual numeric scale of global health rated on a scale of 0 to 100. Health state profiles for each patient will be generated at each assessment time-point using the responses provided for the 5 dimensions. A health state index score (ranging from 0 to 1) will be calculated from the health profiles of the entire cohort using the Australian utility weights.¹ The QLQ-C30 contains 30 items and yields 15 HRQOL domain scales: 5 functioning scales (physical, role, emotional, cognitive and social), global health status quality of life scale, and nine symptom scales (fatigue, nausea, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, financial). They will be scored according to the EORTC QLQ-C30 Scoring Manual ². Raw scores will be transformed to a scale 0-100. A higher-order summary score covering 13 of the 15 domains will be generated for the entire cohort (excluding palliative care patients) from the QLQ-C30 responses, excluding the two Global QOL items and the Financial Impact item.^{3,4}	Linear and quadratic trends across all timepoints Means, SD, MD, effect sizes (95%CI) will be provided for the change from baseline to titration, 1- 2-, and 2-month follow-up for the whole cohort. Trajectory of HRQL graphed by time on study.

Outcome	Research question	Measure(s)	Scoring guidance	Reporting
Pain	Is there a change from baseline to 3 months in pain, for a large cohort receiving medicinal cannabis?	QLQ-C30 (pain subscale) QLQ-C15-PAL (pain subscale)	Pain will be assessed in the entire cohort using the QLQ-C30 (or QLQ-C15-PAL) pain symptom scale which consists of two items. The pain scale will be scored according to the EORTC QLQ-C30 Scoring Manual ² to produce a pain score ranging from 0 to 100. A higher score represents a higher response level (i.e., more pain). Means, SD, and 95% confidence intervals will be provided for the cohort by assessment timepoint. Palliative care patients completed the QLQ-C15-PAL instead of the QLQ-C30. The QLQ-C15-PAL scale for pain items are the same as the QLQ-C30 and are therefore included with the main cohort and scored as above using the EORTC QLQ-C30 Scoring Manual.	Linear and quadratic trends across all timepoints Means, SD, MD, effect sizes (95%CI) will be provided for the change from baseline to titration, 1- 2-, and 2-month follow-up for the whole cohort.
Depression	Is there a change from baseline to 3 months in depression for a large cohort receiving medicinal cannabis?	DASS21	Depression will be analysed for the entire cohort (excluding palliative care patients) with the DASS21. The DASS21 includes three scales each containing 7 items, assessing: depression, anxiety, and stress. The Depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest / involvement, anhedonia and inertia. Ratings for each item range from 0 (not at all) to 3 (very much or most of the time). Scores on the DASS-21 will be multiplied by 2 to calculate the final score. Scores are then categorized into severity levels and described for each timepoint using the following ranges: Depression – 0-9 normal, 10-13 mild, 14-20 moderate, 21-27 severe, 28+ extremely severe.	Linear and quadratic trends across all timepoints Means, SD, MD, effect sizes (95%CI) will be provided for the change from baseline to titration, 1- 2-, and 2-month follow-up for the whole cohort. Categorical data will be summarized by number (n) and percentage (%).

Outcome	Research question	Measure(s)	Scoring guidance	Reporting
Anxiety	Is there a change from baseline to 3 months in anxiety for a large cohort receiving medicinal cannabis?	DASS21	Anxiety will be analysed for the entire cohort (excluding palliative care patients) with the DASS21. The DASS21 includes three scales each containing 7 items, assessing: depression, anxiety, and stress. The Anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. Ratings for each item range from 0 (not at all) to 3 (very much or most of the time). Scores on the DASS-21 will be multiplied by 2 to calculate the final score. Scores are then categorized into severity levels and described for each timepoint using the following ranges: Anxiety - 0-7 normal, 8-9 mild, 10-14 moderate, 15-19 severe, 20+ extremely severe.	Linear and quadratic trends across all timepoints Means, SD, MD, effect sizes (95%CI) will be provided for the change from baseline to titration, 1- 2-, and 2-month follow-up for the whole cohort. Categorical data will be summarized by number (n) and percentage (%).
Sleep	Is there a change from baseline to 3 months in sleep quality for a large cohort receiving medicinal cannabis?	PROMIS Short Form v1.0 Sleep Disturbance 8b	Sleep quality will be analysed for the entire cohort (excluding palliative care patients) with the PROMIS Short Form v1.0 Sleep Disturbance 8b which contains 8 items covering sleep quality, sleep depth, and restoration associated with sleep. Items are rated as 1 (not at all) to 5 (very much so). PROMIS measures generate T-scores. T-scores are standard scores with a mean of 50 and standard deviation of 10 in a reference population. Responses will be transformed to T-scores using the HealthMeasures Scoring Service recommended for PROMIS instruments.	Linear and quadratic trends across all timepoints Means, SD, MD, effect sizes (95%CI) will be provided for the change from baseline to titration, 1- 2-, and 2-month follow-up for the whole cohort.

Outcome	Research question	Measure(s)	Scoring guidance	Reporting
Fatigue	Is there a change from baseline to 3 months in pain for patients accessing medicinal cannabis?	PROMIS Fatigue 13a FACIT-Fat	Fatigue will be analysed for the entire cohort (excluding palliative care patients) with the FACIT-Fat. The FACIT-Fat covers two domains; 5 items representing fatigue experience, and 8 items covering the impact of fatigue on daily activities. Ratings for each item range from 1 (not at all) to 5 (very much so). PROMIS measures generate T-scores. T-scores are standard scores with a mean of 50 and standard deviation of 10 in a reference population. Responses will be transformed to T-scores using the HealthMeasures Scoring Service recommended for PROMIS instruments.	Linear and quadratic trends across all timepoints Means, SD, MD, effect sizes (95%CI) will be provided for the change from baseline to titration, 1- 2-, and 2-month follow-up for the whole cohort.

TABLE 2. Research questions, key PROs, measures, scoring and reporting to address the secondary objectives in the QUEST study

Outcome	Research question	Measure(s)	Scoring guidance	Reporting
HRQL	Are there any long-term changes from baseline to 12 months in health-related quality of life, for a large cohort receiving medicinal cannabis?	EQ-5D (index score) EORTC QLQ-C30 (summary score)	The EQ-5D contains 5 items covering the dimensions of mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. In addition to the 5 items there is a visual numeric scale of global health rated on a scale of 0 to 100. Health state profiles for each patient will be generated at each assessment time-point using the responses provided for the 5 dimensions. A health state index score (ranging from 0 to 1) will be calculated from the health profiles of the entire cohort using the Australian utility weights.¹ The QLQ-C30 contains 30 items and yields 15 HRQOL domain scales: 5 functioning scales (physical, role, emotional, cognitive and social), global health status quality of life scale, and nine symptom scales (fatigue, nausea, pain, dyspnea, insomnia, appetite loss, constipation,	Linear and quadratic trends across all timepoints Means, SD, MD, effect sizes (95%CI) will be provided for the change from baseline to 5-, 7- 9-, and 12-month follow-up for the whole cohort. Trajectory of HRQL graphed by time on study. HRQL change for different health conditions (e.g., pain,

Outcome	Research question	Measure(s)	Scoring guidance	Reporting
			diarrhea, financial). They will be scored according to the EORTC QLQ-C30 Scoring Manual.² Raw scores will be transformed to a scale 0-100. A higher-order summary score for the entire cohort will be generated from the QLQ-C30 responses, excluding the two Global QOL items and the Financial Impact item.^{3,4}	insomnia, PTSD) will be explored. Note: Palliative care patients only followed for 3 months are not included in 12-month analysis.
Pain	Is there a change from baseline to 12 months in pain, for a large cohort receiving medicinal cannabis?	QLQ-C30 (pain subscale)	Pain will be assessed in the entire cohort using the QLQ-C30 pain symptom scale consisting of two items. The pain scale will be scored according to the EORTC QLQ-C30 Scoring Manual² to produce a pain score ranging from 0 to 100. A higher score represents a higher response level (i.e., more pain).	Linear and quadratic trends across all timepoints. Means, SD, MD, effect sizes (95%CI) will be provided for the change from baseline to 5-, 7- 9-, and 12-month follow-up for the whole cohort.
Pain Intensity	Are there any long-term changes from baseline to 12 months in pain for patients accessing medicinal cannabis for Chronic Pain?	PROMIS Scale v1.0 - Pain Intensity 3a;	Pain intensity will be assessed in all patients with a diagnosed pain condition with the PROMIS Scale v1.0 - Pain Intensity 3a.⁶⁷ The PS-PI includes 3 items assessing pain intensity; 2 items cover pain at its worst, and on average, over the previous one week, and one item asks about current pain. Items (rated as 1 (no pain) to 5 (very severe)) will be combined and transformed following PROMIS guidelines to generate an overall Pain Intensity T-score using the HealthMeasures Scoring Service recommended for PROMIS instruments. T-scores are standard scores with a mean of 50 and standard deviation of 10 in a reference population.	Linear and quadratic trends across all timepoints. Means, SD, MD, effect sizes (95%CI) will be provided for the change from baseline to 5-, 7- 9-, and 12-month follow-up for patients with pain conditions. Differences between pain groups (e.g., neuropathic pain vs musculoskeletal pain) will be explored.

Outcome	Research question	Measure(s)	Scoring guidance	Reporting
Pain Interference	Are there any long-term changes from baseline to 12 months in pain for patients accessing medicinal cannabis for Chronic Pain?	PROMIS Short Form v1.0 - Pain Interference 8a	Pain interference will be assessed in all patients with a diagnosed pain condition with the PROMIS Short Form v1.0 - Pain Interference 8a.⁵ The PSF-PI contains 8 items measuring the degree to which pain interferes with physical, emotional, and social activities. Items (rated from 1 - no pain to 5 -very severe) will be combined and transformed following PROMIS guidelines to generate an overall Pain Intensity T-score using the HealthMeasures Scoring Service recommended for PROMIS instruments. T-scores are standard scores with a mean of 50 and standard deviation of 10 in a reference population.	Linear and quadratic trends across all timepoints. Means, SD, MD, effect sizes (95%CI) will be provided for the change from baseline to 5-, 7- 9-, and 12-month follow-up for patients with a pain condition. Differences between pain groups (e.g., neuropathic pain vs musculoskeletal pain) will be explored.
Depression	Are there any long-term changes from baseline to 12 months in depression for a large cohort receiving medicinal cannabis?	DASS21	Depression will be analysed for the entire cohort with the DASS21. The DASS21 includes three scales each containing 7 items, assessing: depression, anxiety, and stress. The Depression scale assesses dysphoria, hopelessness, devaluation of life, self-deprecation, lack of interest / involvement, anhedonia and inertia. Ratings for each item range from 0 (not at all) to 3 (very much or most of the time). Scores on the DASS-21 will be multiplied by 2 to calculate the final score. Scores are then categorized into severity levels using the following ranges: Depression – 0-9 normal, 10-13 mild, 14-20 moderate, 21-27 severe, 28+ extremely severe.	Linear and quadratic trends across all timepoints. Means, SD, MD, effect sizes (95%CI) will be provided for the change from baseline to 5-, 7- 9-, and 12-month follow-up for the whole cohort. Categorical data will be summarized by number and percentage and analysed with Cochran's Q test.
Depression	Are there any long-term changes from baseline to 12 months in	DASS21	Depression will be analysed all patients with diagnosed depression with the DASS21- depression scale.	Linear and quadratic trends across all timepoints

Outcome	Research question	Measure(s)	Scoring guidance	Reporting
	depression for patients accessing medicinal cannabis for depression?			Differences between groups (i.e., depression vs no depression) in DASS-depression scores will be explored.
Anxiety	Are there any long-term changes from baseline to 12 months in anxiety for a large cohort receiving medicinal cannabis?	DASS21	Anxiety will be analysed for the entire cohort with the DASS21. The DASS21 includes three scales each containing 7 items, assessing: depression, anxiety, and stress. The Anxiety scale assesses autonomic arousal, skeletal muscle effects, situational anxiety, and subjective experience of anxious affect. Ratings for each item range from 0 (not at all) to 3 (very much or most of the time). Scores on the DASS-21 will be multiplied by 2 to calculate the final score. Scores are then categorized into severity levels using the following ranges: Anxiety - 0-7 normal, 8-9 mild, 10-14 moderate, 15-19 severe, 20+ extremely severe.	Linear and quadratic trends across all timepoints. Means, SD, MD, effect sizes (95%CI) will be provided for the change from baseline to 5-, 7- 9-, and 12-month follow-up for the whole cohort. Categorical data will be summarized by number and percentage and analysed using Cochran's Q test.
Anxiety	Are there any long-term changes from baseline to 12 months in anxiety for patients accessing medicinal cannabis for anxiety?	DASS21	Anxiety will be analysed all patients with diagnosed anxiety with the DASS21-anxiety scale.	Linear and quadratic trends across all timepoints Differences between groups (i.e., anxiety vs no anxiety) in DASS-anxiety scores will be explored.
Sleep	Are there any long-term changes from baseline to 12 months in sleep for a large cohort	PROMIS Short Form v1.0 Sleep Disturbance 8b	Sleep quality will be analysed for the entire cohort with the PROMIS Short Form v1.0 Sleep Disturbance 8b which contains 8 items covering sleep quality, sleep depth, and restoration associated with sleep.	Linear and quadratic trends across all timepoints. Means, SD, MD, effect sizes (95%CI) will be provided for

Outcome	Research question	Measure(s)	Scoring guidance	Reporting
	receiving medicinal cannabis?		Items are rated as 1 (not at all) to 5 (very much so). PROMIS measures generate T-scores. T-scores are standard scores with a mean of 50 and standard deviation of 10 in a reference population. Responses will be transformed to T-scores using the HealthMeasures Scoring Service recommended for PROMIS instruments.	the change from baseline to 5-, 7- 9-, and 12-month follow-up for the whole cohort.
Sleep	Are there any long-term changes from baseline to 12 months in sleep for patients accessing medicinal cannabis for insomnia?	PROMIS Short Form v1.0 Sleep Disturbance 8b	Sleep quality will be analysed all patients with diagnosed insomnia with the PROMIS Short Form v1.0 Sleep Disturbance 8b.	Linear and quadratic trends across all timepoints. Differences between groups (i.e., sleep disorder vs no sleep disorder) in Sleep Disturbance T-scores will be explored.
Fatigue	Are there any long-term changes from baseline to 12 months in fatigue for a large cohort receiving medicinal cannabis?	PROMIS Fatigue 13a FACIT-Fat	Fatigue will be analysed for the entire cohort with the FACIT-Fat. The FACIT-Fat covers two domains; 5 items representing fatigue experience, and 8 items covering the impact of fatigue on daily activities. Ratings for each item range from 1 (not at all) to 5 (very much so). PROMIS measures generate T-scores. T-scores are standard scores with a mean of 50 and standard deviation of 10 in a reference population. Responses will be transformed to T-scores using the HealthMeasures Scoring Service recommended for PROMIS instruments.	Linear and quadratic trends across all timepoints. Means, SD, MD, effect sizes (95%CI) will be provided for the change from baseline to 5-, 7- 9-, and 12-month follow-up for the whole cohort.
Movement disorder	Are there any long-term changes from baseline to 12 months in motor function in patients accessing medicinal cannabis for movement disorder?	Neuro-QoL v1.0 - Upper Extremity Function (Fine Motor, ADL)	Movement disorder will be analysed for all patients with a movement disorder with the Neuro-QoL v1.0 - Upper Extremity Function (Fine Motor, ADL) which consists of 8 items assessing ability to carry out various activities involving digital, manual and reach-related functions, ranging from fine motor to self-care (activities of daily living) for patients with stroke, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson disease, epilepsy, and muscular dystrophy. Items are rated as 1 (unable to do) to 5 (without any difficulty).	Linear and quadratic trends across all timepoints. Means, SD, MD, effect sizes (95%CI) will be provided for the change from baseline to 5-, 7- 9-, and 12-month follow-up for patients with a movement disorder.

Outcome	Research question	Measure(s)	Scoring guidance	Reporting
			Responses will be transformed to T-scores using the HealthMeasures Scoring Service recommended for Neuro-QoL instruments. T-scores are standard scores with a mean of 50 and standard deviation of 10 in a reference population.	

1. Norman R, Cronin P, Viney R. A Pilot Discrete Choice Experiment to Explore Preferences for EQ-5D-5L Health States. *Applied Health Economics and Health Policy*. 2013;11(3):287-98; doi: 10.1007/s40258-013-0035-z.
2. Fayers PM, Aaronson NK, Bjordal K, et al. The EORTC QLQ-C30 Scoring Manual. 3rd ed. Brussels: *European Organisation for Research and Treatment of Cancer (EORTC)*; 2001.
3. Giesinger JM, Kieffer JM, Fayers PM, et al. Replication and validation of higher order models demonstrated that a summary score for the EORTC QLQ-C30 is robust. *Journal of clinical epidemiology*. 2016;69:79-88; doi: <https://dx.doi.org/10.1016/j.jclinepi.2015.08.007>.
4. Gundy CM, Fayers PM, Groenvold M, et al. Comparing higher order models for the EORTC QLQ-C30. *Qual Life Res*. 2012;21(9):1607-17; doi: <https://dx.doi.org/10.1007/s11136-011-0082-6>.

5. Chen CX, Kroenke K, Stump T, et al. Comparative Responsiveness of the PROMIS Pain Interference Short Forms With Legacy Pain Measures: Results From Three Randomized Clinical Trials. *The journal of pain : official journal of the American Pain Society*. 2019;20(6):664-75; doi: <https://dx.doi.org/10.1016/j.jpain.2018.11.010>.

APPENDIX 3: ETHICS APPROVALS

- CHAPTERS 4-6

Wednesday, 11 November 2020

Dr Claudia Rutherford
Nursing Nursing School Admin; Faculty of Medicine and Health
Email: claudia.rutherford@sydney.edu.au

Dear Claudia,

The University of Sydney Human Research Ethics Committee (HREC) has considered your application.

I am pleased to inform you that after consideration of your response, your project has been approved.

Details of the approval are as follows:

Project No.: 2020/589
Project Title: The QUEST initiative – QUALITY of life Evaluation STUDY: Assessing Health Related Quality of Life in patients receiving Medicinal Cannabis
Authorised Personnel: Rutherford Claudia; Tait Margaret-Ann;
Approval Period: 11 November 2020 to 11 November 2024
First Annual Report Due: 11 November 2021

Documents Approved:

Date Uploaded	Version Number	Document Name
28/09/2020	Version 2	Protocol_final
28/09/2020	Version 2	email invitation_final
28/09/2020	Version 1	Patient Consent form
28/09/2020	Version 1	Validated PRO Questionnaires
28/09/2020	Version 1	QUEST Promotion webpage
28/09/2020	Version 1.1	PIS_final
28/09/2020	Version 1	General questionnaire - patient demographic
28/09/2020	Version 1	QUEST Facebook page and sample posts
04/08/2020	Version 1	Participant consent form
04/08/2020	Version 1	Information used to advertise the study

Condition/s of Approval

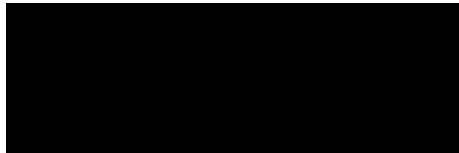
- Research must be conducted according to the approved proposal.
- An annual progress report must be submitted to the Ethics Office on or before the anniversary of approval and on completion of the project.
- You must report as soon as practicable anything that might warrant review of ethical approval of the project including:
 - Serious or unexpected adverse events (which should be reported within 72 hours).
 - Unforeseen events that might affect continued ethical acceptability of the project.
- Any changes to the proposal must be approved prior to their implementation (except where an amendment is undertaken to eliminate *immediate* risk to participants).
- Personnel working on this project must be sufficiently qualified by education, training and experience for their role, or adequately supervised. Changes to personnel must be reported and approved.
- Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, as relevant to this project.

- Data and primary materials must be retained and stored in accordance with the relevant legislation and University guidelines.
- Ethics approval is dependent upon ongoing compliance of the research with the *National Statement on Ethical Conduct in Human Research*, the *Australian Code for the Responsible Conduct of Research*, applicable legal requirements, and with University policies, procedures and governance requirements.
- The Ethics Office may conduct audits on approved projects.
- The Chief Investigator has ultimate responsibility for the conduct of the research and is responsible for ensuring all others involved will conduct the research in accordance with the above.

This letter constitutes ethical approval only.

Please contact the Ethics Office should you require further information or clarification.

Sincerely,



Dr Haryana Dillon
Chair
Human Research Ethics Committee (HREC 3)

The University of Sydney of Sydney HRECs are constituted and operate in accordance with the National Health and Medical Research Council's (NHMRC) [National Statement on Ethical Conduct in Human Research \(2018\)](#) and the NHMRC's [Australian Code for the Responsible Conduct of Research \(2018\)](#)

Research Integrity & Ethics Administration
Human Research Ethics Committee

Wednesday, 3 March 2021

A/Prof Claudia Rutherford
Faculty of Medicine and Health
Nursing School Admin
Email: claudia.rutherford@sydney.edu.au

Dear Claudia,

Your request to modify this project, which was submitted on 04/02/2021, has been considered.

The project has been approved to proceed with the proposed amendments.

Details of the approval are as follows:

Project Title: The QUEST initiative – QUality of life Evaluation STudy: Assessing Health Related Quality of Life in patients receiving Medicinal Cannabis

Project number: 2020/589

Next Annual Report due: 11/11/2021

New Approved Documents:

Date	Document Type	Title / Version Number
04/02/2021	Advertisement/Flyer	Promotion website landing page
04/02/2021	Advertisement/Flyer	Promotion website patient page
04/02/2021	Participant Info Statement	PIS_clean copy - Version 3, 12 January 2021
04/02/2021	Participant Info Statement	PIS_tracked changes - Version 3, 12 January 2021
04/02/2021	Study Protocol	Protocol_clean copy - version 3.0, 2 February 2021
04/02/2021	Study Protocol	Protocol_tracked changes - version 3.0, 2 February 2021

Sincerely,



Katy Wilson
Chair, Executive of the Human Research Ethics Committee

This University's HRECs are constituted and operate in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007), the NHMRC's Australian Code for the Responsible Conduct of Research (2018) and the Therapeutic Goods Administration's (TGA) Note for Guidance on Good Clinical Practice (2000).

Dr Claudia Rutherford
Nursing Nursing School Admin; Faculty of Medicine and Health
Email: claudia.rutherford@sydney.edu.au

Dear Claudia,

Your request to modify this project, which was submitted on 06/03/2023, has been considered.

This project has been approved to proceed with the proposed amendments.

Protocol Number: 2020/589

Protocol Title: The QUEST initiative QUALity of life Evaluation STudy: Assessing Health Related Quality of Life in patients receiving Medicinal Cannabis

Addition of Authorised Persons: White, Kathryn

Annual Report Due: 11/11/2023

Documents Approved:

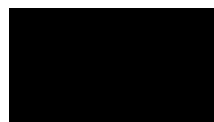
Date Uploaded	Version Number	Document Name
06/03/2023	v.1	QUEST follow-up Consent Form, Version 1
06/03/2023	v.1	QUEST follow-up e-Consent Form, Version 1
06/03/2023	v.1	QUEST follow-up Interview Script, Version 1
06/03/2023	v.1	QUEST follow-up invitation Version 1
06/03/2023	v.1	QUEST follow-up PIS, Version 1

Special conditions of approval:

1. The committee suggested that you consider moving Section 8 of the PIS to the first page of the form. Privacy, anonymity and data storage will be key concerns for potential participants, and it may be advantageous for recruitment to present this information early.

Please contact the ethics office should you require further information.

Sincerely,



Dr Marinda Taha
Chair
Modification Review Committee Chair (MRC 1)

The University of Sydney of Sydney HRECs are constituted and operate in accordance with the National Health and Medical Research Council's (NHMRC) [National Statement on Ethical Conduct in Human Research \(2018\)](#) and the NHMRC's [Australian Code for the Responsible Conduct of Research \(2018\)](#)

From: [Sarah Ambrose](#) on behalf of [Human Ethics](#)
To: [Claudia Rutherford](#); [Margaret-ann Tait](#); [Kate White](#)
Subject: [2020/589] Human Ethics: Compliance with special conditions outcome
Date: Tuesday, 18 April 2023 4:22:45 PM

Dear Dr Rutherford

Project Title: The QUEST initiative QQuality of life Evaluation STudy: Assessing Health Related Quality of Life in patients receiving Medicinal Cannabis
Project number: 2020/589

Compliance with Special Conditions Outcome

Thank you for providing documentation addressing the following special condition(s) of approval:

The committee suggested that you consider moving Section 8 of the PIS to the first page of the form. Privacy, anonymity and data storage will be key concerns for potential participants, and it may be advantageous for recruitment to present this information early.

We are pleased to advise that the above condition(s) have now been met.

You should retain a copy of this email with your study records.

Please contact us if you have any queries.

Regards,
The Ethics Office

Research Integrity and Ethics Administration | Research Portfolio
THE UNIVERSITY OF SYDNEY
Level 3, Administration Building (F23) | The University of Sydney | NSW | 2006
T +61 2 9036 9161 | E human.ethics@sydney.edu.au | W <http://sydney.edu.au/ethics>

HUMAN RESEARCH ETHICS APPROVAL

The University of Sydney confirms that this project meets the requirements of the National Statement on Ethical Conduct in Human Research.

Project identifier:	2020/HE000589
Project title:	The QUEST initiative QQuality of life Evaluation STudy: Assessing Health Related Quality of Life in patients receiving Medicinal Cannabis
Version:	1.01
Chief Investigator:	Associate Professor Claudia Rutherford
Authorised project team:	Professor Kathryn White Ms Margaret-Ann Tait
Date of approval:	Wednesday, 22 May, 2024
Project end date:	10 Nov 2024

Provisos *(if applicable)*

Project summary

This research will use questionnaires to assess health-related quality of life in patients who are prescribed medicinal cannabis under the Special Access Scheme in Australia. The patient-reported outcomes of interest include: global quality of life, pain, sleep, anxiety, depression, fatigue, and functioning. The outcomes will be assessed over time (from baseline through to 1 year), and be compared between different health conditions. The results from this study will 1) help future patients with health conditions indicated for medicinal cannabis make better informed decisions about their treatment, and 2) provide real-world evidence for future regulation and policy-making.

Summary of changes

We are updating our interview script in response to data collected from the first 6 participants.

Documents approved

Document type	File name	Document version	Application version
Application	Application Form.docx	1	1.1
Other	QUEST_interview_script_v2_tracked.docx	1	1.1
Other	QUEST_interview_script_v2.docx	1	1.1

Conditions of Approval

- Research must be conducted according to the approved proposal.

- An annual progress report must be submitted on or before the anniversary of approval and a final report on completion of the project.
- You must report as soon as practicable anything that might warrant review of ethical approval of the project including:
 - Serious or unexpected adverse events (which should be reported within 72 hours).
 - Unforeseen events that might affect continued ethical acceptability of the project.
- Any changes to the proposal must be approved prior to their implementation (except where an amendment is undertaken to eliminate *immediate* risk to participants).
- Researchers working on this project must be sufficiently qualified by education, training, and experience for their role, or adequately supervised. Changes to the project team must be reported and approved.
- Researchers must disclose any actual, potential or perceived conflicts of interest, including any financial or other interest or affiliation, as relevant to this project.
- Research data and primary materials must be retained and stored in accordance with relevant legislation and University guidelines.
- Ethics approval is dependent upon ongoing compliance of the research with the *National Statement on Ethical Conduct in Human Research*, the *Australian Code for the Responsible Conduct of Research*, applicable legal requirements, and with University policies, procedures, and governance requirements.
- If your research project is a clinical trial and is being sponsored by the University or is to be conducted on a University of Sydney site, you must comply with additional University governance requirements prior to commencing your Clinical Trial.
- The University may conduct audits on approved projects.
- The Chief Investigator has ultimate responsibility for the conduct of the research and is responsible for ensuring all others involved will conduct the research in accordance with the above.

Ethics Committee Representative

Joanne Hart
Chair
ASC 3
On behalf of the University of Sydney

The University of Sydney HRECs are constituted and operate in accordance with the National Statement on Ethical Conduct in Human Research and the Australian Code for the Responsible Conduct of Research (NHMRC). All personnel named on the project should be acquainted with these documents.

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ABN 15 211 513 464
CRICOS 00026A

HUMAN RESEARCH ETHICS APPROVAL

The University of Sydney confirms that this project meets the requirements of the National Statement on Ethical Conduct in Human Research.

Project identifier:	2020/HE000589
Project title:	The QUEST initiative QUALity of life Evaluation STudy: Assessing Health Related Quality of Life in patients receiving Medicinal Cannabis
Application version:	2.01
Chief Investigator:	Associate Professor Claudia Rutherford
Project team:	Professor Kathryn White Ms Margaret-Ann Tait
Project start date:	10 Nov 2020
Project end date:	11 Nov 2025
Date of issue:	Monday, 11 November, 2024

Project summary

This research will use questionnaires to assess health-related quality of life in patients who are prescribed medicinal cannabis under the Special Access Scheme in Australia. The patient-reported outcomes of interest include: global quality of life, pain, sleep, anxiety, depression, fatigue, and functioning. The outcomes will be assessed over time (from baseline through to 1 year), and be compared between different health conditions. The results from this study will 1) help future patients with health conditions indicated for medicinal cannabis make better informed decisions about their treatment, and 2) provide real-world evidence for future regulation and policy-making.

Summary of amendments

Project extension of 1-year to 11 November 2025.

Documents approved

Document type	File name	Document version	Application version
Application	Application Form.docx	2	2.01

Conditions of Approval

- Research must be conducted according to the approved proposal.
- An annual progress report must be submitted on or before the anniversary of approval and a final report on completion of the project.
- You must report as soon as practicable anything that might warrant review of ethical approval of the project including:
 - Serious or unexpected adverse events (which should be reported within 72 hours).
 - Unforeseen events that might affect continued ethical acceptability of the project.



- Any changes to the proposal must be approved prior to their implementation (except where an amendment is undertaken to eliminate *immediate* risk to participants).
- Researchers working on this project must be sufficiently qualified by education, training, and experience for their role, or adequately supervised. Changes to the project team must be reported and approved.
- Researchers must disclose any actual, potential or perceived conflicts of interest, including any financial or other interest or affiliation, as relevant to this project.
- Research data and primary materials must be retained and stored in accordance with relevant legislation and University guidelines.
- Ethics approval is dependent upon ongoing compliance of the research with the *National Statement on Ethical Conduct in Human Research*, the *Australian Code for the Responsible Conduct of Research*, applicable legal requirements, and with University policies, procedures, and governance requirements.
- If your research project is a clinical trial and is being sponsored by the University or is to be conducted on a University of Sydney site, you must comply with additional University governance requirements prior to commencing your Clinical Trial.
- The University may conduct audits on approved projects.
- The Chief Investigator has ultimate responsibility for the conduct of the research and is responsible for ensuring all others involved will conduct the research in accordance with the above.

Ethics Committee Representative

Chair

ASC 2

On behalf of the University of Sydney

The University of Sydney HRECs are constituted and operate in accordance with the National Statement on Ethical Conduct in Human Research and the Australian Code for the Responsible Conduct of Research (NHMRC). All personnel named on the project should be acquainted with these documents.

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CRICOS 00026A

APPENDIX 4: SUPPLEMENTARY MATERIAL - CHAPTER 4

Referenced in the publication:

Supplementary 1 Table: Location, ethnicity, and gender identity of participants

Supplementary 2 Table: Health Conditions of QUEST participants and MC products prescribed.

Supplementary 1 Figure: Change in categorized severity levels of anxiety and depression

Supplementary 2 Figure: HRQL change over study period stratified by time on study

Supplementary 5 Table: STROBE checklist

Additional material:

PLOS ONE Correction Request Form

S1 Table. Location, ethnicity, and gender identity of 2327 participants in the QUEST Initiative study.

Australian Location	N=2327	%
New South Wales	899	38.6
Victoria	225	9.7
Queensland	348	15.0
South Australia	103	4.4
Western Australia	743	31.9
Australian Capital Territory	9	0.4
Ethnicity^a		
Aboriginal and/or Torres Strait Islander	54	2.3
Other Australian	1297	55.7
New Zealander	64	2.8
Melanesian and Papuan, Micronesian, or Polynesian	5	0.2
British	371	16.0
Irish	69	3.0
North-West European	117	5.0
Southern and Eastern European	123	5.3
North African and Middle Eastern	18	0.8
South-East Asian	19	0.8
North-East Asian	21	0.9
Southern and Central Asian	23	1.0
North American	35	1.5
Central and South American	30	1.3
Sub-Saharan African	25	1.0
Missing	56	2.4
Gender Identity		
Man	813	34.9
Woman	1372	59.0
Transgender	2	0.1
Genderqueer	4	0.2
Agender	2	0.1
Genderless	1	-
Non-binary	13	0.6
Trans man	1	-
Two-spirit	1	-
Genderfluid	4	0.2
Prefer not to disclose	6	0.3
Missing	108	4.6

^a Self-selected options from list adapted from Australian Bureau of Statistics – Australian Standard Classification of Cultural and Ethnic groups, 2019.

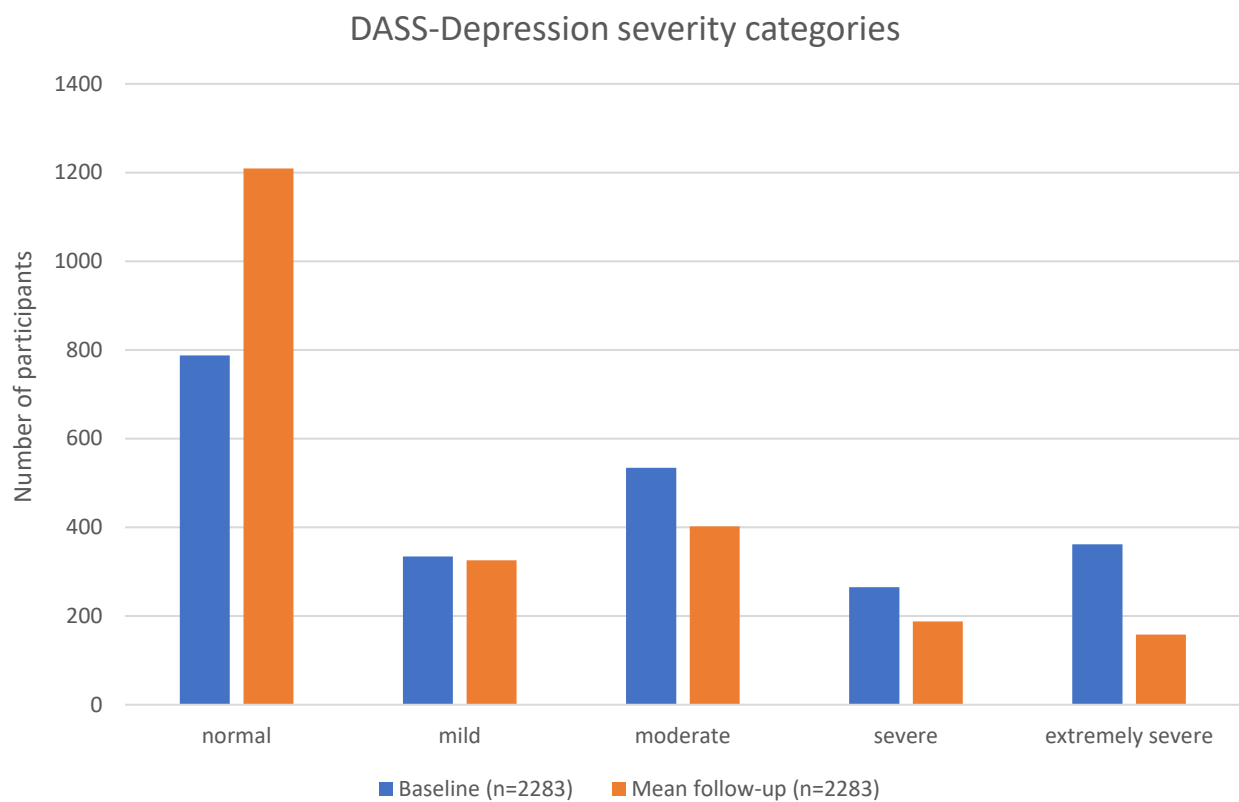
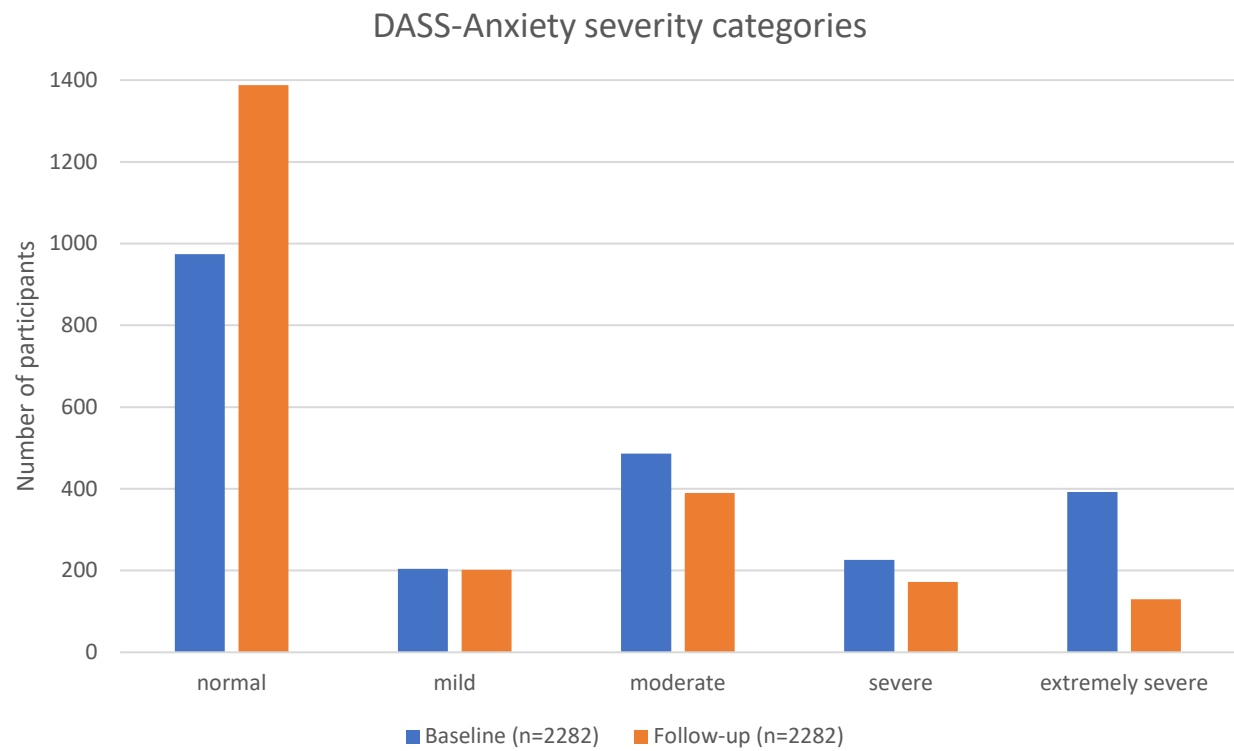
S2 Table. Health Condition Diagnoses of 2327 QUEST participants included in analysis, and medicinal cannabis products prescribed.

Health Condition	n (%) ^a	LGP medicinal cannabis products prescribed ^b										
		1	2	3	4	1,2	1,3	1,4	2,3	2,4	3,4	1,2,3,4
Pain - Chronic neuropathic [MG30.5]	537 (23.1)	182	11	48	204	4	9	44	-	32	2	-
Pain - Chronic widespread [MG30.01]	211 (9.1)	51	3	17	111	1	1	15	-	11	1	-
Pain - Chronic primary visceral [MG30.00]	96 (4.1)	24	1	7	44	-	-	7	-	13	-	-
Pain - Chronic secondary visceral [MG30.4]	18 (0.8)	3	-	3	10	-	-	1	-	1	-	-
Pain - Chronic primary musculoskeletal [MG30.02]	777 (33.4)	173	9	79	388	1	7	64	-	52	3	1
Pain - Chronic secondary musculoskeletal [MG30.3]	107 (4.5)	38	4	20	35	-	-	5	-	2	3	-
Pain - Chronic primary headache/orofacial [MG30.03]	109 (4.6)	22	1	8	60	-	2	9	-	7	-	-
Pain - Chronic secondary headache/orofacial [MG30.6]	18 (0.8)	4	-	1	10	-	-	-	-	2	1	-
Pain - Chronic cancer related [MG30.1]	33 (1.4)	15	-	-	15	-	-	1	1	-	-	-
Pain - Chronic postsurgical or post traumatic [MG30.2]	10 (0.4)	4	1	1	4	-	-	-	-	-	-	-
Movement Disorder - Parkinsonism [8A00]	27 (1.2)	6	-	4	11	-	1	5	-	-	-	-
Movement Disorder - Primary dystonia [8A02.0]	2 (0.1)	-	-	1	1	-	-	-	-	-	-	-
Movement Disorder - Secondary dystonia [8A02.1]	2 (0.1)	-	1	1	-	-	-	-	-	-	-	-
Movement Disorder - Functional dystonia [8A02.3]	3 (0.1)	1	-	1	1	-	-	-	-	-	-	-
Movement Disorder - Paroxysmal dystonia [8A02.2]	9 (0.4)	1	1	3	2	-	1	-	-	1	-	-
Movement Disorder - Ataxia [8A03]	1	-	1	-	-	-	-	-	-	-	-	-
Movement Disorder - Tremor [8A04]	10 (0.4)	2	-	1	5	-	1	1	-	-	-	-
Movement Disorder - Tic disorders [8A05]	1	-	-	-	1	-	-	-	-	-	-	-
Epilepsy or seizures - [8A60]	18 (0.8)	3	1	2	9	-	-	1	-	1	1	-
Nausea and vomiting [MD90]	6 (0.3)	2	-	-	3	-	-	1	-	-	-	-
Inflammatory bowel disease [DD7Z] & IBS	20 (0.9)	3	-	4	13	-	-	-	-	-	-	-
Cachexia [MG20]	6 (0.3)	2	-	1	2	-	1	-	-	-	-	-
Anorexia Nervosa [6B80]	5 (0.2)	1	-	-	3	-	-	-	-	1	-	-
Recurrent depressive disorder [6A71]	25 (1.1)	2	-	1	22	-	-	-	-	-	-	-
Mixed depressive and anxiety disorder [6A73]	256 (11)	50	5	23	139	-	4	19	2	12	1	-
Bipolar disorder [6A60]	11 (0.5)	1	1	2	6	1	-	-	-	-	-	-
Generalised anxiety disorder [6B00]	503 (21.6)	85	9	29	315	3	2	28	1	28	2	1
Post-traumatic stress disorder [6B40]	124 (5.3)	42	5	9	54	1	2	7	-	4	-	-
Chronic insomnia [7A00]	534 (22.9)	153	12	36	243	-	5	34	3	46	1	-
Attention deficit disorder [6A05]	15 (0.6)	6	-	2	4	-	-	1	-	1	-	-
Other	72 (3.1)	19	3	6	33	-	-	1	-	1	2	-

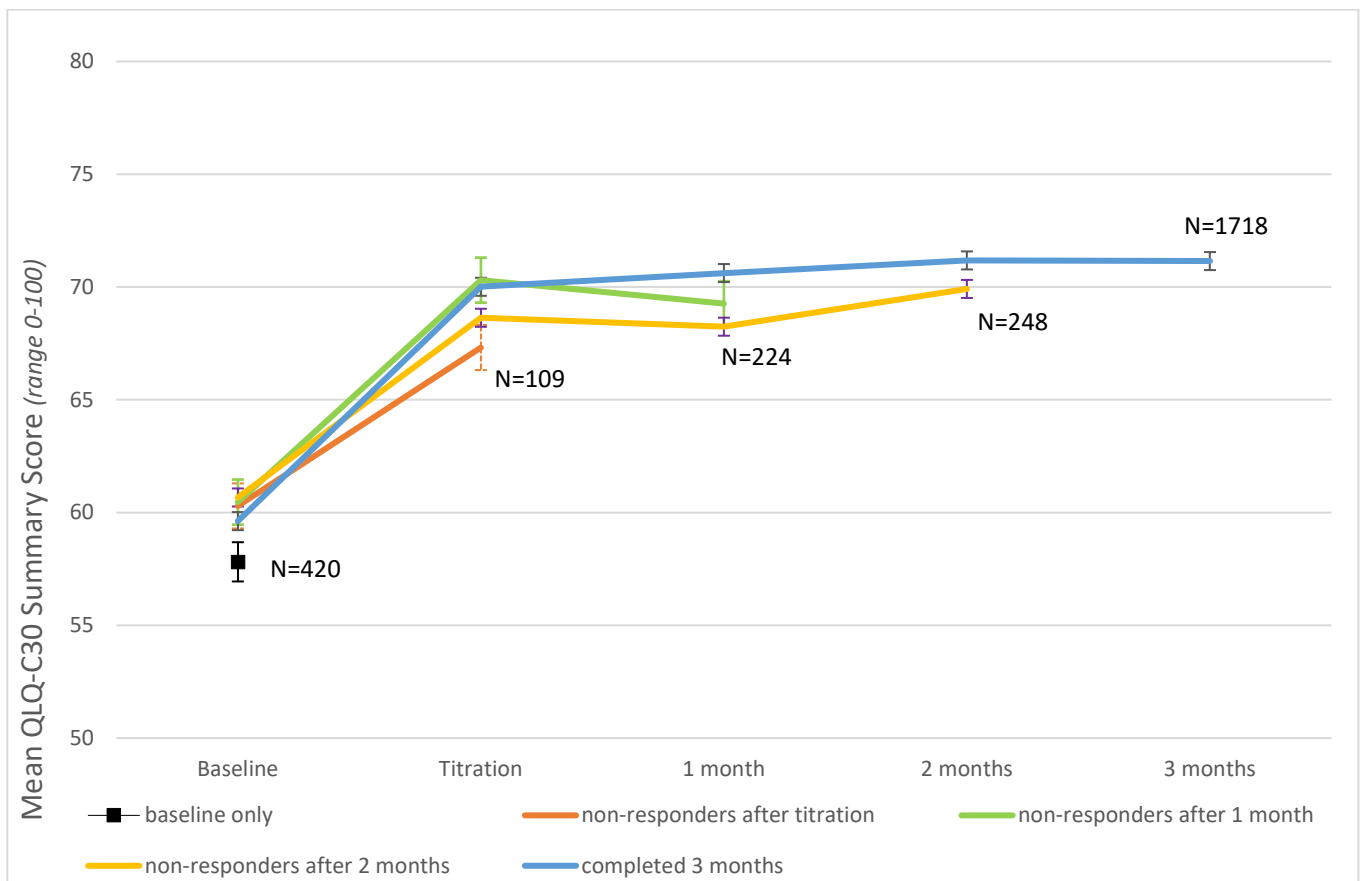
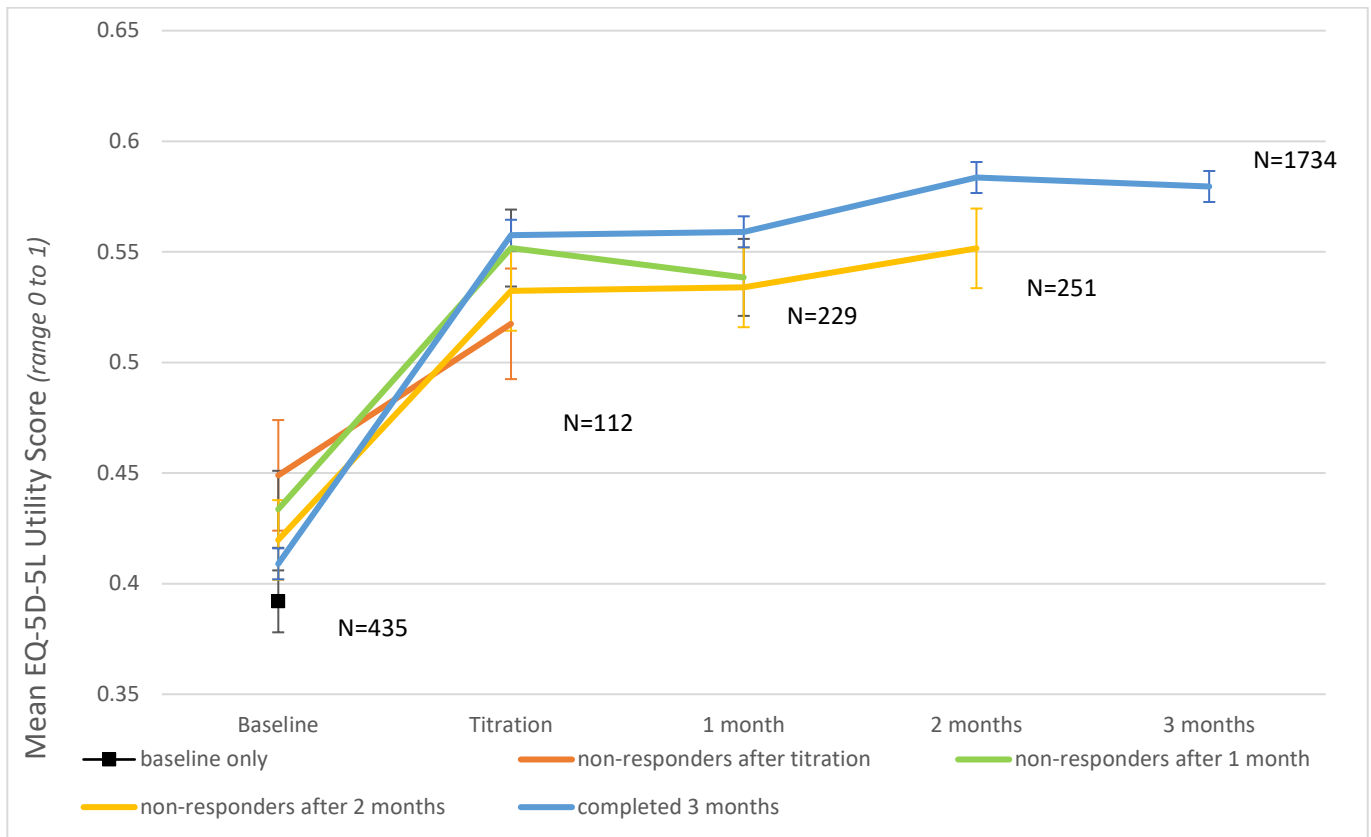
^a % does not add up to 100 as patients can have up to two health conditions.

^b Products: 1= LGP Classic 10:10 (10mg THC and 10mg CBD, per mL); 2= LGP Classic 20:5 (20mg THC and 5mg CBD, per mL); 3= LGP Classic 1:20 (1mg THC and 20mg CBD, per mL); 4= LGP Classic CBD 50 (50mg CBD, per mL).

Note: Data on medicinal cannabis products was collected according to participant, not according to health condition. As a result, each condition in the table lists all products participants with that condition received, including products they received for any other condition. For this reason, the table should not be regarded as product indication recommendations.

S3 Fig. Change in categorized severity levels of anxiety and depression between baseline and mean follow-up.

S4 Fig. Change in Mean EQ-5D-5L Utility Scores and QLQ-C30 Summary Scores over study period stratified by time on study (with standard error bars)



STROBE Statement—checklist of items that should be included in reports of observational *cohort* studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1	3-month follow-up observational study
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Abstract - AMRaC structured
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	Introduction - First 3 paragraphs
Objectives	3	State specific objectives, including any prespecified hypotheses	5	This study is reporting the... which is assessing... We hypothesised that...
Methods				
Study design	4	Present key elements of study design early in the paper	5	Methods - Study population and design
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6	Methods - Study population and design Methods - Data Collection
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6	Methods - Study population and design Methods - Data Collection
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	n/a	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5	Methods - Study population and design
			7-8	Methods - Data Collection Table 1
Data sources/measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7-8	Methods - Data Collection Table 1
Bias	9	Describe any efforts to address potential sources of bias	20-21	Discussion - Strengths and limitations

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Study size	10	Explain how the study size was arrived at	9	Methods – Statistical significance
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7-9	Methods – Data Collection Table 1 Methods – Statistical significance
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	9 13	Methods – Statistical significance Results - PROs
		(b) Describe any methods used to examine subgroups and interactions	9-10	Methods – Statistical analysis
		(c) Explain how missing data were addressed	9	Methods – Statistical significance
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed	9 17	Methods - Study population and design Results – Missed assessments
		(e) Describe any sensitivity analyses	9-10	Methods – Statistical analysis
Results				
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10	Results Figures 1-3 Table 3
		(b) Give reasons for non-participation at each stage		Results Figure 1
		(c) Consider use of a flow diagram		Results Figure 1
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11	Results and Table 2; Appendix A; Appendix B
		(b) Indicate number of participants with missing data for each variable of interest		Figures 2-3
		(c) Cohort study—Summarise follow-up time (eg, average and total amount)	6	Methods – Data Collection
Outcome data	15	Cohort study—Report numbers of outcome events or summary measures over time	13-17	Results and Table 3

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13-17	Results and Table 3
		(b) Report category boundaries when continuous variables were categorized	8	<i>Methods - Table 1</i> <i>Results - Figure 3</i> <i>Appendix c</i>
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	13-17	Results
Discussion				
Key results	18	Summarise key results with reference to study objectives	18	Discussion – Principal findings
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	20-21	Discussion – Strengths and limitations
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	22	Discussion – Clinical implications
Generalisability	21	Discuss the generalisability (external validity) of the study results	20-21	Discussion – Strengths and limitations
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	24	Declarations - Funding

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

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These formal corrections document and correct substantial errors that appear in online articles when these errors significantly affect the content or understanding of the work reported (e.g., error in data presentation or analysis) or when the error affects the publication's metadata (e.g., misspelling of an author's name). These correction notices are also indexed in PubMed. Please note that the original published article and PDF will not be corrected.

You are also welcome to use the Commenting feature on your article to notify readers of any potential errors.

☒ By checking this box, I confirm, as the Corresponding Author, that I have read and understood the PLOS Correction Policy and request for a Formal Notice of Correction. I also confirm that all information provided below are complete, correct, and suitable to be used to publish as a Formal Notice of Correction.

Article Title	Quality of life in patients accessing medicinal cannabis in Australia: The QUEST Initiative results of 3-month follow-up observational study
Original Article DOI Example: pone.1234567	pone.0290549
Description of the Error(s) Include any relevant information like updated ID numbers (e.g. grant numbers, DOIs, URLs, etc.)	Reported findings related to the Sleep outcome were in error. Corrections are listed below. Abstract: The statement ‘and no changes in sleep disturbance.’ is in error. Updated statement: ‘and clinically meaningful improvement in sleep (d=0.67; 95%CI: 0.61 to 0.73).’ Results section: The content related to the Sleep outcome in Table 3 is in error. An updated table is below. Results section: The content under the subheading ‘Sleep’ is in error. Updated content: PROMIS Sleep Disturbance, completed by 2298 participants, displayed significant linear ($t_{(8961)} = -18.98$; $p < 0.001$) and quadratic ($t_{(6826)} = 21.93$; $p < 0.001$) trends of improvement over time (Fig 2d). Sleep improved on average by 5.95 T-scores (SD= 8.49) from baseline (T= 61.03; SD= 8.6) to mean follow-up (T= 54.9; SD= 9.33), indicating clinically meaningful improvement (d= 0.67; 95%CI: 0.61 to 0.73) greater than the recommended PROMIS MCID of 3 T-scores. Similarly, when looking at the 534 participants with an insomnia diagnosis (of which 460 (86%) had a secondary diagnosis), mean T-scores improved by 8.13 (SD= 8.36) from baseline (64.1; SD= 7.42) to follow-up (55.74; SD=9.37), indicating clinically meaningful improvement (d= 0.94; 95%CI: 0.82 to 1.06).

Results section: The figure displaying change over time for the Sleep outcome in **Figure 2(d)** is in error.

An updated figure is attached.

Discussion section: The final sentence of the first paragraph under the subheading '**Principal findings**' contains errors regarding sleep.

Corrected paragraph:

As hypothesized, this study found overall HRQL improved over 3-months in patients accessing prescribed MC in Australia. Results showed both statistically significant and clinically meaningful improvements in overall HRQL, sleep, and fatigue for people with chronic health conditions. Similar improvements were found in pain scores for participants with chronic pain; depression scores for patients with depression; and anxiety scores in patients with anxiety.

Discussion section: The first sentence in the fourth paragraph under the subheading '**Comparison with other medicinal cannabis studies assessing PROs**' is in error.

Corrected sentence:

Similar to our findings, an observational study published in 2021 found significant improvements in Pittsburgh Sleep Quality Index scores after 3-months in 36 chronic pain patients prescribed CBD:THC.

Discussion section: The paragraph under the subheading '**Clinical implications**' contains errors.

Corrected paragraph:

Our findings suggest that prescribing MC in clinical practice may alleviate symptoms of pain, fatigue, sleep disorders, anxiety, and depression in patients with chronic health conditions and improve overall HRQL. More research is needed to understand the full effects of MC for treating these symptoms and possibly identify optimal MC formulations, dosing, and routes of administration. Current clinical guidelines recommend clinicians consider trialing MC with patients who have chronic conditions not responding to first line treatments,(79) but acknowledge more evidence and education is needed for clinicians to put this into practice. At the very least, prescribing MC may avoid potential risks of cannabis abuse by self-medicating while enabling clinicians to monitor possible adverse effects.

Conclusion section: The first sentence contains errors.

Updated sentence:

Short-term findings over 3-months indicate that patients prescribed MC in practice have improved HRQL and sleep, and reduced fatigue. Patients experiencing anxiety, depression, or chronic pain also improved in those outcomes over 3-months.

How did this error occur?	The four reverse scored items in the downloaded REDCap version of the sleep measure, PROMIS Short Form v1.0 Sleep Disturbance 8b, were mistakenly reversed again in the data file. Scores erroneously showed an increase in sleep disturbance for responses that indicated a decrease in sleep disturbance, and vice versa.
How do the error(s) affect the results, conclusions, and overall scientific understanding of your study?	The results and conclusions incorrectly stated that there were no improvements in sleep. Re-analysis on the correctly scored sleep disturbance measure indicate statistically significant and clinically meaningful improvements in the patient-reported sleep outcome.

Please check any of the boxes below for the relevant category of error and complete the additional information sections below related to the selected error(s). If your error is not related to these areas, simply fill out the information in the first table.

- ☐ [Affiliation Error](#)
- ☒ [Figure/Figure Legend Error](#)
- ☒ [Table Error](#)

☒ I confirm that I have provided all relevant, corrected files that should be used in publishing the formal correction.

APPENDIX 5: SUPPLEMENTARY MATERIAL

- CHAPTER 5

Referenced in the publication:

Supplementary 1 Table: Condition-specific PROMs for chronic pain or movement disorder

Supplementary 2 Table: Patient-reported gender identity and ethnicity of participants

Supplementary 3 Table: Conditions treated with medicinal cannabis

Additional material:

STROBE checklist

S1 Table. Condition-specific outcomes assessed including characteristics, scoring, and details of use, for PROMs administered to QUEST participants with diagnosed chronic pain or movement disorder.

Outcome	PROM	Number of items	Description	Rating	Recall period	Scoring	Details
Pain							
	PROMIS Scale v2.0 - Pain intensity 3a	3	How much pain hurts at its worse, on average, and right now.	Items rated 1 (no pain) to 5 (very severe).	Past 7 days and now	PROMIS pain measure generates a T-score with a mean of 50 and standard deviation of 10 in a reference population of the US general population (US 2000 Census). ¹ Higher scores reflect greater pain intensity. [‡]	PROMIS Pain intensity has been validated and used extensively in studies of inflammatory arthritis. ²
	PROMIS Short Form v1.0 - Pain Interference 8a	8	The extent to which pain hinders sleep, enjoyment in life, and engagement with social, cognitive, emotional, physical, and recreational activities.	Items rated 1 (not at all) to 5 (very much so).	Past 7 days	PROMIS pain measure generates a T-score with a mean of 50 and standard deviation of 10 in a reference population of the US general population (US 2000 Census). ¹ Higher scores reflect greater pain interference. [‡]	PROMIS Pain interference has been validated and used in studies of inflammatory arthritis and chronic back pain. ^{2,3}
Motor function							
	Neuro-QoL Adult Upper Extremity Function – Fine Motor, Activities of Daily Living – Short Form v1.0	8	The ability to perform activities involving digital, manual, and reach-related functions, including self-care.	Items rated 1 (unable to do) to 5 (without any difficulty).	now	Neuro-QoL measures generate a T-score with a mean of 50 and standard deviation of 10 in a reference general population. ¹ Higher scores indicate better functioning. [‡]	Neuro-QoL Upper Extremity Function is a validated measure, ⁴ used to detect change in patients with stroke, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson disease, epilepsy, and muscular dystrophy. ⁵

Neuro-QoL Quality of Life in Neurological Disorders; PROM patient-reported outcome measure; PROMIS Patient-Reported Outcomes Measurement Information System

[‡]The HealthMeasures Scoring Service recommended for NeuroQoL and PROMIS instruments was used to calculate T-scores using item level calibrations more accurately than manually transforming total raw scores⁶

All other PROMs administered to QUEST participants are described in detail elsewhere.⁷

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7. Tait M-A, Costa DSJ, Campbell R, et al. Health-related quality of life in patients accessing medicinal cannabis in Australia: The QUEST initiative results of a 3-month follow-up observational study. *PLOS ONE*. 2023;18(9):e0290549; doi: 10.1371/journal.pone.0290549.

S2 Table. Patient-reported gender identity and ethnicity of 2744 participants recruited to the QUEST Initiative by those included in the 12-month analyses and those who completed baseline only.

Participant Characteristics (n=2744)	Completed baseline only (n=391)	Completed baseline + follow-up (n=2353)	P value (χ^2)
Gender identity, n (%)			
Man	142 (36.3)	836 (35.5)	0.857
Woman	224 (57.3)	1404 (59.7)	
Transgender	1 (0.3)	2 (0.1)	
Genderqueer	-	4 (0.2)	
Agender	-	2 (0.1)	
Genderless	-	1 (0.0)	
Non-binary	4 (1.0)	13 (0.6)	
Trans Man	-	1 (0.0)	
Two-Spirit	-	1 (0.0)	
Genderfluid	1 (0.3)	4 (0.2)	
Undisclosed	19 (4.9)	85 (3.7)	
Ethnicity, n (%)			
Aboriginal or Torres Strait Islander	14 (3.6)	54 (2.3)	0.145
Other Australian	216 (55.2)	1309 (55.6)	
New Zealander or Polynesian	6 (1.3)	71 (3.0)	
British	52 (13.3)	374 (15.9)	
Irish	9 (2.3)	71 (3.0)	
North-West European	19 (4.9)	119 (5.1)	
Southern and Eastern European	17 (4.3)	125 (5.3)	
North African and Middle Eastern	6 (1.5)	18 (0.8)	
South-East Asian	4 (1.0)	20 (0.9)	
North-East Asian	4 (1.0)	21 (0.9)	
Southern or Central Asian	7 (1.8)	24 (1.0)	
North American	8 (2.0)	35 (1.5)	
South or Central American	5 (1.3)	31 (1.3)	
Sub-Saharan African	9 (2.3)	24 (1.0)	
Undisclosed	15 (3.8)	57 (2.4)	

S3 Table. Conditions treated with medicinal cannabis for 2744 participants recruited to the QUEST 12-month study.

Conditions treated with MC	Completed baseline only (n=391)	Included in analysis (n=2353)	P value (χ^2)
(clinicians selected up to two conditions per patient)	n (%)	n (%)	
			0.074
Pain - musculoskeletal	140 (35.8)	896 (38.1)	
Pain – neuropathic	79 (20.2)	547 (23.2)	
Sleep disorder	99 (25.3)	546 (23.2)	
Generalised anxiety disorder	90 (23)	520 (22.1)	
Mixed depressive and anxiety disorder	53 (13.6)	263 (11.2)	
Pain - widespread	24 (6.1)	212 (9.0)	
Pain - headache or orofacial	15 (3.8)	128 (5.4)	
Post-traumatic stress disorder	19 (4.9)	127 (5.4)	
Pain – visceral	16 (4.1)	114 (4.8)	
Movement disorder (any) ^a	10 (2.6)	60 (2.5)	
Pain - Cancer related	9 (2.3)	28 (1.2)	
Recurrent depressive disorder	2 (0.5)	25 (1.1)	
Epilepsy	3 (0.8)	18 (0.8)	
Bipolar disorder	0	12 (0.5)	
Pain - Chronic postsurgical or post traumatic	3 (0.8)	10 (0.4)	
Other ^b	22 (5.6)	71 (3.0)	

^a Movement disorders included: Parkinsonism, tremor, paroxysmal dyskinesias, dystonia, ataxia, and tic disorders.

^b Other conditions included: attention deficit hyperactivity disorder, autism spectrum disorder, anorexia, bladder irritation with dysuria, bloating, cachexia and wasting, chronic fatigue, chronic gum disease, Congenital Adrenal Hyperplasia, dysmenorrhea, eosinophilic gastroenteritis, Hashimoto's thyroiditis, Irritable bladder syndrome, irritable bowel syndrome, inflammatory bowel diseases, Mast cell activation, nausea and vomiting, Nystagmus, Obsessive compulsive disorder, Perimenopause, Peripheral Neuropathy, Polymyalgia rheumatica, premenstrual dysphoric disorder, Severe eczema, topical steroid withdrawal syndrome.

STROBE Statement—checklist of items that should be included in reports of observational *cohort* studies

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	1	12-month follow-up observational study
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2	Abstract - AMRaC structured
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4	Introduction - First 2 paragraphs
Objectives	3	State specific objectives, including any prespecified hypotheses	5	This study reports... to determine if... and to explore... We hypothesised that...
Methods				
Study design	4	Present key elements of study design early in the paper	5	Methods - Study population and design
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-6	Methods - Study population and design Methods - Data Collection
Participants	6	(a) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5-6	Methods - Study population and design Methods - Data Collection
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed	n/a	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5	Methods - Study population and design
			6	Methods - Data Collection
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5	Methods - Study population and design
			6	Methods - PROMs
Bias	9	Describe any efforts to address potential sources of bias	30	Discussion - Strengths and limitations

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Study size	10	Explain how the study size was arrived at	7	Methods – Statistical analysis
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7	Methods – Statistical analysis
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	7	Methods – Statistical analysis
		(b) Describe any methods used to examine subgroups and interactions	7	Methods – Statistical analysis
		(c) Explain how missing data were addressed	26	Results – Missed assessments
		(d) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed	7	Methods - Study population and design
			24	Results – Missed assessments
		(e) Describe any sensitivity analyses	7	Methods – Statistical analysis
Results				
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9	Results and Figure 1 Table 1
		(b) Give reasons for non-participation at each stage		Results and Figure 1
		(c) Consider use of a flow diagram		Results Figure 1
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11	Results Tables 1-2; S2; Figure 12
		(b) Indicate number of participants with missing data for each variable of interest		Figures 2-9
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	6	Methods – Data Collection
Outcome data	15	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	9-18	Results and Tables 3 and 5
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	13-23	Results Tables 3-6
		(b) Report category boundaries when continuous variables were categorized	8 16-20	Methods - Statistical analysis Results - Figures 5-8 and Figure 10
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a	

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	15-24	Results
Discussion				
Key results	18	Summarise key results with reference to study objectives	24	Discussion – Principal findings
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	28-29	Discussion – Strengths and limitations
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	24 30	Discussion – Principal findings Discussion – Conclusions
Generalisability	21	Discuss the generalisability (external validity) of the study results	28-29	Discussion – Strengths and limitations
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	sup	Declarations - Funding

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

APPENDIX 6: SUPPLEMENTARY MATERIAL - CHAPTER 6

Referenced in the publication:

Supplementary 1: Interview Script

Additional material:

COREQ checklist

Interview Script

The QUEST Initiative: Follow-up Interview Study

[Spoken by researcher]: Thank you for agreeing to participate in this interview. I have some questions about your experience of being prescribed medicinal cannabis. There are no right or wrong answers. The interview will be audio-recorded, and I will let you know when I start the recorder.

Please let me know if you would like to take a break at any point or wish to stop the interview.

I will start recording now.

- 1) To begin, can you please tell me a little about your health condition that was being treated with medicinal cannabis when you were on The QUEST study.
 - a) How long had you had this condition?
 - b) What impact did this have on your daily life?
 - c) Did your doctor prescribe medicinal cannabis for any other condition?

- 2) When you joined the QUEST study, do you remember how you felt about being prescribed medicinal cannabis?
 - a) What were your expectations?
 - b) Did you read or search for information about taking medicinal cannabis for your condition?
 - i) What did you learn? What stood out to you? What would that mean for you?
 - c) Did you have any concerns?
 - d) Who suggested trying medicinal cannabis?
 - e) Did you feel that your health care provider was knowledgeable about medicinal cannabis? And your condition?
 - i) Can you describe an occasion that gives an example of that? (what did they say?)

- 3) After taking medicinal cannabis did your condition change the way you expected?
 - a) Better/worse
 - b) What aspects changed? What were your thoughts about that?
 - c) Was anything unexpected?
 - d) Did you experience any side effects?
 - e) What did you think of administering it as an oil? (taste, measurement, etc)

- 4) When adjusting your medicinal cannabis doses, what were you monitoring for signs of improvement?
 - i) What signalled an improvement, or that the dose is too high?
 - b) Did you experience any benefits in other areas?
 - c) Are you currently managing your condition with medicinal cannabis?

- i) what would be the main reasons for continuing/stopping?
- ii) If stopped, how are you managing your condition?

[Spoken by researcher]: That is the end of all my questions. Is there anything else you would like to add relating to your medicinal cannabis therapy that we haven't covered?

Thank you for your time today.

COREQ (Consolidated criteria for REporting Qualitative research) Checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
<i>Personal characteristics</i>			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	5
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	5
Occupation	3	What was their occupation at the time of the study?	5
Gender	4	Was the researcher male or female?	5
Experience and training	5	What experience or training did the researcher have?	5
<i>Relationship with participants</i>			
Relationship established	6	Was a relationship established prior to study commencement?	5
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	5
Interviewer characteristics	8	What characteristics were reported about the interviewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	5
Domain 2: Study design			
<i>Theoretical framework</i>			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	4
<i>Participant selection</i>			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	5
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	5
Sample size	12	How many participants were in the study?	6
Non-participation	13	How many people refused to participate or dropped out? Reasons?	6
<i>Setting</i>			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	6
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	6-7
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	6-7
<i>Data collection</i>			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	Sup 1 and p.5
Repeat interviews	18	Were repeat interviews carried out? If yes, how many?	no
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	6
Field notes	20	Were field notes made during and/or after the interview or focus group?	5
Duration	21	What was the duration of the interviews or focus group?	6
Data saturation	22	Was data saturation discussed?	6
Transcripts returned	23	Were transcripts returned to participants for comment and/or	no

Topic	Item No.	Guide Questions/Description	Reported on Page No.
		correction?	
Domain 3: analysis and findings			
<i>Data analysis</i>			
Number of data coders	24	How many data coders coded the data?	6
Description of the coding tree	25	Did authors provide a description of the coding tree?	7
Derivation of themes	26	Were themes identified in advance or derived from the data?	7
Software	27	What software, if applicable, was used to manage the data?	6
Participant checking	28	Did participants provide feedback on the findings?	no
<i>Reporting</i>			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	7-19
Data and findings consistent	30	Was there consistency between the data presented and the findings?	7-19
Clarity of major themes	31	Were major themes clearly presented in the findings?	7
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	7-19

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Once you have completed this checklist, please save a copy and upload it as part of your submission. DO NOT include this checklist as part of the main manuscript document. It must be uploaded as a separate file.

APPENDIX 7: ADDITIONAL ANALYSES FOR PEOPLE WITH CANCER

Abstract presented at the 2023 MASCC/ISOO Annual Meeting

Tait M, Costa DSJ, Campbell R, Rutherford C, CANCER-16: Change in quality of life and pain outcomes for cancer patients accessing prescribed medical cannabis: the QUEST Initiative 3-month results. *Supportive Care in Cancer* 2023; 31(Suppl 1): S399 (S23-S24).

Change in quality of life and pain outcomes for cancer patients accessing prescribed medical cannabis: the quest initiative 3-month results.

Introduction

Since Australia legalised medicinal cannabis in 2016, more than 10,000 cancer patients have received prescriptions for symptom management. Clinical practice guidelines favour cannabis due to patients' placing high value on small improvements, and willingness to accept small-modest risks of adverse effects. However, reporting of patient-reported outcomes in clinical practice is limited. We aimed to assess changes in pain and overall quality of life (QoL) for cancer patients prescribed medicinal cannabis.

Methods

This sub-study includes participants with any cancer diagnosis recruited to QUEST; a prospective observational study of adult patients prescribed medicinal cannabis oil between Nov2020-Dec2021, by 117 clinicians across Australia. QoL and pain were assessed using EQ-5D-5L, and QLQ-C30 pain subscale respectively, at baseline, titration, then monthly for 3 months. Change over time was analysed using linear mixed models adjusted for age, sex, pain duration, and prior use of cannabis.

Results

Of 145 patients diagnosed with cancer invited to the study, 98 provided consent and completed both baseline and at least one follow-up questionnaire. Participants mean age was 61.3years (SD:13.1), 58.2% female, and 10.2% in palliative care (see Table 1 for further demographics). Improvements were observed from baseline to follow-up in QoL (MD=0.11, SD=0.27; $t_{(363)}=3.87$, $p<0.001$)(Figure 1) and pain scores (MD=11.53, SD=25.78; $t_{(366)}=4.43$,

$p < 0.001$)(Figure 2). Following questionnaire interpretation guidelines, these changes indicated clinically meaningful improvement.

Conclusions

Clinically meaningful improvements in pain and QoL for cancer patients prescribed medicinal cannabis in a real-world setting were observed following titration and maintained over 3 months. Findings suggest that prescribing medicinal cannabis in clinical practice may alleviate cancer patients' symptoms and improve overall QoL while avoiding potential risks of cannabis abuse by self-medicating and enabling clinicians to monitor possible adverse events. Lack of control group limits interpretation of results. The QUEST Initiative continues to follow patients over 12-months to determine whether 3-month improvements are maintained long-term.

Table 1. Baseline characteristics of 98 cancer patients participating in the QUEST Initiative study

Characteristic	N=98	%
Type of cancer		
Breast	31	31.6
Prostate	15	15.3
Lung	5	5.1
Colorectal	5	5.1
Non-Hodgkin Lymphoma	5	5.1
Melanoma	4	4.1
Multiple Myeloma	3	3.1
Head & Neck	3	3.1
Brain	3	3.1
Thyroid	2	2.0
Pancreas	2	2.0
Ovarian	2	2.0
Liver	2	2.0
Other Cancer	16	16.3
Condition treated		
Pain – Chronic cancer pain	29	29.6
Pain – Chronic musculoskeletal	27	27.6
Pain – Chronic neuropathic	11	11.2
Generalised anxiety disorder	8	8.1
Chronic insomnia	6	6.1
Pain – Chronic widespread	4	4.1
Pain – Chronic headache	3	3.1
Pain – Chronic visceral	3	3.1
Mixed depressive & anxiety disorder	2	2.0
Nausea & vomiting	2	2.0
Epilepsy or seizure	1	1.0
Other symptoms	2	2.0
Marital status		
Married	57	58.2
Divorced	13	13.3
Cohabiting	12	12.2
Single	10	10.2
Separated	3	3.1
Widowed	3	3.1
Highest education level		
University Degree or higher	33	33.7
Certificate or Diploma	32	32.7
High School	32	32.7
Primary School	1	1.0
Living arrangements		
Live with partner	69	70.4
Live alone	17	17.3
Live with other	12	12.2

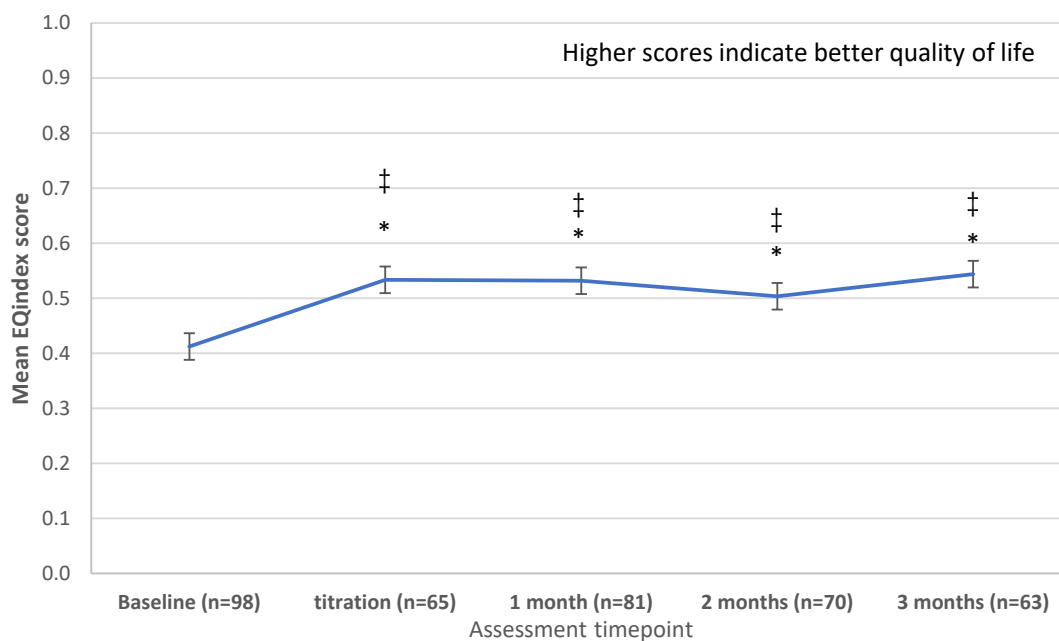


Figure 1. Change over time in mean EQ-5D-5L utility index scores for 98 participants prescribed medicinal cannabis in the QUEST Initiative cancer sub-study (with SE bars; *indicates significant change from baseline, $p < 0.05$; ‡ indicates clinically meaningful change from baseline ≥ 0.07 points).

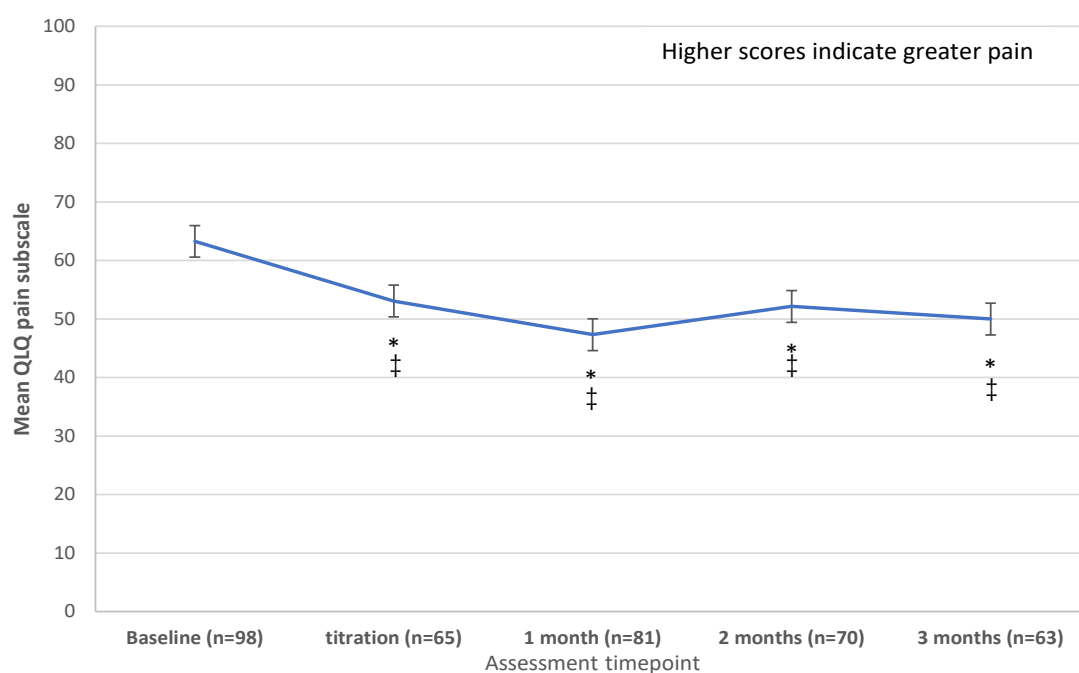


Figure 2. Change over time in mean QLQ-C30 pain subscale scores for 98 participants with cancer prescribed medicinal cannabis in the QUEST Initiative study (with SE bars; *indicates significant change from baseline $p < 0.05$; ‡ indicates clinically meaningful change from baseline ≥ 10 points).

Abstract presented at the 2023 NSW Cancer Conference

Quality of life and pain outcomes for cancer patients prescribed medicinal cannabis: the quest initiative 12-month results.

M Tait, DSJ Costa, K White, R Campbell, C Rutherford, Sydney Nursing School, and School of Psychology, University of Sydney

Introduction

Since 2018, more than 11,000 Australian patients have received medicinal cannabis prescriptions for cancer-related pain and symptoms.¹ However, reporting of patient-reported outcomes associated with medicinal cannabis use in clinical practice is limited. We aimed to assess changes in overall health-related quality of life (HRQL), pain intensity, and pain interference, for cancer patients prescribed medicinal cannabis.

Methods

This sub-study includes patients with any cancer diagnosis recruited to the QUEST Initiative; a longitudinal observational study of patients prescribed medicinal cannabis oil between Nov2020-Dec2021, by 117 clinicians across Australia. Outcomes were assessed using EORTC QLQ-C30², PROMIS Scale v1.0 - Pain Intensity 3a³, and PROMIS Short Form v1.0 - Pain Interference 8a⁴, pre-treatment, after 2-week titration, then 1-,2-,3-,5-,7-,9-, and 12-months post-titration. Change over time was analysed using linear mixed models adjusted for age and gender.

Results

Of 127 eligible cancer patients, 89 consented and completed both baseline and at least one follow-up questionnaire. Participants were between 33 and 91 years old, mean age 61.8 years (SD:13.3), and 56.2% were female. Most common diagnoses were breast cancer (27/89, 30%) and prostate cancer (16/89, 18%), and most participants were prescribed medicinal cannabis for pain (76/89, 85%), particularly musculoskeletal pain in joints, bones, muscle, or tendons (30/89, 34%) and cancer pain caused by the cancer itself or its treatment (25/89, 28%). Questionnaire completion rates for each timepoint ranged between 88% at 1 month to 29% at 1 year. Statistically significant improvements in QLQ-C30 Summary scores

were observed at all follow-up timepoints compared with baseline, and from baseline to mean follow-up (MD=6.37, SD=14.96; $t_{(437)}=4.02$, $p<0.001$). In the absence of formal guidelines for interpreting within group change for QLQ-C30 summary scores, Cohen's d 0.43 indicated a small to medium improvement in HRQL. Pain Intensity T-scores improved from baseline to mean follow-up (MD=3.23, SD=6.45; $t_{(366)}=4.45$, $p<0.001$), and Pain interference T-scores improved similarly (MD=3.10, SD=8.23; $t_{(341)}=3.34$, $p<0.001$). Following PROMIS interpretation guidelines, improvements in pain outcomes were clinically meaningful (>3 T-scores).

Conclusions

We observed clinically meaningful improvements in pain outcomes and small to medium improvements in HRQL for cancer patients prescribed medicinal cannabis in a real-world setting over 12 months. Findings suggest prescribing medicinal cannabis may alleviate cancer patients' pain symptoms and improve HRQL while allowing clinicians to monitor adverse events, prevent drug-drug interactions, and avoid risks of cannabis abuse through self-medicating. Lack of control group limits interpretation of the results.

References

1. Therapeutic Goods Administration (TGA). Medicinal cannabis Special Access Scheme Category B data: SAS-B Indications [SAS-B Bulk Data]. [online]: *Australian Government*; 2024 [Available from: <https://www.tga.gov.au/products/unapproved-therapeutic-goods/medicinal-cannabis-hub/medicinal-cannabis-access-pathways-and-patient-access-data/medicinal-cannabis-special-access-scheme-category-b-data> [Last accessed: 2 May 2025].
2. Aaronson NK, Ahmedzai S, Bergman B, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst.* 1993;85(5):365-76.

3. Cella D, Yount S, Rothrock N, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS): Progress of an NIH Roadmap Cooperative Group During its First Two Years. *Medical Care*. 2007;45(5).
4. Chen CX, Kroenke K, Stump T, et al. Comparative Responsiveness of the PROMIS Pain Interference Short Forms With Legacy Pain Measures: Results From Three Randomized Clinical Trials. *The journal of pain : official journal of the American Pain Society*. 2019;20(6):664-75; doi: <https://dx.doi.org/10.1016/j.jpain.2018.11.010>.