Framing the use of cannabis as a medicine in New Zealand: Regulatory, Clinician and Patient contexts

BY

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Abstract

A medicine is a substance developed for administration to humans for therapeutic purposes that achieves its action by pharmacological, immunological or metabolic means. Pharmaceutical medications undergo years of pre-clinical and clinical trials to establish their safety, tolerability and efficacy. Cannabis, whether in raw or processed form, sits predominantly outside this remit. Its use falls broadly into four categories; recreational, plant used for medicinal purposes, cannabis-based products marketed for medical purposes and pharmaceutical grade cannabinoid medications. The use of cannabis as a medicine involves complex interactions across social, health and political domains, at both a global and national level. New Zealand has attempted to address this with the implementation of the Medicinal Cannabis Scheme in April 2020.

This research was undertaken to develop an understanding of what effect cannabis regulations have had on multiple jurisdictions enacting them and applying this to the New Zealand context, and to understand specific groups of patient-doctor interactions regarding the use of cannabis as a medicine.

First, I undertook a meta-narrative qualitative review synthesising themes relating to the outcomes of cannabis regulatory change across multiple jurisdictions. Five super-ordinate themes were identified in the meta-narrative review; Normalisation, Gatekeeping, Economics, Community and Health, which were applied in framing the conclusion of this thesis.

I then completed a systematic review / meta-analysis examining label accuracy and contaminants in cannabis-based products in regulated markets. Labelling accuracy ranged from 17 to ~86%. Contaminants included microbes, solvents, pesticides and adulterants. Meta-analysis of pesticide contamination showed that the overall proportion of contaminated samples was 0.25 (95% CI: 0.10 to 0.40, Heterogeneity: I^2=79%, X_1^2=4.74, p=0.03).

Finally, I completed six observational studies within New Zealand to determine knowledge, beliefs and reported interactions of doctors and patients regarding the use of cannabis as a medicine in three medical disciplines; general practice (GP), oncology and neurology.

Doctors reported that patients were requesting medical cannabis prescriptions (GP: 55%, Neurology: 63%. Oncology: 84% respectively), and informing them of using illicit cannabis for medical symptoms. All doctors were concerned about prescribing cannabis as a medicine due to lack of evidence and lack of understanding of the prescription processes. Despite this, the majority

were willing to prescribe a funded cannabis-based product backed by evidence of efficacy in traditional clinical trials.

Patients in all three disciplines indicated comfort discussing cannabis with GPs and specialists (GP patients: 91.7%, 92.1%, neurology patients: 88.2%, 90.6%, oncology patients: 85.8%, 88.2% respectively). All groups reported low levels of prescriptions received (<20%). Patients reported illicit use of cannabis for medical reasons (11.2%, 34.6% and 35.5% in GP, neurology and oncology patients respectively), with reported effectiveness of illicit cannabis for their condition ranging from 86.7 to 94.0%. Patients in all three fields wished to know the benefits, side effects and availability of cannabis-based products and had concerns regarding access and cost.

The use of cannabis as a medicine remains a complex situation within the NZ context. Significant implementation issues remain for the Medicinal Cannabis Scheme to ensure the safety and wellbeing of patients in New Zealand.

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List of Publications

The following is a list of articles directly arising from the development of this thesis that have been published:

1. **Oldfield K.** Braithwaite I. Beasley R. Eathorne A. Newton-Howes G. Semprini A. Medical cannabis: knowledge and expectations in a cohort of North Island New Zealand general practitioners. *New Zealand Medical Journal* 2020; 133(1508): 12-28. [Study Three, Included in Chapter 4]
2. **Oldfield K**, Eathorne A, Maijers I, Beasley R, Semprini A, Braithwaite I. Knowledge and perspectives about the use of cannabis as a medicine: a mixed methods observational study in a cohort of New Zealand general practice patients. *New Zealand Medical Journal*. 2020 Sep 25; 133(1522):96-111. PMID: 32994620. [Study Six, Included in Chapter 5]
3. **Oldfield K**, Ryan J, Doppen M, Kung S, Braithwaite I, Newton-Howes G. A systematic review of the label accuracy of cannabinoid-based products in regulated markets: is what's on the label what's in the product? *Australasian Psychiatry*. November 2020. [Epub ahead of print] doi:10.1177/1039856220965334 [Study Two, Included in Chapter 3]
4. **Oldfield K**, Eathorne A, Tewhaiti-Smith J, Beasley R, Semprini A, Braithwaite I. Experiences, patient interactions and knowledge regarding the use of cannabis as a medicine in a cohort of New Zealand doctors in an oncology setting. *Postgraduate Medical Journal* [Published Online First: 20 November 2020]. doi: 10.1136/postgradmedj-2020-139013 [Study Five, Included in Chapter 4]

Permission to reuse material from these publications has been sought and granted from the publishers and permissions may be found in the Appendix (7.1).

The following is a list of articles for publication directly arising from the development of this thesis that have been submitted for publication or are in press:

1. **Oldfield K**, Evans S, Braithwaite I, Newton-Howes G. Don't make a hash of it! A thematic review of the literature relating to outcomes of cannabis regulatory change. *Drugs: Education, Prevention and Policy*, 2021;[In press] doi: 10.1080/09687637.2021.1901855 [Study One, Included in Chapter 2]

2. **Oldfield K,** Eathorne A, Rosemergy I, et al. The use of cannabis-based products as a medicine: Knowledge and expectations in a cohort of New Zealand neurologists. 2020;(Manuscript Submitted for Publication) [Study Four, Included in Chapter 4]

Additional publications completed during the candidature for this thesis:

1. Braithwaite I. Newton-Howes, G. **Oldfield K**. Semprini A. Cannabis-based medicinal products and the role of the doctor: Should we be cautious or cautiously optimistic? *New Zealand Medical Journal*. 2019; 132(1500):82-88
2. Berg MVD. John M. Black M. Semprini A. **Oldfield K.** Glass M. Braithwaite I. Cannabis-based medicinal products in arthritis, a painful conundrum. *New Zealand Medical Journal* 2020; 133(1515):35-45.
3. Braithwaite I. Bhagavan C. Doppen M. Kung S. **Oldfield K.** Newton-Howes G. Medicinal applications of cannabis/cannabinoids. *Current Opinion in Psychology*. [Published online first: October 2020.] 2021;38:1-10 doi:10.1016/j.copsyc.2020.06.002
4. Bhagavan, C. Kung, S. Doppen, M. John, M. Vakalalabure, M. **Oldfield, K**. Braithwaite, I. Newton-Howes, G. Cannabinoids in the Treatment of Insomnia Disorder: A Systematic Review and Meta-Analysis. *CNS Drugs* 2020 [Published Online First: 26 November 2020] https://doi.org/10.1007/s40263-020-00773-x

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Abbreviations

2-AG	2-arachidonoglycerol
5HT	5-hydroxytryptamine
9HPT	Nine-hole peg test
ACRE	Australian Centre for Cannabinoid Clinical and Research Excellence
ACT	Australian Capital Territory
AEA	Anandamide
AIDS	Acquired Immune Deficiency Syndrome
CB_1	Cannabinoid Receptor 1
CB_2	Cannabinoid Receptor 2
CBC	Cannabichromene
CBD	Cannabidiol
CBE	Cannabielsoin
CBG	Cannabigerol
CBL	Cannabicyclol
CBN	Cannabinol
CBND	Cannabinodiol
CBT	Cannabitriol
CINV	Chemotherapy induced nausea and vomiting
CME	Continuing Medical Education
COVID-19	Coronavirus Disease 2019
CTP	Cannabis for therapeutic purposes
CUD	Cannabis use disorder
DHB	District Health Board
Fast RP-HPLC/UV	Fast Reverse phase-high performance liquid chromatography/ultraviolet detection
FDA	Food and Drug Administration
FTE	Full time equivalent
$GABA_A$	Gamma-amino butyric acid
GC-MS	Gas chromatography-mass spectrometry
GCMS/MS	Gas chromatography-tandem mass spectrometry
GLyR	Glycine receptor
GMP	Good Manufacturing Practice
GP	General Practitioner
GPR_{18}	G-protein coupled receptor 18

GPR_{55}	G-protein coupled receptor 55
HIV	Human Immunodeficiency Virus
HPLC	High performance liquid chromatography
HPLC- MS/MS	High performance liquid chromatography-mass spectrometry
IT	Information Technologist
ITT	Intention to treat
LC-QTOF-MS	Liquid chromatography-quadrupole time of flight-mass spectrometry
MAD	Multiple Ascending Dose
MCA	Medical Cannabis Agency
MCID	Minimal important clinical difference
MCRC	Medical Cannabis Research Collaborative
MCS	Medical Cannabis Scheme
MOH	Ministry of Health
MRINZ	Medical Research Institute of New Zealand
MS	Multiple sclerosis
NASEM	National Academies of Science, Engineering and Medicine
NICE	The National Institute for Health and Care Excellence
NRS	Numerical Rating Scale
NSAID	Non-steroidal anti-inflammatory drug
NZ	New Zealand
OEA	Oleoylethanolamide
PHARMAC	Pharmaceutical Management Agency
PHO	Primary Health Organisation
PIC	Pharmaceutical Inspection Convention
PIS	Participant Information Sheet
PONV	Postoperative nausea and vomiting
PP	Per protocol
PPARγ	Peroxisome proliferator-activated receptor gamma
PRISMA	Preferred Reporting Items for Systematic Review
RCT	Randomised Control Trial
REDCap	Research Electronic Data Capture
SAD	Single Ascending Dose
SMO	Senior Medical Officer
TGA	Therapeutic Goods Administration
THC	Tetrahydrocannabinol
$TRPV_2$, $TRPV_3$, $TRVP_4$	Vanilloid type 2, 3 and 4 receptors

UHPLC(-PDA)	Ultra high-performance liquid chromatography-photodiode assay
UK	United Kingdom
UN	United Nations
US	United States
VAS	Visual Analogue Scale
Δ-8 THC	Delta-8-tetrahydrocannabinol
Δ-9 THC	Delta-9-tetrahydrocannabinol

Chapter 1 Introduction and Literature Review

1.1 What is 'cannabis'?

The word cannabis invokes different responses in different people. Some consider it a harmless drug with euphoric effects, whilst others see it as harmful drug of abuse. Different responses are also present when considering the potential medical therapeutic effects of cannabis, where beliefs range from cannabis having unlimited medical benefits to no benefits at all. Cannabis legal policy typically reflects local and global socio-cultural constructs and a prohibitionist stance in the 1930s led to limited medical research output in the last 100 years. Globally this stance is now changing, with resultant pressure to enact legislation allowing increased access to cannabis for both recreational and medical purposes. These changes in global legislation provide not only an opportunity for increased research of cannabis for medical purposes, but also a platform to reflect on the social and health effects of cannabis legislative change.

In this thesis, I primarily examine the use of cannabis as a medicine in the New Zealand (NZ) context, drawing from overseas examples of legislative and regulatory implementation and exploring local patient-doctor interactions. I then relate these findings to evolving legislative change in NZ.

In this chapter, I provide an overview of cannabis, its proposed physiological actions in the human body, the types of medical products available, and the health effects and harms observed within the literature. The legal status of cannabis and the impact of these laws are discussed in depth in Chapter 2.

1.2 Cannabis sativa L. and phytocannabinoids

The plant genus, *Cannabis sativa L*. is broadly diverse, with the varieties *sativa* and *indica* considered the most important for their cultivations for cannabinoid content.[1] The plant itself is a described by ElSohly et al. as a "*dicotyledonous (flowering plant with two leaves at germination), herbaceous (non-woody plant of which the aerial parts die after fruiting), diecious (the male plants are distinct from the female plants), apetalous (the flower has no corolla), annual herb*".[1(p4)] It is thought to have possibly originated from the Himalayas, and spread throughout the Asian continent, subsequently through the Middle East and then to Europe, South America and then NorthAmerica.[1] For approximately five to six thousand years the plant species has been used as a textile and fibre

source, as well as for recreational, medical and spiritual purposes.[1,2] Approximately 560 naturally occurring compounds have been isolated within the cannabis plant; including cannabinoids and terpenoids.

1.2.1 Phytocannabinoids

Phytocannabinoids are the chemical compounds produced by the glandular trichomes of the plant and are primarily found in the leaves and buds. Cannabinoids are defined as having a C_{21} terpenophilic skeleton. The first phytocannabinoid, cannabinol (CBN) was isolated at the end of the 19th century and its structure elucidated in the 1930s, with cannabidiol (CBD) isolated in 1940 and delta-9-tetrahydrocannabinol (Δ9-THC or THC) isolated in 1942.[3] Following this, at least 120 cannabinoids have been isolated and are commonly grouped into eleven classifications; delta-9-*trans*-tetrahydrocannabinol, delta-8-*trans*-tetrahydrocannabinol (Δ8-THC), cannabidiol, cannabigerol (CBG) , cannabinol, cannabichromene (CBC), cannabinodiol (CBND), cannabielsoin (CBE), cannabitriol (CBT), cannabicyclol (CBL) and miscellaneous types.[1]

Of these, those cannabinoids of primary interest to researchers and the main focus of this thesis, are Δ9-THC and CBD. These have been used to determine the primary chemotaxonomy of the cannabis plant.[1,4] Phenotypically, *Cannabis sativa* can be divided into three groups, with exemplars of the range of cannabinoids associated with these groups below:[4]

- THC-type: 0.5-15 % Δ9-THC and CBD 0.01-0.16% (CBD: Δ9-THC ratio <0.02)
- Hybrid: 0.5-5 % Δ9-THC and CBD 0.9-7.3% (CBD: Δ9-THC ratio 0.6-4)
- CBD-type: 0.05-0.7% Δ9-THC and CBD 1.0-13.6% (CBD: Δ9-THC ratio >5), with plants that have less than 0.35% THC classified as industrial hemp in NZ and are primarily used for fibre and textile production.

THC-type plants are sometimes referred to as 'drug type'[1], as the high levels of THC are responsible for the euphoric effects that have been observed in human use. CBD-type plants on the other hand do not appear to induce euphoria, however the phytocannabinoid cannabidiol has become the focus of much research due to its purported anti-inflammatory, anti-anxiety and anti-seizure activity. There is much speculation regarding how the ratio of phytocannabinoids as well as the interactions with terpenoids in the plants affect the physiological impact in humans, and this has been termed the entourage effect. This term, coined by Mechoulam in 1988, supports the interest in the development of whole plant medicines, rather than synthetically producing individual cannabinoids.[5]

1.3 The endocannabinoid system and endocannabinoids

The discovery of the human endocannabinoid system was not made until long after the isolation of plant-based phytocannabinoids. In the mid-1980s the first evidence of cannabinoid receptors existing was found, with the eventual discovery of the G-protein coupled cannabinoid receptor one (CB_1) in 1990 and subsequently cannabinoid receptor two (CB_2) receptor in 1992.[3] The CB_1 receptor is primarily found within the central nervous system, whilst the CB_2 receptors are found mainly on the peripheral immune cells.[3] Whilst CB_1 and CB_2 are considered the main receptors within the endocannabinoid system, others such as the orphan receptors G-protein coupled receptor 55 (GPR_{55}) and G-protein coupled receptor 18 (GPR_{18}) have been show to interact with both phytocannabinoids and endogenous cannabinoids.[6] These are regarded as putative cannabinoid receptors.

1.3.1 Endocannabinoids

Endogenous cannabinoids were discovered in 1992. These are cannabinoids produced within the human body. The first endogenous cannabinoid discovered was anandamide, or AEA, which is a cannabinoid receptor agonist. The second most studied endocannabinoid is 2-arachidonyl glycerol (2-AG), which is also a cannabinoid receptor agonist. Other endogenous cannabinoids include virodhamine, palmitoylethanolamide, oleoylethanolamide (OEA) and noladin ether.[6] The synthesis of endogenous cannabinoids occurs on demand in the post-synaptic nerve terminal. Following release into the synapse they bind to the cannabinoid receptors on the pre-synaptic terminal, undergoing a cellular reuptake process where they are broken down by mono-acelyglycerol lipase.[3] (Figure 1.1)

1.4 Interaction of phytocannabinoids, the endocannabinoid system and other receptor systems

There is still limited understanding of phytocannabinoid interactions with human endogenous cannabinoid receptors, which appears to be a complex process. THC has been determined to be a moderate partial agonist of both CB_1 and CB_2 receptors, dependent on expression of the receptors, the cell type involved and the level of endo-cannabinoids present.[7] CBD may be a weak antagonist of CB_1 and CB_2, however much research reports that it has a lack of affinity for the primary

cannabinoid receptors.[7] CBD has also been proposed as a negative allosteric modulator of THC, in keeping with the effects seen *in vivo*.[7] In regards to GPR_{55}, CBD has been shown to have an antagonistic effect.[6]

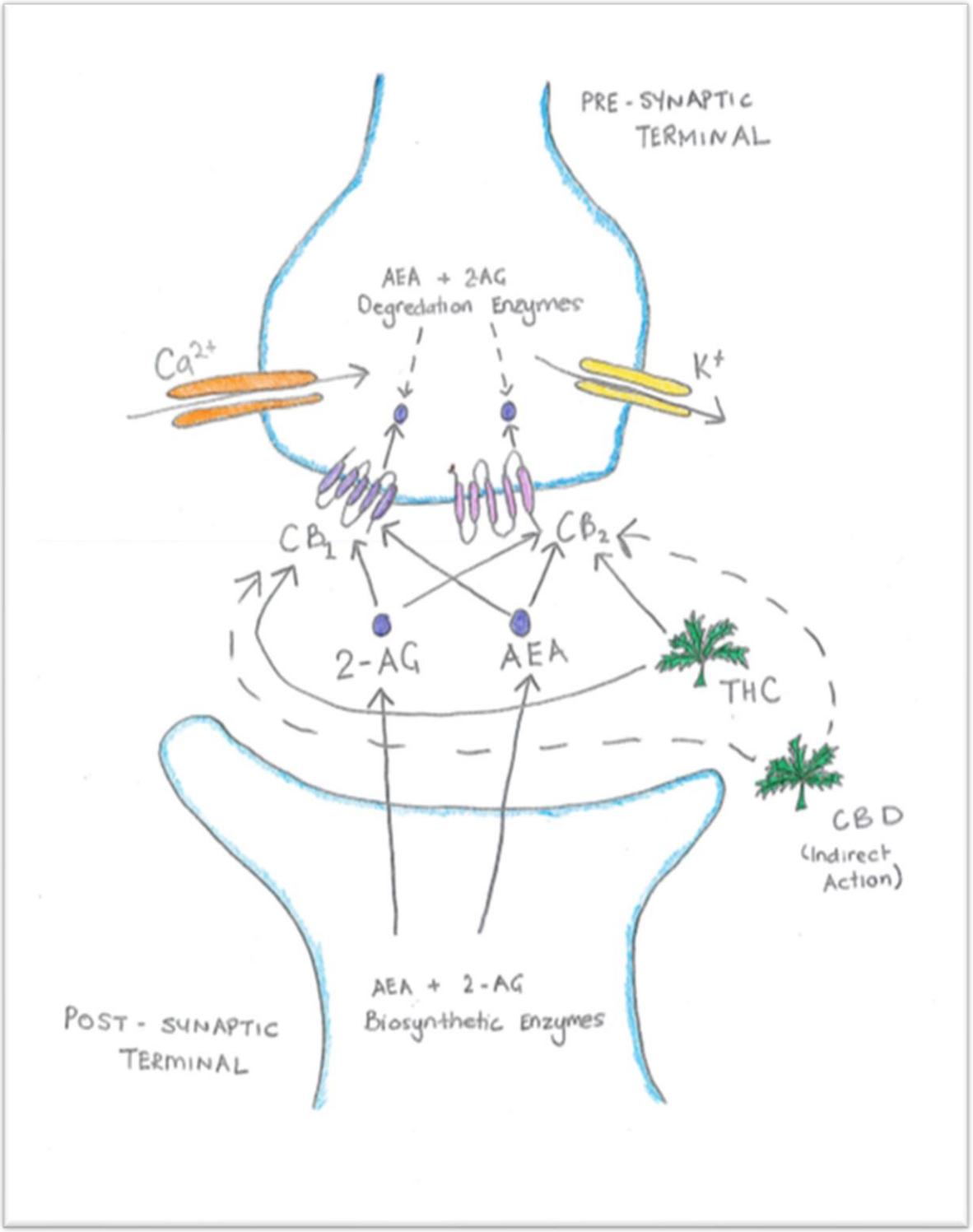

Figure 1.1. The endocannabinoid system- production, uptake and degradation of endogenous cannabinoids and proposed phytocannabinoid interactions. Adapted from Aizpurua-Olaizola et al., Drug Discovery Today[8]

As well as targeting receptors within the endocannabinoid system, research has shown that phytocannabinoids may be ligands for other receptor systems within the human body.

THC has been proposed to be a serotonin 5-hydroxytryptamine three ($5HT_3$) antagonist, an allosteric modulator of opioid receptors, as well as agonising peroxisome proliferator-activated receptor gamma (PPARγ), and vanilloid type two, three and four receptors ($TRPV_2$, $TRPV_3$ and $TRVP_4$).[7]

CBD has also been shown to target receptors outside of the endocannabinoid system- within the serotonin system it is a $5HT_{1A}$ agonist, a $5HT_{2A}$ partial agonist and a non-competitive antagonist of $5HT_3$.[7] CBD is also an agonist of PPARγ, $TRPV_1$, $TRPV_2$ and $TRPV_3$, as well as showing allosteric modulation at opioid receptors, gamma-amino butyric acid ($GABA_A$) and glycine (GLyR) receptors.[7]

Despite the fact that there is knowledge of the molecular targets of phytocannabinoids and hence a large number of therapeutic targets for the medical applications of cannabis-based products, the mechanisms of action remain somewhat unknown, further compounding the complexity surrounding the use of cannabis as a medicine.

1.5 Cannabis-based products

The term 'cannabis-based product' is broad and can refer to a range of products from pharmaceutical grade medicines through to raw plant material. Such a heterogeneous group contributes to the difficulty in assessing the efficacy and safety of the use of cannabis as a medicine.

In NZ a medicine is defined under the Medicines Act 1981 as: *"(a)…any substance or article that - (i) is manufactured, imported, sold, or supplied wholly or principally for administering to one or more human beings for a therapeutic purpose; and (ii) achieves, or is likely to achieve, its principal intended action in or on the human body by pharmacological, immunological, or metabolic means; and (b) includes any substance or article—(i) that is manufactured, imported, sold, or supplied wholly or principally for use as a therapeutically active ingredient in the preparation of any substance or article that falls within paragraph (a); or (ii) of a kind or belonging to a class that is declared by regulations to be a medicine for the purposes of this Act;"*.[9(p16)] If a product meets this description, it is regulated by Medsafe, the NZ Medicines and Medical Devices Authority, and must be approved for distribution in NZ. This includes pharmaceutical grade medicines developed overseas, meaning such medicines may be available internationally but not be approved for

distribution in NZ. Unapproved medicines may be prescribed only under special considerations as described as Section 25 of the Medicines Act.[9]

The term 'pharmaceutical grade' means that the product meets Good Manufacturing Practice (GMP) standards at all levels, encompassing both the individual active pharmaceutical ingredients and the completed medicine as a whole. This helps ensure that products are "*consistently safe, effective and of acceptable quality*".[10] In NZ, GMP requirements were harmonised with the 1992 Pharmaceutical Inspection Convention (PIC) Guide, ensuring processes in NZ drug manufacturing are in line with international best practice.[10] It is possible to meet some of the GMP standards for active ingredients during the manufacturing process and still not be considered a pharmaceutical grade medication in NZ.

The following sections discusses the breakdown the different groups of cannabis-based products, looking at composition, formulation, indications and side effects of the products if known.

1.5.1 Pharmaceutical Grade Products

There are four medications globally that are considered pharmaceutical grade and have undergone clinical trials. These can be divided into synthetically derived (dronabinol and nabilone) and plant derived (nabiximols and cannabidiol (Epidiolex®). Only one, nabiximols, has approval for distribution in NZ.

Dronabinol (Marinol®) consists of synthetically derived THC and was approved for use by the Food and Drug Administration (FDA) in 1985 for the treatment of both anorexia associated with weight loss in Acquired Immune Deficiency Syndrome (AIDS) and chemotherapy induced nausea and vomiting (CINV) in patients with a lack of response to conventional antiemetics.[11] Dronabinol comes in gelatin capsules (2.5mg, 5mg and 10mg) and is an oral medication. Associated adverse effects include: psychiatric adverse reactions such as exacerbation of mania, depression or schizophrenia; cognitive impairment and altered mental state; cardiovascular changes such as hypotension, syncope or tachycardia; seizures; and paradoxical nausea, vomiting and abdominal pain.[11]

Nabilone (Cesamet®) is a synthetic analogue of THC, and is also approved by the FDA for the treatment of chemotherapy induced nausea and vomiting.[12] It comes in 1mg capsules for oral administration. Associated adverse effects are similar to dronabinol and are mediated through the CB_1 receptor.

Nabiximols (Sativex®) is a combination of two plant extracts from *Cannabis sativa L.,* and contains both THC and CBD at a ratio of 1.08:1. It has approval for use in NZ, Australia, Canada, the United Kingdom and multiple European countries. Within NZ it is approved for the adjunct treatment of spasticity in multiple sclerosis (MS). It is an oro-mucosal spray and each dose of 100 microlitres contains 2.7mg THC and 2.5mg CBD. The most common side effects associated with nabiximols are dizziness and fatigue, with anorexia, mood changes and nervous system disturbances being less common.[13]

Epidiolex is a >98% pure CBD extract. Whereas the other three products have generic names that are not associated with other cannabinoid products, Epidiolex's generic name, cannabidiol, is often used in products that are not pharmaceutical grade. The FDA approved Epidiolex in 2018 for use in the treatment of severe refractory epilepsy syndromes of childhood, such as Dravet syndrome and Lennox-Gastaut syndrome. It is an oral solution of 100mg/mL CBD. Associated side effects include elevated liver transaminases (alanine aminotransferase and aspartate aminotransferase), sedation, suicidal thoughts, appetite change and gastrointestinal disturbances such as diarrhoea.[14]

1.5.2 Near pharmaceutical grade products

Tilray (Canada) and Bedrocan (Netherlands) are producers of a range of whole plant medical cannabis products that have GMP certification throughout their manufacturing process. Despite this, within NZ, Tilray products are not considered pharmaceutical grade medicines, and have not been through the Medsafe approval process.[15]

1.5.3 Non-pharmaceutical grade products

Non-pharmaceutical grade products are not manufactured to GMP standards and as a result may have limited regulatory oversight. Such products are commonly found in jurisdictions where medical cannabis dispensaries are found. Products within this group may include raw plant material, joints, plant extracts; resins, oils, tinctures, vape liquids, wax and edibles; baked, sweets and beverages. Due to the natural variation within plant materials, even within the same strain, there is potential for great inter-batch variability for these products. The levels of cannabinoids in each product is not constant, rather the expected ratio of THC to CBD may be given for the plant of origin, however this may not be what is actually present in the final product that the patient receives. This variation limits the ability to make efficacy claims or to examine the side effects associated with each product. This is complicated by the increasing potency of products that are

being developed, as higher potency products are more likely to be associated with significant side effects due to a dose response.

1.5.4 Cannabidiol related products

Within NZ cannabidiol products are classified as those that contain less than 2% THC of the total cannabinoid content and as such are not considered controlled medications.[16] Any doctor in NZ may prescribe cannabidiol products. Despite this, there are no Medsafe approved cannabidiol products available in NZ.[17]

Overseas there are many unregulated cannabidiol products available, and it is outside the scope of this thesis to name them. This is especially noticeable in the United States of America, where since the approval of Epidiolex as a regulated medicine, the FDA considers all other CBD products to be unapproved, and therefore prohibited from making associated health claims. This runs counter to the expectations of individual producers in those states where medical cannabis is legalised, contributing to the unease surrounding cannabis-based products in the United States. Patients may easily access CBD products through the internet, with little to no requirement for evidence of the medical provenance of the product that they are receiving.

1.6 Prescribing Guidelines for cannabis-based products in New Zealand

The Medical Cannabis Agency (MCA) provides information for health care professionals regarding the prescription of medical cannabis products. There are no qualifying conditions identified for the prescription of medicinal cannabis products. All patients must have a prescription from a registered doctor in order to access products, which specifies the brand (no generic substitutions allowed). Smoked products are not permitted. Prescriptions must be handwritten on a controlled drug prescription form (excluding CBD only products) for a period of one-month supply.[17]

Nabiximols does not need ministerial approval for prescription for off-label use, as any doctor may prescribe this for patients in their care where this is within their scope of practice. Unapproved medical cannabis products may be prescribed by doctors under two conditions; either the product has been determined to meet the minimum quality standard OR "*approval for a named patient has been granted by the Minister of Health following an application by a relevant medical specialist or the Chief Medical Officer of the District Health Board"*.[17] Ministerial applications are reviewed

against a range of criteria. These criteria include the severity of the patient's condition, evidence that other treatments have been trialled with poor symptom control, that the health risks have been assessed by relevant clinical specialists and that the prescriber sought peer review. Applications should also include a certificate of analysis for the proposed unapproved products and if the patient provided informed consent. Unapproved medications must then be prescribed under Section 25 of the Medicines Act.[9,18,19]

All doctors are able to prescribe CBD products on a regular script, for a period of three months, as this is no longer a controlled prescription, however currently all CBD medications in NZ are unapproved and as such are also prescribed under Section 25 of the Medicines Act.[9]

1.7 Cannabis and health

Cannabis use may relate to health in two ways. From a purely medical perspective, there is great interest in potential therapeutic pathways where cannabinoid use may be indicated to alleviate symptoms and disease. However, the use of cannabis for recreational purposes is generally associated with concerns regarding health-related harms. Balancing these two paradigms is important to ensure that health-related harms are not an outcome of the increasing use of cannabis in the medical field.

This section summarises the body of literature examining the efficacy of the use of cannabinoids in specific medical conditions and the currently understood health harms associated with the use of cannabis.

1.7.1 Evidence in medical conditions

There are varying levels of evidence for the use of cannabis in medical conditions, much of it inconsistent and poor quality.[20] The National Academies of Sciences, Engineering and Medicine (NASEM) issued an extensive report in 2017, stating that there were three conditions that demonstrated evidence for use of cannabinoids; the adjunct treatment of spasticity in multiple sclerosis (MS), the treatment of chemotherapy induced nausea and vomiting (CINV) and the use in chronic neuropathic pain.[4] Following the release of this report, there has been research to support the use of cannabinoids in refractory childhood epilepsy syndromes, such as Lennox-Gastaut and Dravet syndrome.

1.7.1.1 Multiple Sclerosis

There has been investigation for the potential use of cannabis in multiple sclerosis since the 1980s, prior to the discovery of the endo-cannabinoid system receptors. Reports of the effect of cannabis use on pain and spasticity following spinal cord injury were recorded in 1974 by Dunn and Davis[21] (n=10), with Petro and Ellenberger undertaking a small crossover trial of multiple sclerosis patients (n=9) comparing synthetic THC with placebo in 1981.[22] They reported that following the ingestion of either 5 or 10mg synthetic THC, four out of nine patients showed improvement in spasticity scores by two standard deviations from the mean.[22] Further small trials were undertaken throughout the late 1980s to early 2000s, showing disparate outcomes; Ungerleider et al. (n=13) demonstrated a subjective improvement in spasticity scores, Greenberg et al. (n=10) demonstrated impaired posture and balance following smoked cannabis and Killestein et al. (n=16) showed no improvement in spasticity with either oral THC or a cannabis plant extract.[23–25]

The early 2000s saw the advent of larger clinical trials exploring the use of cannabinoids in MS. Up until 2007, trials focusing on MS primarily used dronabinol or oral cannabis extract capsules as their investigational medical products. Subsequent to this, primary research investigating MS primarily involved using the oro-mucosal spray nabiximols (2.7mg THC: 2.5mg CBD), with less focus on oral and smoked administration routes.

In 2003, Shakespeare et al. undertook a Cochrane review exploring the effectiveness of anti-spasticity agents for MS, including placebo controlled randomised control trials (RCTs) of greater than seven days duration.[26] They found two relevant studies looking at the use of cannabinoids, including Killestein et al. above and Wade et al.(n=24)[27] who examined three oro-mucosal whole plant cannabis extracts vs placebo (THC-rich, CBD rich and THC: CBD 1:1).[26] Shakespeare et al. reported that both studies found no significant change in the mean score of the Ashworth scale, an objective measurement of biological impairment related to spasticity.[26] The reviewed studies demonstrated different outcomes for functional and subjective scores. Killestein et al. noted worsening outcomes in both the plant extract (brainstem functional scores) and THC groups (total MS functional score and patient subjective global rating) compared with Wade et al. who reported significant improvements in mean visual analogue scale (VAS) for pain, spasms and spasticity and numerical rating scores (NRS) for severity of spasticity and spasm frequency when compared with placebo.[26] Shakespeare et al. made no firm recommendations to change practice to use cannabinoids following this review.

Another Cochrane review by Mills et al. in 2007 explored treatments of ataxia in MS.[28] This included blinded placebo controlled RCT comparing two or more treatments for a period of greater than seven days (n=3). These were Killestein et al. as described above, a double-blind parallel study by Wade et al. examining THC:CBD oro-mucosal spray vs placebo (n=160) on MS symptoms, and a small study Fox et al. (n=14) examining oral cannador (cannabis extract) effect on tremor.[28] Mills et al. reported that in regards to ataxia scores (VAS, nine-hole peg test (9HPT)) there was either no change or worsening of scores, with 9HPT scores significantly worse with dronabinol. They also reported that disability outcomes were largely unchanged, and the overall conclusion from all studies that there was no significant improvement in tremor following the use of cannabis based medicines.[28]

Jawahar et al. 2013, systematically reviewed the pharmacological management of pain in MS unrelated to spasticity and trigeminal neuralgia. They included four studies (n=589) examining the use of cannabinoids, three which used nabiximols and one used dronabinol.[29] Two of the three nabiximols trials reported a significant reduction in mean pain intensity (Cohen's *d*:-0.61 and -0.13 respectively) compared with the third which reported no improvement (Cohen's *d*: 0.93). The pooled effect size for these three studies (n=565) was reported as 0.08 (95% CI: -0.74 to 0.89).[26] The single dronabinol study, Svendsen et al. (n=24), found those receiving dronabinol had a lower median spontaneous pain response than those receiving placebo (p=0.02),[30] with a moderate effect size (Cohen's *d*: -0.6).[29] Jawahar et al. concluded that whilst nabiximols showed promise, the meta-analysis did not support the use for central pain syndromes in MS patients.[29]

These three reviews concentrated on targeted symptom management in MS rather than cannabinoids specifically, however there have been further reviews specifically examining the use of cannabinoids in MS and other neurological conditions.

Lakhan and Rowland, 2009, systematically reviewed the use of whole-plant cannabis extracts (THC: CBD, doses between 2.5mg to <120mg daily, ratios not specified) in the treatment of spasticity in MS, including a planned meta-analysis of mean change in Ashworth scale.[31] They included six RCTs in their analysis (two previously included in Shakespeare et al.'s review, and four subsequent studies), (n=820) however excluded the results from study comparators that were not whole-plant extracts, e.g. excluding the dronabinol arm of Zajicek et al.'s [32] study (total participants=630, n=395 for the purposes of Lakhan and Rowland). Overall, only one study demonstrated a significant improvement in the Ashworth scale, Vaney et al. (n=57), -2.2 points (p=0.002), with the other studies showing little to no improvement.[31] The meta-analysis of the Ashworth scale was not undertaken due to lack of reporting of adequate data from three studies and

significant heterogeneity between the remaining studies (X^2=5.35,p=0.07, I^2=62%).[31] Despite a lack of change in Ashworth scale, patient subjective rating scales of spasticity were significantly improved in five of the six studies,[31] leading to the conclusion whole plant extracts may reduce spasticity in MS and that the "*distinction between perceived symptom relief and objective physiological changes*"[31(p5)] be the primary focus of future trials. This is consistent with Zajicek et al., who in their study, acknowledged that the Ashworth scale has limitations in assessing spasticity and proposed that newer patient-orientated scales may need to be developed to fully assess the complexity of the responses seen.[32]

Koppel et al., 2014, undertook a systematic review looking at the use of medical cannabis in specific neurological conditions, primarily MS (spasticity, central pain, bladder dysfunction, and involuntary movements) and presented the analysis by type of cannabinoid studied. Studies were classed according to level of evidence, with Class I being high-quality RCTs, Class II being lower quality RCTs and prospective matched cohort trials and Class III all other controlled trials. Conclusions were primarily drawn from Class I and II studies. Seventeen studies were included that studied spasticity, investigating nabiximols (six trials), oral cannabis extract and THC (seven trials), smoked cannabis (two trials).[33] Overall, Koppel et al. concluded that oral cannabis extracts are effective for reducing patient measured spasticity scores, with nabiximols and THC probably effective. This differed with objective scores, where all were ineffective at six to fifteen weeks, and oral cannabis extracts and THC possibly effective at one year.[33] Smoked cannabis showed insufficient evidence to comment on efficacy. These findings were similar for central pain or painful spasms (13 studies), again with oral cannabis extracts being determined effective for reduction of central pain and nabiximols and THC probably effective.[33] Regarding bladder dysfunction (five studies), nabiximols was probably effective at decreasing total daily bladder voids at 10 weeks, but unknown efficacy for other bladder symptoms, whilst THC and oral cannabis extracts were probably ineffective for bladder symptoms.[33] Finally, when studying tremor, (five studies), all cannabinoid classes were determined to either be probably or possibly ineffective.[33] Koppel et al. did not perform a meta-analysis.

Subsequent research has involved various pragmatic trials using nabiximols as adjunct therapy. Flachenecker et al., 2014, observed the clinical use of nabiximols in the treatment of spasticity for 3-4 months (n=300), with a withdrawal rate of 44.7% (n=134) at 3 months.[34] At one month, there was significant decrease in spasticity ($p<0.0001$) and sleep disturbance NRS scores ($p<0.0001$), and the decrease in the modified Ashworth Scale ($p< 0.0001$) which was maintained in those continuing

treatment at three months.[34] A further 52 participants were followed up for a period of 12 months showing sustained mean spasticity NRS scores for this period of time ($p<0.0001$).[35]

Langford et al., 2013, undertook a 14-week RCT assessing response rate to nabiximols vs placebo for central pain (n=339) with a primary endpoint of 30% reduction in mean pain NRS score (Phase A). This was followed by a further 12 week open plan treatment phase (n=58) and four week double-blind placebo randomised-withdrawal phase to explore time to treatment failure (Phase B).[36] The initial 14 week RCT demonstrated a primary endpoint reduction of mean pain NRS of 30% in 50% of the nabiximols group and 45% of placebo (OR 1.31, 95% CI: 0.84 to 2.04, p=0.234).[36] A mean reduction in pain score difference of -1.93 in the nabiximols group was seen, compared with -1.76 in the placebo group (treatment difference seen on mean reduction in pain score in favour of nabiximols= 0.17, 95% CI: -0.62 to 0.29, p=0.47).[36] They did note a significant difference at the 10 week time point in favour of nabiximols (OR 1.61, 95% CI: 1.01 to 2.57, p=0.046). In Phase B, 24% of the nabiximols group compared with 57% of placebo failed treatment (Hazard ratio 0.374, Log rank test p=0.040), with worsening symptoms in those changed from nabiximols to placebo in the randomised withdrawal phase.[36] These differences in findings were attributed to study design, with Phase A demonstrating a significant placebo effect, which was considered in part to be related participants being able to self-titrate their own dose, whilst in Phase B patients were maintained on the same dose. They concluded that there was some support for the use of nabiximols for central pain syndromes in MS, and that future trials should employ careful study design.[36]

Markova at al., 2019, evaluated nabiximols as an add-on therapy in treatment-resistant known responders (defined as >20% change from baseline spasticity score in initial four-week treatment). Participants were randomised to nabiximols vs placebo following a wash out period, (n=106) and following 12 weeks of treatment the proportion of patients showing a 30% change in NRS from baseline (determined a clinically important difference) was significantly higher in the nabiximols group (adjusted OR 7.0, 95% CI: 2.95 to 16.74, p<0.0001).[37] Reported treatment related adverse events were mild to moderate, primarily somnolence, dizziness, diarrhoea and nausea.[37]

Chisari et al., 2020, followed treatment resistant MS patients (n=1845) using nabiximols as an adjunct therapy for a period of 18 months. They reported 81.4% (n=1502) of patients achieved an improvement in spasticity NRS of greater than 20%, finding an association that those who had a higher baseline NRS score, with initial greater reported effect at 12 weeks would be more likely to continue therapy after 18 months. However, 48.3% of participants who showed an initial NRS reduction abandoned therapy due to decreased efficacy or adverse events.[38]

This summary demonstrates that despite forty years of research in this area, the majority of trials have been small, with significant variation in both the active cannabinoid used and the MS symptoms studied, overall providing little opportunity for meta-analysis. This limits the ability to draw strong conclusions about the efficacy of cannabinoids in treating MS related symptoms, which is supported by a recent systematic review of reviews in 2018. This review concluded that there was evidence to support trialling cannabinoids in spasticity and pain related to MS, although effect sizes in studies are small and only a modest effect may be expected.[39] It is clear that objective measures of spasticity show limited evidence of effect, whereas studies based on patient subjective scoring, such as pain scores and self-spasticity assessments, show stronger evidence for use. The placebo effect may complicate cannabinoid studies, as well difficulties in masking the associated psychoactive nature of medications containing THC. This likely contributes to observational trials showing a greater level of cannabinoid efficacy than RCTs. Recent trials, whose focus is on subjective rather than objective response, continue to demonstrate modest effects for nabiximols as an adjunct therapy for spasticity treatment-resistant multiple sclerosis, however pain relief remains equivocal.

1.7.1.2 Chemotherapy Induced Nausea and Vomiting

The majority of research relating to the use of cannabis-based products for the management of chemotherapy induced nausea and vomiting (CINV) was undertaken during the 1970s and the 1980s, surrounding the advent of the synthetic THC derivatives and analogues, dronabinol and nabilone, with minimal studies examining plant-based extracts. There has been a paucity of research examining the use of cannabis-based products compared with modern anti-emetics such as $5HT_3$-antagonists like ondansetron and tropisetron, with a need for further research in this area.

Smith et al., 2015, undertook a Cochrane review including 23 RCTs from the years 1975 to 1991, which looked at RCTs investigating acute chemotherapy induced nausea and vomiting, with the cannabinoids involved being either oral nabilone or dronabinol.[40] Due to lack of availability there were no studies included which used the newer anti-emetic medications as comparators. This review also excluded the use of cannabinoids in the paediatric and adolescent population.

This was a comprehensive review and compared the relative effects if cannabinoids when compared with placebo, and other anti-emetics, both alone and in combination. When compared with placebo, they found low-quality evidence that people receiving cannabinoids would report a complete absence in vomiting (three trials, n=168, RR 5.7 95% CI: 2.6 to 12.6) and a moderate quality evidence that cannabinoids would result in complete absence of nausea and vomiting (three trials,

n=288, RR 2.9, 95% CI 1.8 to 4.7).[40] They also found a very low quality evidence of a high level of withdrawals due to adverse events in those who had received cannabinoids (two trials, n=276, RR 6.9, 95% CI: 1.96 to 24) compared with less change of withdrawals due to lack of efficacy (one trial, n=228, RR 0.05 95% CI: 0.0 to 0.89).[40] People who received cannabinoids were also more likely to report 'feeling high' (three trials, n=137, RR 31; 95% CI 6.4 to 152) and preferred cannabinoids over placebo (two trials, n=256, RR 4.8, 95% CI: 1.7 to 13), however this had significant heterogeneity (I^2= 71%, Chi^2 test for heterogeneity, p=0.06).[40]

There were varying anti-emetics included as comparators in the other studies reviewed. The majority of studies included prochlorperazine, with less evidence presented when metoclopramide, domperidone and chlorpromazine were comparators. Comparing cannabinoids with prochlorperazine showed no significant difference in those participants who reported a complete absence of nausea and vomiting (four trials, n = 414, RR 2.0 95% CI 0.74 to 5.4, I^2= 60%), however people had more chance of withdrawing for adverse events and lack of efficacy (one trial, n=42, RR 3.5, 95% CI: 1.4 to 8.9). Despite this patient reported outcomes indicated that they preferred cannabinoids to prochlorperazine (seven trials, n=695, RR 3.3, 95% CI: 2.2 to 4.8, I^2= 51%). None of the trials involving domperidone, chlorpromazine or metoclopramide reported anti-emetic efficacy outcomes. Patients reported no significant preference for cannabinoids when compared with metoclopramide (one trial, n= 64, RR 1.2, 95% CI 0.61 to 2.4), and no evidence of a difference for feeling high (one trial, n= 30, RR 3.0; 95% CI: 0.35 to 26). Those receiving cannabinoids when compared with domperidone showed no difference withdrawing for lack of efficacy (one trial, n= 38, RR 0.14; 95% CI: 0.01 to 2.7) or feeling euphoria (one trial, n=38, RR 5.0, 95% CI: 0.26 to 98). Patients receiving cannabinoids compared with chlorpromazine did not show evidence of a difference of preference between groups (one trial, n=20, RR 2.0, 95% CI: 0.83 to 4.8).[40]

When cannabinoids were added on to other anti-emetic regimens and compared with anti-emetic monotherapy (two trials, n =105) there was no evidence of a difference in groups reporting no nausea (RR 11, 95% CI: 0.61 to 182), no vomiting (RR 1.5, 95% CI: 0.69 to 3.1) or both (RR 1.6, 95% CI 0.68 to 3.6).[40]

Smith et al. concluded that "*cannabinoids were more effective than placebo and were similar to conventional anti-emetics for treating chemotherapy induced nausea and vomiting*",[40(p19)] with weak evidence showing a patients preferred cannabinoids when compared with placebo and stronger evidence for preference compared with conventional anti-emetics.[40] Due to the lack of evidence comparing cannabinoids with modern regimens, they found no evidence to support the use of cannabinoids in the place of current treatment regimens, which typically consist of $5HT_3$

antagonists, steroids +/- neurokinin-1 (NK-1) inhibitors with the addition of an older class of anti-emetics in refractory cases.[40] Despite this, they acknowledged that cannabinoids are a useful adjunctive treatment in those patients with refractory nausea who have exhausted all other options.

A systematic review of reviews undertaken by Schussel et al. in 2018 that examined the use of cannabis for chemotherapy induced nausea and vomiting included five systematic reviews with 34 primary studies (RCTs only) from the years 1975 to 2007.[41] Of the five reviews that were included, one was rated as high quality, Smith et al. 2015, which was a Cochrane review. Schussel et al.'s review included studies that involved a wide range of cannabinoid products that compared to a wide range of anti-emetics, meaning that an overall meta-analysis could not be undertaken. This review concluded that cannabinoids were superior to placebo alone and were similar to standard anti-emetics, with patient reported outcomes indicating that they preferred the use of cannabinoids to placebo and other anti-emetics, but they reported higher levels of adverse reactions.

The most recent systematic review published in this area, Chow et al., 2020, undertook a systematic review and meta-analysis, reviewing oral cannabinoids for the prophylaxis of chemotherapy-induced nausea and vomiting. They included only seven RCTs from the years 1979 to 2007, despite previous reviews identifying up to 34 primary studies, and included three studies that Smith et al. had excluded.[42] Their overall findings were consistent with the previous systematic reviews, reporting that oral cannabinoids are more effective than placebo (OR 3.45, 95% CI: 1.39 to 8.58) and as efficacious as others against vomiting (OR 2.51, 95% CI: 0.33 to 19.16) and nausea (OR 2.01, 95% CI: 0.49 to 8.26). However, this review has limitations due to the lack of inclusion of relevant studies.

As noted, the majority of studies performed have been done using dronabinol and nabilone, however there is starting to be some interest in the use of whole plant extract medicines such as nabiximols. Whilst there has been a lack of studies regarding modern anti emetic regimens, research in this area is starting to emerge.

In 2007, Meiri et al. undertook a double-blind placebo controlled parallel group trial (n=64) comparing dronabinol against placebo, ondansetron only and an ondansetron/dronabinol combination for efficacy in the management of delayed chemotherapy induced nausea and vomiting.[43] Participants were randomised to one of four groups (three active and one placebo). The three active arms received the same pre/post anti-emetic regimen on day zero and day one (dexamethasone + ondansetron + dronabinol) and different regimens on days two to five (either dronabinol alone, ondansetron alone or ondansetron + dronabinol), whilst those in the placebo

group received no dronabinol on day zero, and placebo only on days one to five.[43] Due to difficulty enrolling patients due to patient concerns about being randomised to the placebo arm, the study was terminated early (original sample target was n=464). When analysed, they concluded that those participants obtaining a total response to delayed nausea and vomiting were similar in the dronabinol (54%), ondansetron (58%) and combination (47%) groups when compared with placebo (20%). This was not statistically significant, but implied a clinically relevant improvement.[43] There was a significant difference in the absence of nausea in all active groups compared with placebo (dronabinol 71%, ondansetron 64%, dronabinol + ondansetron 53%, placebo 15%, $p < 0.05$), as well as the mean intensity of the nausea experienced (mm on VAS: dronabinol 10.1mm, ondansetron 24.0mm, dronabinol + ondansetron 14.3mm, placebo 48.4mm, $p <0.05$). They found no significant improvement in efficacy with the combined therapy, and concluded that dronabinol and ondansetron were similarly effective anti-emetic treatments.[43]

In 2010, Duran et al., undertook a small double-blind RCT (n=16) assessing the efficacy and tolerability of nabiximols as add on therapy to modern standard anti-emetic therapy (including $5HT_3$ antagonists and steroids) in patients who had previously experienced refractory/delayed CINV.[44] They found that the proportion of patients reporting a response with complete reduction in nausea and vomiting over the observation period was higher in the nabiximols group than the placebo group (5/7 (71.4%) vs 2/9 (22.2%), a difference of 49.2%, 95% CI 1 to 75), which was all attributed to the delayed response and not the acute response.[44] There was one withdrawal in the nabiximols arm due to an adverse event (anxiety, somnolence and visual hallucinations).[44] Duran et al. concluded that there was a potential contribution of cannabinoids in reducing CINV as an adjunct to modern regimes.

Both Meiri et al. and Duran et al. assessed delayed CINV rather than acute CINV, providing evidence to the potential use of cannabinoids as an adjunctive medicine in the management of delayed CINV. The studies were small, with heterogeneous sample populations, reinforcing the need for larger randomised control trials to further confirm the validity of these findings.

Within a paediatric and adolescent population there has been more limited research. No pharmaceutical grade products have been approved for use for this reason in the paediatric population, however doctors have prescribed these products in an off-label capacity. Wong and Wilens, 2017, undertook a systematic review of the literature and found six studies from 1979-2015 (five of which were prior to the year 2000) (n= not stated) examining the use of cannabinoids in children and adolescents for CINV. These studies used nabilone, dronabinol, delta-8-THC and delta-9-THC as investigational products. Wong and Wilens concluded that the evidence "*parallels*

adult literature" and provides evidence that cannabinoids are effective anti-emetics in children undergoing chemotherapy, with similar side effects being common such as dizziness and drowsiness.[45] Polito et al. undertook a retrospective review in 2018 of 110 paediatric patients using nabilone for CINV, primarily in conjunction with standard anti-emetic therapy ($5HT_3$) for acute CINV.[46] They found that the proportion of patients obtaining a complete response to combined therapy was low (50.6% in moderate emetogenic chemotherapy and 53.8% in high emetogenic chemotherapy) and similar to previously described mono-therapy.[46]

There has been interest in the use of cannabinoid-based medicines in other areas of nausea relief, specifically in the areas of radiotherapy and post-operative care. Kleine-Brueggeney et al. undertook a double-blind placebo controlled RCT (n=40) in the use of intravenous THC (administered at the end of surgery) for the use of post-operative nausea and vomiting (PONV). This study was discontinued early due to unacceptable side effects (sedation and confusion) and uncertain antiemetic effect (RRR in THC group 12%, 95% CI:-37% to 43%).[47] Côté et al., 2016, completed a double-blind placebo controlled RCT (n=56) comparing nabilone and placebo for the improvement of quality of life in patients undergoing radiotherapy for head and neck cancers, with a secondary outcome of assessing effect on nausea.[48] They found no significant difference in the nabilone group (p=0.715) to placebo in addition to usual anti-emetic regimens. This was also true of adverse events, where there was no difference in drowsiness (p=0.3166) and anxiety (p=0.9163).[48]

As previously stated, there is a paucity of literature examining the use of plant-based extracts such as nabiximols in the use of prophylaxis for CINV, as well as limited evidence investigating use compared with the modern anti-emetic regimens. This gap affects clinical practice, as doctors are relying on out of date evidence to make recommendations to their patients regarding the best management of symptoms. As such, and until further larger trials have been undertaken, the use of cannabinoids for the management of CINV will remain as an adjunct when all other anti-emetic options have been exhausted.

1.7.1.3 Chronic Neuropathic Pain

The use of cannabis as medicine in chronic pain was initially investigated in the 1970s, with early studies by Noyes et al., who undertook a small pilot trial (n=10) using single ascending doses of THC oral capsules (5mg, 10mg, 15mg and 20mg) as an analgesic in cancer patients with chronic pain. This study reported correlation of increased doses of THC with increased pain relief ($p<0.001$).[49] Noyes et al. then undertook a further trial comparing placebo against the effects of codeine with THC in a similar group of patients (n=36).[50] This demonstrated a significant pain

difference between placebo and a single dose of 20mg THC ($p<0.05$) and no significant difference between a single dose of 10mg THC and 60mg codeine ($p<0.05$).[50] These small studies were in a heterogeneous group of patients who were on a regular analgesic regimen that was stopped the morning of the trials, and used a five point scale to report pain relief effects.[49,50] Despite a case study being undertaken by Maurer et al. in 1990 (n=1) which reported that 5mg THC had an analgesic effect compared with placebo,[51] trials exploring the use of cannabinoids in chronic pain have not been widely reported in the literature until after the year 2000. At this point studies separated chronic non-cancer pain and cancer pain, and the following section deals with chronic non-cancer pain, primarily neuropathic in nature.

Since that time, there have been many studies of various designs investigating the use of cannabinoids in chronic pain, however many of these cover short treatment periods. Stockings et al., 2018, performed a systematic review and meta-analysis that included not only randomised control trials (47 studies) but observational studies (57 studies), from the year 1990 to 2017.[52] Of these, eight studies showed that compared with placebo, cannabinoids were significantly associated with a 30% pain reduction (n=1734, OR 1.46, 95% CI: 1.16 to 1.84, I^2=52%), however five studies showed no significance at the 50% pain reduction level (OR 1.43, 95% CI: 0.97 to 2.11).[52] The number needed to treat for benefit (NNTB) was reported as 24 (95% CI: 15 to 61) and the number needed to treat for harm (NNTH) was reported as six (95% CI: 5 to 8).[52] Thirty studies were able to be meta-analysed involving pain reduction intensity. This analysis showed a standardised mean difference of 0.14 in favour of cannabinoids (95% CI: -0.20 to -0.08) which was calculated to be the equivalent of 2.9mm on a 100mm scale, well below the 30mm considered to show a minimal clinical important differences (MCID). This is similar to the findings of Wong et al., 2020, who included 33 trials in a meta-analysis of the analgesic effects of cannabis on chronic non-cancer pain and found that there was a significant reduction in pain scores (-0.70 ($p<0.001$)), however this had a small effect size, where a reduction in two points would be considered the MCID.[53] A significant limitation was the establishing equivalency across pain scores used in different studies. Both of these reviews had significant overlap in the studies that they included for meta-analysis. They both included studies involving the effect of cannabinoids on neuropathic pain in various conditions (26 in Stockings et al., 31 in Wong et al.) primarily MS, but also Human Immunodeficiency Virus (HIV), diabetes, nerve lesions, spinal cord injuries, avulsion injuries and chemotherapy induced nerve damage.[52,53] Those studies investigating non-neuropathic pain had a lower quality of evidence reported.[52] Stockings et al. concluded that the findings of their review were specific to neuropathic and MS-related pain, whereas Wong et al. undertook a meta-regression and concluded that the analgesic effect for chronic neuropathic pain and non-neuropathic pain was similar (Difference=-

0.14, p=0.262). Wong et al. reported a mean pain reduction of -0.60 (p=0.001, Q=15.8, p=0.027, I^2= 55.7) (n=12 studies) and called for further studies into the use of cannabis for non-neuropathic pain.[53]

Mücke et al., 2018, undertook a Cochrane Systematic review of cannabis-based medicines for chronic neuropathic pain in adults, using the standards of Cochrane Pain, Palliative and Supportive Care (PaPaS).[54] This review included 16 randomised, double-blind control trials (n= 1750) that were at least two weeks in duration (though all were less than 26 weeks), with at least 10 participants per arm. Primary outcomes included 50% pain reduction, with secondary outcomes of 30% pain reduction and mean pain intensity. Eight studies were analysed for the primary outcome variable of 50% pain reduction (n=1001) with the risk difference towards cannabinoids being 0.05 (95% CI: 0.00 to 0.09, p=0.04, I2=29%, NNTB=20 (11 to 100), low quality evidence). Ten studies (n=1586) reported on 30% pain reduction (RD 0.09, 95% CI: 0.03 to 0.15, p=0.004, I2=34%, NNTB= 11 (7 to 33), moderate evidence), with 14 studies reported a reduction in mean pain intensity (SMD -0.35, 95% CI -0.60 to -0.09, p=0.008, I^2=84%) favouring cannabinoids (low quality evidence).[54] In respect to harms, cannabis was found to increase nervous system disorders (RD 0.38, 95% CI: 0.18 to 0.58, NNTH=3 (2 to 6), nine studies, low quality evidence).[54] Mücke et al. concluded that the potential benefits of cannabinoids might be outweighed by their potential harms. This review was declared as stable in July 2020, following an updated search in June 2020.[54]

Whilst these reviews looked at subjective outcome measures in the form of changes in visual analogue scales to analyse pain scores there have been fewer studies investigating quantitative sensory testing. Mun et al., 2020, undertook a review examining this in healthy individuals (27 studies, n=648) and those with chronic pain (13 studies, n= 693). In the healthy participants the use of inhaled cannabis (eight studies) showed variable effects in experienced cannabis users, primarily in heat, mechanical and electrical stimulations, with everything from null results through to hyperalgesia at higher doses.[55] Synthetic cannabinoids (15 studies, primarily dronabinol and nabilone) predominantly showed no analgesic effect across the various testing modalities, with only one study reporting an analgesic effect, and five reported hyperalgesia in response to cannabinoids. There was one study using a combined 2:1 (THC:CBD) product (n=18), which did not have consistent results across stimuli types, primarily no analgesic effect in heat and mechanical stimuli, and mixed effects, primarily hyperalgesia in response to electrical stimuli. When looking at patients with known chronic pain, inhaled cannabis (five studies) demonstrated no analgesic effect overall in relation to heat and mechanical stimulation, with only one study noting a positive effect.[55] Synthetic cannabinoids (four studies) showed a response to mechanical pain stimuli in one study of MS

patients, with the other studies reporting a null effect. Three studies examined nabiximols, with two reporting an analgesic effect- one to mechanical stimulation and the other to electrical pain thresholds. Overall Mun et al. concluded that there was "*poor consistency of findings for efficacy of cannabis as an analgesic agent*."[55(p15)]

As with MS and CINV, it is apparent that the evidence for the use of cannabis-based products in chronic pain is primarily low to moderate quality, with the majority of more recent reviews concluding that the benefits of use may be outweighed by the potential harms. From a clinical perspective, those places that have guidelines or statements concerning the use of cannabinoids in chronic pain generally recommend it as a third or fourth line treatment (Canadian guidelines for prescribing in primary care),[56] or not at all (National Institute for Health and Care Excellences (NICE) guidelines).[57] Alternatively groups may specify that whilst they do not endorse the use of cannabinoids in chronic non-cancer pain, patients who are treated with cannabinoids should be monitored often, and primarily be involved in research projects or clinical audits (Faculty of Pain Medicine, Australia and New Zealand College of Anaesthetists).[58]

1.7.1.4 Severe Refractory Epilepsy Syndromes

Evidence for the use of cannabidiol, primarily Epidiolex, in severe refractory epilepsy syndromes emerged in 2016, with the publication of Devinsky et al.'s open label trial of Epidiolex as an adjunct treatment in drug resistant epilepsies (n=162) primarily those with Dravet syndrome (n=33) and Lennox-Gastaut syndromes (n=31).[59] This demonstrated a mean monthly reduction in motor seizures over a 12 week period of 36.5% (IQR 0 to 64.7), with adverse events reported in 79% of participants, primarily somnolence, decreased appetite, diarrhoea and fatigue.[59]

Devinsky et al., 2017 and 2018, went on to undertake double blind, placebo randomised controlled trials in both Dravet syndrome (n=120) and Lennox-Gastaut syndrome (n=225). They found that there was a decrease in monthly convulsive seizures in Dravet syndrome in the active treatment group compared with the placebo group (adjusted median difference -22.8%, 95% CI: -41.1 to -5.4, p=0.01), with 93% of the active treatment group reporting adverse events (compared with 75% of the placebo group).[60] In the Lennox-Gastaut trial, which compared two doses of cannabidiol (10mg/kg and 20mg/kg) with placebo, change in number of drop seizures from baseline was 41.9% in the 20mg/kg group (p=0.005 compared with placebo) and 37.2% in the 10mg/kg group (p=0.002 compared with placebo). Adverse events reported in 94% of the high dose group, 84% of the low dose group and 72% of the placebo group.[61] Both of these trials involved a 14-week treatment period.

Participants in both the Dravet syndrome and the Lennox-Gastaut trials were able to continue on an open label extension trial. Interim analysis of the Lennox-Gastaut cohort at 48 weeks showed a sustained reduction of drop seizures of 48.2%, with 92.1% of participants reporting adverse events (AE) and 9.6% discontinuing treatment due to these.[62]

Within the Dravet syndrome open label extension trial the median reduction in baseline seizures ranged from 39-51% for total seizures, with 93.2% of participants reporting adverse events, of which 6.4% of participants withdrew.[63]

In both extension trials there was concern with raised liver transaminases to greater than three times the upper limit of normal, the majority of which occurred in patients who were taking valproic acid. The majority of these returned to normal with dose modification to either the cannabidiol or concomitant medication. This highlights the potential for drug interactions, as cannabidiol is metabolised through the cytochrome P450 pathway.

Chen et al., 2018, investigated the use of cannabidiol (Epidiolex) as an adjunct treatment in 40 children with drug resistant epilepsy in Australia.[64] They found that there was no significant difference in the number of emergency department visits compared with the preceding 12 months ($p=0.28$) and that there was no significant difference in the number of rescue medications used from baseline ($p=0.88$).[64] Twelve participants were rated as much improved by their caregivers, and seven by their physicians.[64] Thirty-nine participants experienced adverse events, with the primary adverse events attributed to CBD being somnolence (n=13) and diarrhoea (n=4) and anorexia (n=4).[64]

Marchese et al., 2020, evaluated the effectiveness of an adjunctive sublingual non-pharmaceutical grade CBD oil preparation (24% CBD; 1 drop= 7mg CBD) in an open label retrospective study of 37 patients with treatment resistant epilepsy, who received titrating doses to up to 50mg/kg/day, with an average follow up period of 68 weeks.[65] The epilepsy diagnoses across the group were heterogeneous in nature. Efficacy was assessed on the most prevalent seizure type reported by the caregivers. At the end of the trial, 19% of patients were seizure free, and 73% of patients had a 50% reduction in seizures, with a median therapeutic dose of 4.2mg/kg/day. Adverse events were experienced by nine participants, including somnolence and loss of appetite.[65]

The evidence for the use of cannabidiol in treatment resistant epilepsy syndromes is some of the strongest available for the use of medicinal cannabinoids. It is of note that most of the research has been done in a single pharmaceutical grade medication, which limits the applicability of the

evidence to other non-standardised formulations, with only small studies available in other non-pharmaceutical grade formulations.

The impact that non-pharmaceutical grade cannabis medications may have for patients if they are not regulated is discussed in Chapter 3.

1.7.2 Evidence of associated health harms

Whilst the use of cannabis within the medical field has potential therapeutic effects, like all other drugs it is not without its harms. Due to the illicit nature of cannabis during the period of prohibition, there has been ongoing social discourse about the harms associated with cannabis and its use. As the chemical structure associated with cannabis that is used for medicinal purposes and recreational purposes in many areas of the world is unable to be separated, the need to examine and acknowledge these potential health harms is important to mitigate these harms to people accessing cannabis, whatever reason they may have for use.

This section summarises the significant known health harms from a review of the recent scientific literature, with a focus on NZ specific data at the end of the section. These harms have been into mental health harms and physical health harms.

In February 2020, Campeny et al., published a systematic review of systematic reviews exploring the harms and risks of the use of cannabis. This review did not include studies that explored synthetic cannabinoids, or studies based on efficacy of treatments or interventions. They included 44 studies in their analysis, primarily looking at mental health harms, somatic health harms, and injury and mortality harms.[66]

1.7.2.1 Mental health

Nineteen systematic reviews were included when looking at mental health harms, with the primary outcomes of these reviews encompassing psychosis, affective disorders, anxiety disorders, gambling, personality disorders and cannabis use disorder.[66]

Psychosis has been a primary concern surrounding the use of cannabis. A clear relationship has been established between the use of cannabis and psychotic symptoms. The review undertaken by Le Bec et al., 2009, (seven prospective cohort trials) reported psychotic symptoms increasing in those with heavy use (at least five times per month- OR 2.2, 95% CI: 1.5 to 3.3; up to 50 times per month- OR 3.1, 95% CI: 1.7 to 5.5). Increasing psychotic symptoms were also seen in those who

consume cannabis prior to the age of 15 years of age (OR 4.5, 95% CI 1.1 to 18.2).[67] Marconi et al., 2016, (10 trials) reported the risk of schizophrenia and other psychotic disorders to be higher in cannabis users with an OR 3.90 (95% CI: 2.84 to 5.34).[68] Despite this, cannabis use has still been determined as an association rather than a causal link in the development of schizophrenia. It remains unknown if people with a genetic predisposition to schizophrenia may take up cannabis use to try and manage their symptoms prior to formal diagnosis, however a genetic link has shown that those with a genetic susceptibility are at a greater risk of developing psychotic disorders.[66] It has also been established that the onset of psychosis is two years earlier in cannabis users compared with non-users (95% CI: -0.526 to -0.301, $p<0.001$).[69] Campeny et al. reported that one study did not find an association between cannabis use and psychosis, which was a review which looked at studies with a cross-sectional design[66].

There have been a small number of systematic reviews of cannabis use and anxiety and affective disorders with Campeny et al.'s review including four examining depression and three examining anxiety. The use of cannabis in the long term and with heavy use has been proposed to be a risk factor for depression by Moore et al. (eight trials) (OR 1.49 95% CI: 1.15 to 1.94), with varying findings on whether age of first use impacts on this association.[70] Twomey, 2017, (10 studies) established that the use of cannabis is associated with the development of anxiety symptoms (OR 1.15, 95% CI: 1.03 to 1.29), though the odds ratio is small, and when including only high quality studies (five studies) this decreased (OR 1.04, 95% CI: 0.91 to 1.19) to lacking significance.[71]

The effect of cannabis use on suicidal ideation and behaviour has also been a subject of research, with three systematic reviews establishing a link between cannabis and suicidal behaviour. Heavy or frequent cannabis use is associated with a higher risk of suicidal ideation (heavy use, weak association- OR 2.53, 95% CI: 1.00 to 6.39, frequent use- OR 4.55, 95% CI: 1.37 to 15.11) with heavy use also associated with suicidal attempts (OR 3.20, 95% CI: 1.72 to 5.94).[66]

Campeny et al. reported limited reviews encompassing pathological gambling (one review), personality disorders (one review) and cannabis dependence (two reviews). No conclusive comments were made on the association of cannabis use and pathological gambling and personality disorders. Cannabis dependence has a higher level of evidence associated with it. Schlossarek et al., 2016, identified 26 studies that reviewed impacts on transition to cannabis dependence, identifying regular cannabis use and early cannabis use (11-15 years) as a predictive factor, as well as having a comorbid mental disorder.[72] Peters et al., 2017, reviewed 11 studies examining cannabis use disorder and identified that co-existing tobacco use increased the likelihood of cannabis use

disorders, with poorer cannabis cessation outcomes when compared with those who those who only use cannabis alone.[73]

1.7.2.2 Physical Health

Physical health harms are those that are associated with somatic complaints. Campeny et al., 2020, and the NASEM report both comment on physical health harms. Despite great interest in the physical effects of cannabis use, there are limited numbers of studies that have reviewed its effects. Some areas of interest are respiratory health, cancer harms, cardiovascular impairment, gastro-intestinal effects, cognitive effects, nervous system disorders and pregnancy/post-natal disorders.

Systematic reviews of respiratory effects (three reviews) have demonstrated that there is an increased risk of wheezing (OR 2.01, 95% CI: 1.50 to 2.70), cough (OR 1.73, 95% CI: 1.21 to 2.47) and chronic sputum production (OR 1.53, 95% CI: 1.08 to 2.18).[66] Shortness of breath is present in those users who inhale cannabis, primarily by smoking and this association increases with moderate to heavy use.

Two reviews provide evidence for the association of cannabis use with cancers. One reviewed the development of testicular germ-cell tumours (based on three case-control studies) with current cannabis use more than weekly having the greatest association with the development of non-seminoma tumours (OR 2.59, 95% CI: 1.60 to 4.19), and a lesser association with all tumour types (OR 1.92, 95% CI: 1.35 to 2.72).[74] The other review examined the association with head and neck cancers (10 case-control studies) and found no evidence for an association of the use of cannabis with head and neck cancers, following adjustment for age, gender, race and tobacco use (OR 1.021, 95% CI: 0.912 to 1.143).[75] Whilst no single review addressed lung cancer directly, Campeny et al. reported that studies addressing this question were heterogeneous in study design. They reported an indication that there is an increased risk of lung cancer in cannabis users who used inhaled cannabis, with the increase in risk ranging from 8% to 410% when compared with the risk in non-users (controlled for confounding variables), however no odds ratio was reported within the review.[66]

Campeny et al. found gastrointestinal effects associated with the use of medical cannabis products, in a single review by Wang et al. in 2008 that involved 31 studies of the adverse events associated with medicinal cannabis (23 randomised control trials and eight observational studies). Wang et al. found that of the 164 serious events in the RCT cannabinoid exposure groups, 27 (16.5%) were gastrointestinal in nature, and of the non-serious adverse events 758 (out of 4615) (16.4%) were

gastrointestinal in nature (OR 1.52, 95% CI 1.19 to 1.93).[76] Within this review, the most prominent non-serious adverse events seen in the RCTs were nervous system disorders, with 1695 (36.7%) experiencing these (OR 1.87, 95% CI: 1.53 to 2.30), with dizziness being the most commonly reported event. Within the observational group (n=3353 events) the most commonly reported adverse events were nervous system disorders (39.8%), psychiatric disorders (35.6%) and gastrointestinal disorders (15.7%). Of interest, respiratory adverse effects were minimal (RCTs, 0.8%, OR 1.42, 95% CI: 0.77 to 2.62. observational studies 0.1%), reflecting the fact that the medicinal products examined in this review were oro-mucosal and oral preparations.[76]

Cannabis hyperemesis syndrome, a disorder pathognomonic to cannabis use, was not described in Campeny et al.'s review. Madireddy et al., 2019, undertook a retrospective cohort study (n=9601) and reviewed the trend of emergency department presentations for patients with intractable vomiting associated with cannabis use disorder within a five year period following the legalisation of cannabis in United States (2010-2014).[77] This showed that there was an increasing trend in presentations (28.6%, $p<0.001$) over the 5 year period. They also noted that anxiety disorders increased over the five-year period (20.8% to 30.8%, $p<0.001$) whilst depression decreased (19.2% to 16.4%, $p <0.001$). These findings were consistent with Bollom et al., who demonstrated an increased rate of vomiting presentations with cannabis use disorder (CUD) to emergency departments from 2006-2013 from 2.4/100000 visits to 13.3/100000 visits.[78]

The cognitive effects of cannabis use have a substantial number of studies to provide evidence of effects. These effects may be present during the period of intoxication; however, evidence has demonstrated that the effects may continue after the acute effects have dissipated. Campeny et al. found six systematic review and meta-analyses within their search. Multiple studies have found that cannabis use leads to memory and learning deficits.[66] Following a period of abstinence from cannabis use, Ganzer et al., 2016, undertook a systematic review that identified 38 studies with a prolonged abstinence phase, which demonstrated that chronic cannabis users might experience sustained deficits in cognitive functioning. This is seen in the domains of memory (ES=0.229, 95% CI: 0.130 to 0.323) and motor function (ES 0.478, 95% CI: 0.394 to 0.555).[79] Whilst many studies concentrate on the effect of cannabis use in adolescents, it is important to note that with the growing access to medicinal cannabis products there is a growing older population using cannabis, and that the cognitive harms associated with cannabis use in older age are associated with lower processing speeds, sustained attention and verbal memory.[66]

Maternal and foetal outcomes following the use of cannabis are another area of concern. Corsi et al., undertook a retrospective cohort study of 661,617 women in Canada from 2012 to 2017, and

reviewed their pregnancy outcomes. Self-reported use of cannabis during pregnancy was indicated by 1.4% of the cohort.[80] Cannabis use during pregnancy was significantly associated with small for gestational age babies (RR 1.53, 95% CI: 1.45 to 1.61), placental abruption (RR 1.72, 95% CI: 1.54 to 1.92) and transfer to neonatal intensive care (RR 1.40, 95% CI: 1.36 to 1.44).[80] Paul et al., 2020, examined the effect of prenatal exposure to cannabis on childhood outcomes (N=11489, n= 655 with prenatal cannabis exposure), and found *"that cannabis prenatal exposure after maternal knowledge of pregnancy was associated with a greater risk of psychopathology in middle childhood"*,[81(pE10)] which remained after controlling for potential confounders (Beta >0.02, FDR corrected p <0.02).[81]

The above review of health harms shows that the use of cannabis, is not without risk, and that these harms may be present for those who are using for medical reasons, as well as recreationally. It is important to consider these harms when reviewing legislative and policy changes to ensure the safety of both patients and the public when exposed to cannabis.

The following section reviews evidence that is specific to the health harms found within the NZ population.

1.7.3 Observed health effects of cannabis in the NZ population

Of significance to New Zealand, two cohort studies have contributed to the understanding of the health effects of cannabis use. These studies are both prospective- longitudinal correlational cohort studies with 2302 participants enrolled at birth. These studies commenced in Dunedin (1972) and Christchurch (1977). The numbers of Māori participants in these studies (7% in the Dunedin study and 13% in the Christchurch study) is lower than seen in the current general NZ population (16.5%),[82] however they were representative of the Māori population at birth at the time of the start of the cohort. This somewhat limits the ability to analyse the impact of cannabis use specifically in the Māori population. It has previously been reported that Māori are more likely to use cannabis than non-Māori, with 25% of Māori adults reporting previous 12 month cannabis use in the NZ Health Survey 2012/2013 compared with 11% of European/others.[83]

These studies have identified that the levels of cannabis use determined to be problematic (when looking at participants when they were in their 20s) was around 4-10% of the total population (which is 9-20% of those who had used cannabis).[84] There was an association between cannabis and other drug use, where all participants who had tried other drugs had tried cannabis first, which was stronger in those used during adolescence.[84] Māori were disproportionately affected by problematic

cannabis use, with 18.3% of the cohort reporting a period of cannabis dependence prior to the age of 25 years, compared with 12.5% of the overall sample.[82]

When examining the mental health effects of cannabis use in NZ, both studies report that the risk of experiencing psychotic events is elevated. The Dunedin study reported that the risk of experiencing schizophrenia symptoms at age 26 was higher in early cannabis users (by both age 15 years and 18 years respectively) than non-cannabis users,[85] and the Christchurch study reported that rates of psychosis was one and a half times higher in users than that of non-users.[84] These risks are after controlling for confounding variables such as report of psychotic symptoms at age 11 years, tobacco and alcohol use. This association appears to be most prominent in a sub-group of individuals who are at greater generic risk for developing schizophrenia independent of cannabis use, as previously commented above.[84]

There is some evidence from the Christchurch study regarding the association of the use of cannabis and relation to increased depressive symptoms, however the direction of a causative relationship has not been established.[86] Boden et al., 2020, undertook a latent trajectory analysis of cannabis use and found that an increased risk of mental health harms is more likely to be significant in those whose cannabis consumption was included in membership of trajectories with higher levels of use at age 30-35 years (adjusted OR=1.4 to 4.6).[87]

There is evidence from the Dunedin study that cannabis has an effect on lung function, with a decreased FEV1/FVC ratio in those cannabis users with dependence (36% compared with 20%, p=0.04), independent of tobacco use.[88] The Dunedin study also reports that there is double the risk of increased morning cough and sputum production in frequent cannabis users when compared with non-users, however cessation of cannabis use is associated with resolution of these symptoms to a rate similar to non-users.[89]

The Dunedin study found no association between early cannabis use and cardiovascular disease and diabetes,[90] however this is limited by the age of the participants who are only now entering the age where these diseases are typically diagnosed, requiring further cohort analysis to be undertaken.

Of significance, early onset persistent cannabis use (during adolescence) has been shown to have a relationship with lower level scores of cognitive abilities in the Dunedin study, even with controlling for educational level, with emerging evidence that this damage may be irreversible.[91] Educational attainment was also shown to affected by cannabis use, where no use of cannabis before 18 years was associated with higher odds of completing high school (OR:3.7, 95% CI: 2.1 to

6.5) and attending university (OR: 2.1, 95% CI: 1.3 to 3.6) when compared with early-onset cannabis use (prior to age 15 years) and when controlled for other variables.[84,92]

This rich data set continues to grow and provides a pool of data that will be useful in observing the effects of cannabis use within the NZ population, as the participants in the cohorts grow older.

1.8 Why prescribe or recommend cannabis-based products?

The previous sections demonstrate that there is limited evidence for the use of cannabis as a medicine in specific medical conditions. It is also not without its harms. Despite this, there is a growing movement within sections of the medical community to recommend or prescribe cannabis and cannabis-based products, in various forms, to patients. In NZ, doctors are expected to follow good prescribing practice for all medications, as outlined by the Medical Council. This ensures that they are aware of the "*indications, adverse events, contraindications, major drug interactions, appropriate dosages, monitoring requirements, effectiveness and cost-effectiveness*"[93] of medicines they prescribe with additional requirements when prescribing unapproved medications where they take responsibility for overseeing patient care and monitoring.[93] In order to truly fulfil these requirements there is a need for quality products that have undergone randomised controlled trials, however as I have shown, the majority of cannabis-based products do not fall under this umbrella, giving cannabis-based products an unusual position within the regulations of medications within NZ. In the US this is navigated by the fact that doctors in states where medical cannabis is legal and regulated may recommend but do not actually prescribe cannabis products that fall outside the remit of approved pharmaceutical grade medications.

This leads to the question as to why doctors prescribe cannabis-based products. The reasons for this are multifaceted. It is clear that those products that fall into the pharmaceutical-grade category and show medical provenance should be included within the remit of any other medication and prescribed when appropriate in specific medical conditions. However, access to such medications may be limited due to cost to the patient or availability of the product within the country that the prescriber is in and the prescribing conditions associated with it. For example, nabiximols is not available in the US and Epidiolex is not available in NZ, which may lead prescribers to recommend unapproved products. This is further complicated given that many of the conditions for which cannabis-based products have shown some efficacy for are primarily chronic in nature and not

always responsive to approved medicines. Therefore, if patients have tried a litany of approved medications or treatment options without success, a prescriber may be more likely to discuss/recommend/prescribe an unapproved cannabis-based product to such a patient, balancing out the potential benefit/ratio with particular patients in mind. This approach involves the application the principles of biomedical ethics- beneficence, nonmaleficence, respect for autonomy and justice- as guidance for discussing cannabis-based products with patients.[94]

Personal attributes of the prescriber are also a factor in when making prescribing decisions. These factors include clinical experience, specialty and access to continuing professional development. Davari et al., 2018, reviewed factors influencing prescribing decisions of physicians, and found that increased clinical experience may lead to doctors forming their own informal list of treatments that may be outside of guidelines.[95] The doctors' perception of patient expectations to receive a specific treatment is strongly associated with prescribing practices (OR 2.87, 95% CI: 1.16 to 7.08), though this may not match the patients actual expectations.[96] In respect to cannabis-based products, doctor's beliefs about potential effectiveness, extrapolation of trial data using approved cannabinoid products and applying this to unapproved products, as well ongoing interactions with patients who report using illicit cannabis for self-management of their symptoms will also influence their prescribing practices.

Overseas research exploring doctor knowledge, patient interactions and experiences surrounding the use of cannabis as a medicine are described in Chapter 4. From a NZ perspective there is a gap in the literature exploring how doctors view prescribing cannabinoid products and reported interactions with patients in this field.

1.9 Patient demand for cannabis-based products

As described above, doctor's perceptions of patient's expectations for prescribing may influence their prescribing practice. This is may be true of cannabis-based products as well. It is important to consider what demand there is for cannabis-based products from a patient perspective.

Lintzeris et al., 2018, undertook a survey of medicinal cannabis users investigating the use of cannabis as medicine (CAMS-16, n=1748) in Australia.[97] This was immediately prior to the 2016 legislation that provided a framework for its use. This survey was then repeated in 2018 (CAMS-18, n=1388).[98] The majority of participants in the CAMS-16 survey, who predominantly used illicit cannabis for medicinal symptoms indicated that they believed that cannabis should be legal for all uses (88.8%).[97] A further 11.0% indicated it should be legal for medical purposes only, with

approximately 90% indicating they 'strongly agreed or agreed' that medicinal cannabis should be part of routine health care in Australia. Participants indicated that they would be willing to pay mean $11.00 (SD $9.80) per day for this.[97] Of interest, 70% indicated that they 'strongly agreed' or 'agreed' with the statement that a person should be able to buy and use medicinal cannabis without approval by a medical practitioner.[97] The CAMS-18 survey, undertaken after there was increased access to medicinal cannabis products through legislative change, demonstrated little change in responses, though those few participants who had accessed prescription cannabis (n=25) preferred it to illicit cannabis across a spectrum of domains, including cost and effectivness.[98] Rychert et al., 2020, surveyed self-reporting medicinal cannabis users in NZ (n=3634), of which only 4.7% reported accessing cannabis-based products through prescription, with 14.1% stating they had requested a prescription from their healthcare practitioner.[99] They reported an average of $305NZD per month on illicitly sought cannabis products, compared with an average $656NZD on prescribed products. Just under 40% wanted to be able to access products through prescription, with the majority wanting to grow their own plants at home.[99] From the NZ health survey in 2012/2014, 42% of cannabis users stated they were using illicit cannabis for medical purposes,[83] indicating that a not insignificant number of cannabis users have medicalised their cannabis use to self-manage symptoms of illnesses for which there may be limited substantiated evidence for use.

Prior to the legalisation of recreational cannabis, an estimated one million (4%) Canadians reported using cannabis to treat self-managed illnesses, yet only 28,115 had accessed through a legal source.[100] Belle-Isle et al., 2014, surveyed users of cannabis for therapeutic purposes (CTP) (n= 628) to look at barriers related to access through their medical cannabis programme, which requires an application to access medicinal cannabis products. They found that patients reported difficulties accessing doctors who supported their applications, as well as difficulties in accessing product from dispensaries.[100] Cost was also a factor, with just over half of respondents indicating that concerns regarding money interfered with their access to cannabis-based products.

Turna et al., 2020, surveyed a community sample of cannabis users prior to legalisation in Canada (n=709) to examine the overlap of patterns of recreational and medical cannabis use.[101] They found that 38.6% of users reported some level of medical use, with only 7.5% using exclusively for medical reasons. Of all medical users, 23.4% reported authorisation for use from a health-care professional. Purely recreational users reported lower daily use (5.1%) than all medical users (40.5%). Of interest, more medical users had scores indicating possible cannabis use disorder (cannabis use disorder identification test- revised (CUDIT-R) scores over 13) than those who used recreationally alone (21.9 % vs 10.3%, $\chi 2(1)=17.78, p>0.0001$), though this was reduced to 13.9%

of all medical users when the frequency item was removed.[101] Those who exclusively used for medical reasons did not have higher levels of CUDIT-R scores than recreational users only.

Morean and Lederman, 2019, surveyed authorised medical cannabis users in the US, exploring additional recreational use of medical cannabis products (n=348). They reported 55.5% indicated dual use, with this associated with being female, using medical cannabis for pain and mental health outcomes, preference for high THC products and positive expectancies for use. Use of high CBD products was protective against concurrent recreational use.[102] Total negative consequences overall did not differ between dual use and medical use only, however at an individual level, dual users were more likely to report consequences associated with risky use.[102]

Whilst these studies concentrated on medical cannabis users, other overseas research has concentrated on specific patient groups, including those with neurology and oncology diagnoses, where there is some evidence of clinical efficacy for the use of cannabis-based products. This research into specific patient groups exploring their beliefs and interactions around the use of cannabis as a medicine is discussed in Chapter 5. To date, there has been no such equivalent research undertaken in specific NZ patient populations.

These studies all demonstrate that there is a demand for cannabis to treat medical conditions, whether specifically talking to medicinal cannabis users or targeted patient groups. Medicinal cannabis users may self-identify or may have been recommended or prescribed a cannabis-based product by a healthcare practitioner. An overlap is seen where some patients who use cannabis for medical conditions are also using for recreational reasons. These reasons for use may in turn influence why patients want access non-pharmaceutical grade products and plants to self-manage their conditions. Such potential for dual use complicates the place of prescribing of cannabis-based products in the medical paradigm.

1.10 Summary

In this chapter, I have reviewed what cannabis is and how phytocannabinoids interact with the endocannabinoid system. I have defined different types of global cannabis-based products and placed these within the NZ context. In addition, I have discussed the current evidence for medical use in specific conditions and the known health harms associated with use, whilst summarising the known effects of cannabis use from a NZ perspective. Finally, factors for both prescribing practices amongst doctors and patient demand for cannabis-based products have been explored.

1.11 Thesis aim and outline

The following section outlines the research undertaken during this thesis. I aimed to understand what the outcomes of global legislation and regulation relating to cannabis and cannabis products were and to apply these to NZ. As previous NZ research has focused on medicinal cannabis users, I wanted to understand what NZ health care professionals and patients within specific diagnostic groups knew and believed about the use of cannabis as a medicine to identify areas of concern that need to be considered as NZ goes through a potential period of legislative change.

I developed this research with a view to inform the implementation of the use of cannabinoids as a medicine in NZ. To achieve this, I undertook eight studies in four areas of interest:

Exploring the implementation of global regulations related to cannabis and the development of regulations around its use in a NZ context;

> Study One: A systematic review of the literature with qualitative thematic data synthesis relating to the outcomes of cannabis legislation

Exploring how accurately cannabis-products worldwide are labelled and how these findings apply to the NZ regulatory environment to ensure patients are receiving a safe, reliable product;

> Study Two: A systematic review and meta-analysis using quantitative methodology examining the label accuracy and presence of contaminants in cannabinoid-based products in regulated markets

Eliciting what selected NZ health care professionals know about medicinal cannabis products, their potential clinical indications, and previous patient interactions;

> Study Three: An observational study of the knowledge and expectations regarding the use of cannabis as a medicine in General Practitioners
>
> Study Four: An observational study of the knowledge and expectations regarding the use of cannabis as a medicine in doctors in a neurology setting
>
> Study Five: An observational study of the knowledge and expectations regarding the use of cannabis as a medicine in doctors in an oncology setting

Eliciting what selected NZ patient groups believe about the use of cannabis as a medicine and how it applies to their medical conditions, their previous interactions with healthcare professionals and their thoughts about future doctor-patient communication about the use of cannabis as a medicine;

Study Six: A mixed methods observational study in a cohort of NZ general practice patients regarding knowledge and beliefs about the use of cannabis as a medicine

Study Seven: A mixed methods observational study in a cohort of NZ neurology patients regarding knowledge and beliefs about the use of cannabis as a medicine

Study Eight: A mixed methods observational study in a cohort of NZ oncology patients regarding knowledge and beliefs about the use of cannabis as a medicine

Chapter 2 The outcomes of cannabis legislative change

Study One: A systematic review of the literature with qualitative thematic data synthesis relating to the outcomes of cannabis legislation

2.1 Background

Global legislative change relating to cannabis is a relatively recent phenomenon, with discussions primarily taking place in Western nations. This relates to both medicinal use and recreational use. In the modern medical era *Cannabis sativa* was part of the Pharamacopaeia[103] until a 1930s law change in the United States saw it become illegal. Later, a series of United Nations (UN) treaties in 1961 (Single Convention on Narcotic Drugs)[104] 1971 (Convention of Psychotropic Substances)[105] and 1988 (United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances)[106] saw a globalization of this prohibitionist stance. Despite this, cannabis has remained the most widely used illicit drug globally.[107] This use has been deemed recreational although many individuals consider their use 'medicinal'.[108,109]

Within the last 30 years, this prohibitionist position has slowly been changing. Various countries have implemented legislation that allows access to medicinal cannabis and cannabis-based products (for example, 33 states in the United States of America[110], Australia, NZ, Canada). Some countries have decriminalised the use of cannabis for personal use, by *de facto* (Netherlands) or *de jure* (Portugal, South Africa) means. Additionally, few countries (Canada and Uruguay) and states within the United States of America, (currently 11 in total, with further states voting on this in the November 2020 elections) and Australia (one territory, the Australian Capital Territory, ACT) have legalised cannabis for recreational use.

NZ is undergoing its own period of legislative change. In November 2017, the Misuse of Drugs Amendment Regulations removed cannabidiol from requiring Ministerial approval for prescription. The subsequent Misuse of Drugs (Medicinal Cannabis) Amendment Act 2018 then removed the need for CBD to on a controlled drug prescription. It also provided a statutory defence for those patients with a palliative diagnosis who are in possession of cannabis and related utensils and required the development of a regulatory scheme that increased access to quality medicinal cannabis products in NZ, which came into effect in April 2020.

Since 2017, NZ has also been considering cannabis legalisation for recreational use with a referendum asking whether the public agreed with the proposed Cannabis Control and Legalisation Bill. This occurred at the same time as the 2020 NZ General Election. The proposed Bill garnered 48.4% support, however 50.7% voted against it. This concurrent discussion of medicinal and recreational cannabis led to some confusion in the public about the impact of the proposed Bill has in regards to medicinal cannabis, and blurred the lines of discussion within many fora.

Because of these discussions, cannabis and cannabis-based products are not only increasingly socially and politically acceptable, but the global regulatory changes have brought them back into the socio-political limelight. Efforts to legalise medicinal and/or recreational use have raised questions about the effects of these changes. The prolonged period of cannabis prohibition prevented the development of pharmaceutical and clinical trials that have been done with other medicines and medical disciplines over that time. Consequently, legislative policy change relating to the use of cannabis as a medicine lacks strong clinical evidence-based input. This subsequently affects the understanding of the effects of cannabis regulatory change more broadly.

Despite the lack of high-quality evidence in medical research there is a substantial body of literature that explores cannabis use and cannabis-based products more generally. This is unsurprising considering the impact of cannabis on society appears to be a 'wicked problem'.[111,112] Wicked problems affect multiple spheres of interest, have no 'right' answer and are hard to study as the areas of interest themselves evolve and change. There is no specific right answer to the question, 'What is the best regulatory approach to take towards cannabis regulation?' Rather various elements of interest in the empirical literature guides decision makers towards the area of greatest importance. This breadth makes any effort to synthesise the literature difficult. Recent reviews have focused primarily on the public health implications of cannabis law implementation[113,114] and tend to take an 'expert opinion' or quantitative perspective. This offers valuable individual insights but does not rely on the whole of the literature and tends to examine a narrow part of this wicked problem. Standard meta-analytic approaches are difficult to use, as both outcome measures, definitions of cannabis and the social and judicial regulations in different jurisdictions vary. No one target of interest for analysis can be identified *a priori* using this approach. Nonetheless, systematically searching and thematically reviewing the literature base across multiple disciplines is likely to inform the rapidly evolving landscape of reform by developing an understanding of the underlying themes that are emerging from the broad body of work evaluating the impacts of regulatory change, and as such was chosen for this study.

2.1.1 Note

This study involved a team of four investigators. Dr Sean Evans contributed to the duplicate title/abstract screening for inclusion and full-text review/data extraction/analysis/thematic synthesis. Assoc. Professor Giles-Newton Howes and Professor Braithwaite contributed to dispute resolution, full-text review/data extraction/analysis/thematic synthesis. Ms Susan Hope, reference librarian, contributed to the development of the search strategies. A modified version of this chapter has been submitted for publication in Drugs: Education, Prevention and Policy and is currently in press.

2.2 Aims and Objectives

The aim of this study was to use a systematic process to search the broad literature base relating to cannabis regulatory change and to then thematically review and synthesise the data to the point of thematic saturation, establishing super-ordinate themes. The intended outcome of this was to identify the underlying commonalities across the full breadth of disciplines that have considered the impact of legislative change relating to cannabis. I wanted to clarify how these underlying themes might affect future research design and policy development and how these may be subsequently applied to the NZ situation.

2.3 Method

2.3.1 Theoretical approach

Following discussion with the study group, a meta-narrative approach[115] was considered most appropriate given the literature covered real world situations, with a variety of jurisdictional changes embedded within various global social constructs. This approach enabled a coherent management process for reviewing the very broad literature and simplified the data extraction allowing for meaningful answers and the development of super-ordinate themes. These themes were determined to be descriptive in nature, with inferred directionality due to the pre/post design of the literature reviewed. This style of review is relatively new; however, it provides a framework for which quality can be maintained, whilst enabling a wide array of information to be included. The problem with a review such as this is it could be almost infinitely large, so care was taken to ensure that each step of the review focused on the key question of the outcome of cannabis-related legislative or regulatory change.

The Preferred Reporting Items for Systematic Review (PRISMA) guidelines[116] were used to manage the literature search.

2.3.2 Literature search

Initial scoping was undertaken by reading the literature and talking to experts in the field. This included discussion with members of the Medicinal Cannabis Research Collaborative (MCRC) and the Australian Centre for Cannabinoid Clinical and Research Excellence (ACRE). This enabled experts in policy development, medicine, pharmacology and regulation to help shape the requirements for review and data extraction. A specialist librarian was engaged to develop appropriate search strategies for each of the data platforms of interest.

It was recognised that a broad search strategy would be needed, and platforms to search would need to cover social and medical academic areas. The search was designed to identify as many different research traditions examining 'pre-post' change as possible. It was decided early that the law literature would not be explicitly reviewed, as it was not considered likely to provide data on the outcomes of legislative change, the key focus of this review. In the USA, where cannabis remains illegal at the federal level, but has been legalised in some states, each state was considered a separate jurisdiction. Although this approach is open to critique, there is no rigidly appropriate way to manage such situations. Most research examines states individually, and as they are self-governing, this approach had face validity. The study group decided that in order to encompass the full temporal effect of cannabis regulatory reform the dates of the literature searched would not be limited.

2.3.3 Search strategy

The search strategy focused on the primary domains of 'cannabis' and 'cannabinoids' AND 'regulations' OR 'jurisprudence' OR 'legalisation', using Boolean specifiers. These primary domains were discussed with the specialist IT/librarian who assisted in development and expansion of the appropriate search terminology needed to capture relevant literature. The detailed search strategies used for each database are in the appendix (7.2, Supplement 1). Seven databases were searched: Ovid MEDLINE, EMBASE, PsycINFO, EBSCO, ProQuest, Web of Science and SCOPUS. Development of a specific 'outcome' domain was not attempted (akin to the Cochrane highly specific search strategy) as this was felt likely to omit potentially important papers and no *a priori* outcome can be developed using the analytic approach chosen.

All study designs were considered during the process of the review. Studies were included if they involved countries or states that had some form of cannabis regulations in place, and some 'pre-post' effect described following legislative change. Other specific inclusion / exclusion criteria were not defined *a priori* in order to capture as wide an array of literature as possible. Commentary and editorial papers that did not include primary data were reviewed for references. Citation tracking was utilised from papers of high utility and the 'time travel' function in Scopus used. This additional searching occurred during the extraction and analysis phase of the project as it became clear which papers were of greatest relevance.

2.3.4 Screening

I undertook a primary and secondary title and abstract review with another investigator, with two further investigators acting as referees in cases of disagreement. The Covidence program was used to assist with data management.[117] In the process of screening, reported outcomes were used to guide inclusion. Outcomes were required to be a change identified from within each paper's own epistemic position. Unlike Cochrane style systematic reviews, where formal mathematical data is extracted for analysis, data from multiple epistemic traditions were searched for with an iterative process of review to ensure no data was overlooked early in the screening and extraction process.

2.3.5 Data extraction

All study investigators undertook concurrent data extraction and full-text review. Descriptive data were extracted from the papers to provide an understanding of both the basis of the researcher's perspective of cannabis regulation and to ground the data geographically (details in Appendix 7.3). The data extracted from each paper was designed to ensure the primary changes related to judicial or policy change were appropriately captured. This was undertaken by extracting phrases from each paper that encapsulated the outcome. Comment and insights were managed in NVivo 12 software.[118] This form of data extraction was designed to enable a rich picture of the outcomes of cannabis regulation to be built up from the evidence as opposed to using an *a priori* hypothesis to test. As the analysis unfolded, and domains of interest emerged, the use of NVivo 12 enabled a process of iteration and refinement of the data extraction. This enabled the domains to be refined sufficiently to both capture the areas of interest across research fields and to potentially be of direct and implementable value.

2.3.6 Data analysis plan

Constant comparative analysis was used to collect and generate data to discover emerging themes .[119] An iterative comparative analysis to code and categorise data was undertaken, revisiting the primary literature from the literature search until data saturation occurred.[119] This occurred over multiple rounds whereby each investigator brought extracted data which was then analysed by the group. In group discussion the principles of pragmatism, pluralism, historicity, contestation, reflexivity and review guided the discussion. Following this each investigator then reconsidered the data available (with the opportunity to further extract data) before reconvening to repeat the process. The rationale for utilizing the constant comparative method was both to ensure a high-quality methodology was used and to provide a clear frame of reference for the reviewers to align and refine data extraction.

As an example of this process, in the first round of coding another investigator and I used an open coding technique to develop themes with supporting quotes from the primary literature. Memo writing was used to facilitate discussion as codes emerged. A round table review with all investigators was then undertaken. After consideration of these themes, and the data supporting them, a selected group of higher order themes were agreed upon. Consideration was given to the context of these themes, by research type/orientation, geography, judicial change and other unexpected contextual factors. Following this, all four investigators then continued to review the primary literature to modify and validate the themes already noted and to identify any further themes. This iterative process continued until no further themes or areas of sub-interest emerged, indicating saturation.[120]

2.3.7 Assessment of quality

I considered a variety of tools to assess the quality of the included studies. The approach of utilizing the frame of the researcher to assess quality was considered, however it was agreed within the group that ultimately a uniform approach was needed. Although it is arguably more robust to use a variety of quality tools specific to the epistemic grounding of the individual work, it was considered this more complex approach would detract from the simple outcome of the impact of cannabis regulation. Therefore, a single tool thought most likely to be widely applicable to the predominantly qualitative nature of the included papers was selected, the Hawker Quality Assessment for qualitative research.[121] This tool was developed by Hawker et al., 2002, to help examine the quality of the disparate literature commonly found in qualitative research that may not fit within traditional

quantitative research tools. Papers received one of four grades (Very Poor, Poor, Fair, Good) with pre-determined criteria across nine domains (Abstract and title, Introduction and aims, Method and data, Sampling, Data analysis, Ethics and bias, Finding/results, Transferability/generalizability, Implications and usefulness).[121] All included papers were graded at least once, with a random selection graded twice. The higher of the two grades was applied where there were disagreements. Papers were then given a score out of 36 to determine the overall quality of the study (0-9= Very Poor quality, 10-18= Poor quality, 19-27= Fair quality and 28-36= Good quality). Due to the complexity of the type of papers involved it was found at times that not all domains could be graded, which in turn affects the overall grading of a paper, and has potential to underestimate the overall quality of the paper.

2.4 Results

2.4.1 Characteristics of the included documents

The primary search was undertaken in all databases for all studies published until December 14th 2018, and updated on November 25th 2019. A total of 13,450 papers were identified by the search as potentially containing information of interest. 627 studies were selected for secondary consideration of inclusion and 155 were reviewed prior to thematic saturation. Of the 155 papers that were reviewed, 92 contributed to the development of the themes, and 63 were deemed ineligible (paper details in the Appendix (7.4, Supplement 3)). This process of searching the literature is displayed in the PRISMA diagram (Figure 2.1).

During the initial synthesis process, a random selection of papers were reviewed from the 627 available. These considered for inclusion, whilst concurrently coding the paper and synthesizing thematic codes. Following the extraction of the first 26 papers, I met with another investigator to discuss the initial coding process and to iterate the emerging themes of interest, of which we established 14 sub-themes. All four investigators then continued to randomly review papers, coding for new sub-themes and comparing to previously established themes, meeting to discuss findings at three further meetings. At each point of reconsideration (following round table discussion) each investigator examined these papers iteratively to further develop and understand the results identified prior to a further round table discussion. During discussions, mapping and interactions of sub-themes was undertaken using a brainstorming approach, allowing investigators to identify how each sub-theme fit into a super-ordinate theme, considering that the purpose of the study was not to

identify specific outcomes of use as super-ordinate themes in their own right. Saturation of themes, or the point at which no further themes were uncovered, was reached after four rounds of review.

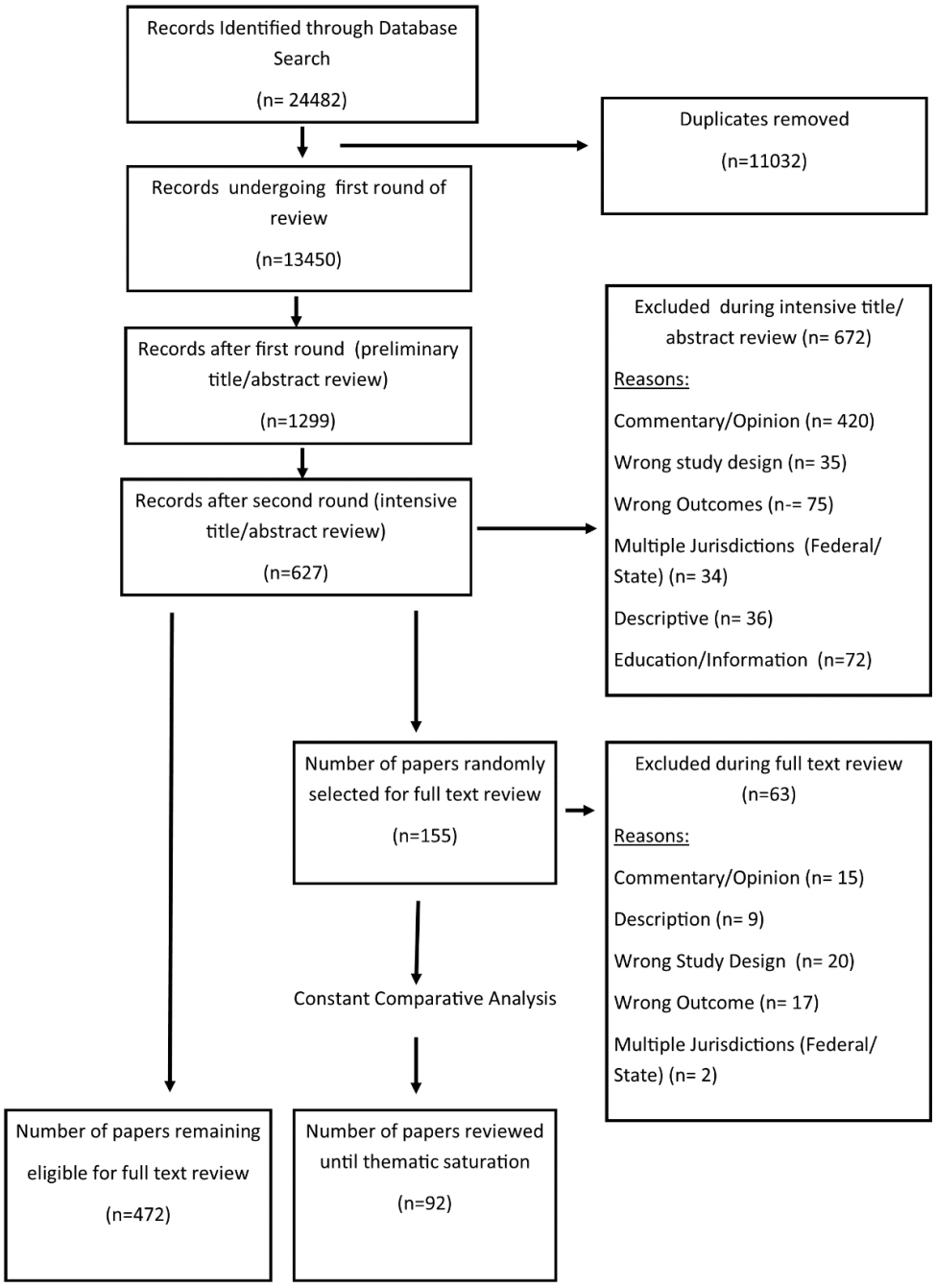

Figure 2.1. PRISMA diagram showing selection of included papers

2.4.2 Principal Finding

Five overarching super-ordinate themes emerged which I call Normalisation, Economics, Gatekeeping, Community and Health. The themes relate to societal and health changes observed in the wake of judicial or legislative regulation change related to cannabis, and are described in detail below. Examples of supporting quotes from the literature relating to each theme can be found in the Appendix (7.5, Supplement 4), and the relevant quote number cited within the main text.

2.4.2.1 Normalisation

Many papers described a process of normalisation of cannabis use associated with judicial changes to cannabis regulations. This occurred whether changes were intended to enable medical access, decriminalise (or relax policing policy) or legalise. Normalisation occurred globally and across societal sub-groupings. For example, enabling access to cannabis led to a decreased perception of risk in youth),[1] (Quotes 1, 2)[122–126] though this was not present across all jurisdictions (Quotes 3, 4).[122,127] Youth perception of risk was lower in jurisdictions preparing to enact medical cannabis laws compared with those that had no medical cannabis access (Quote 5).[124] With the introduction of legalisation for both medical and recreational use, a sense of increased legitimacy was conferred both in youth and adults, where perception of the 'low risk' associated with cannabis use contributed to its normalisation (Quote 6, 7).[123,128] This in turn contributed to the growing societal belief of cannabis as being 'good for you' (Quote8).[123,124] In jurisdictions that allowed medical cannabis marketing, youth exposure to cannabis related advertisements was associated with increased intention to use cannabis and positive expectations associated with cannabis use (Quotes 9, 10).[129,130] Recreational cannabis laws increased youth's perception of ease of access, however the presence of recreational cannabis stores near schools did not appear to have the same effect, unlike markets such as alcohol and tobacco (Quote 11).[131] The potential detrimental impacts of normalisation both in terms of increased uptake, and potentially damaging behavioural change, such as driving whilst intoxicated were described (Quotes 12, 13).[132,133] As the use of cannabis normalised, differing ways of administering cannabis became accepted, as opposed to simply smoking (Quotes 14-21).[133–135] There was acknowledgement within cannabis users that some forms of products may be more dangerous than others, such as concentrates (Quote 22),[135] however this was not a deterrent to the availability of these products within the market (Quote 23).[136]

2.4.2.2 Economics

The implementation of cannabis regulations, whether medical or recreational, had a positive effect on the economics of the jurisdictions that implemented these laws. In those jurisdictions that undertook both medical and recreational cannabis regulations differing taxation policies were applied depending on whether the product was for recreational or medical use, with recreational products being subject to higher taxes than medical products (Quotes 24, 25).[137] Some jurisdictions then directed the revenue received from taxation into research and public health messaging (Quote 26).[138]

Despite higher levels of taxation, the enactment of recreational cannabis regulations was often associated with a drop in price (Quote 27).[128,134] This related to all forms of cannabis products, despite increasing potency levels of THC in concentrates and oils (Quotes 28, 29).[136] Changes in potency may result from jurisdictional taxation policy. For example, if taxation is based on the weight of product rather than THC content, then a higher potency product will have less tax applied as it will weigh less than products with a lower concentration of THC (Quote 30).[127]

Neither medical nor recreational regulations stopped the existence of a black market for cannabis (Quotes 31, 32).[133,139] Some studies related this to prices remaining lower on the black market due to taxation on legal products. Other concerns such as gaps in the legal supply chain, privacy concerns around federal programs and the perceived ease with which consumers and patients felt that they could develop their own products also drove a black/grey market (Quotes 33, 34).[128,140] It was noted the potential for the diversion of legal product into jurisdictions where cannabis use remained illegal contributed to the black market presence (Quotes 35, 36).[134,139]

From a criminal justice perspective, judicial changes in cannabis regulation may have led to reduced costs in policing and justice departments (Quote 37)[141] although the effect of cannabis and crime, specifically related to judicial cases fell outside the scope of this review and we did not examine case law (as described in the Methods).

2.4.2.3 Gatekeeping

The implementation of judicial change in cannabis regulations resulted in the emergence of various ‘Gatekeeper’ effects. The gatekeeper for access to cannabis varied with differing regulations, and could be seen in the progression of the cannabis legislation within some jurisdictions. Generally, legislation tended to follow a ‘tight medical’ followed by ‘publicly available’ route (Quotes 38,

39)[142] though there have been exceptions where recreational legalisation was enacted first.[139] If initially broad, it was not unusual for jurisdictions to significantly amend their cannabis regulations over the first year of implementation across the spectrum of production, from cultivation through to labelling and marketing of products (Quotes 40, 41).[134,143] Within medical cannabis legislation, doctors usually became the gatekeepers while other legislative structures allowed for producers, suppliers, dispensaries or regulators to fulfil this role.[134,139]

Where regulations for medical cannabis were initially implemented the role of doctor as gatekeeper was not always well received by would-be patients or doctors. Patients complained of the deleterious effects of limiting access to cannabis-based products through doctors (Quote 42).[128] Some doctors perceived the gatekeeping role to be an 'unfair burden on physicians'.[144] There were a limited number of physicians who were willing to prescribe, and physician charges for the service were unregulated .[100] This led to the emergence of the 'medical cannabis specialist'. For example, in Colorado, '70% of the medicinal cannabis recommendations were completed by only 15 physicians'(Quote 43).[145] It was not unusual for some physicians to be associated with a medical cannabis dispensary, creating a de facto 'cannabis specialty' clinic (Quote 44).[145,146]

The gatekeeper theme included other perceived barriers to access such as cost, the negative stigma associated with asking for cannabis as a medicine, the authorization paperwork and the requirement in some jurisdictions for users to be registered (Quotes 45, 46).[100,128] Within some medical cannabis programs there was a lack of trust in the cannabis strains that the government produced (Quote 47),[128] resulting in some patients not utilizing the scheme. Some patients found the process of accessing the program too costly, despite the government produced product being priced lower than the black market (Quote 48).[100,128]

In jurisdictions that required registration and identification (ID) for medical cannabis, but also allowed recreational cannabis, there was less uptake in cannabis programs as patients could access recreational products instead (Quote 49).[137] There was a clear preference in registered users to access products through a pharmacy (Quote 50).[147]

2.4.2.4 Community

Literature considering the effect of judicial change on the community as a whole focused on cannabis use in youth, the impact on socially disadvantaged groups, the impact on work and driving as well as inter-jurisdictional tensions and crime rates.

There were disparate views on the effect of cannabis laws on use by youth. Medical cannabis legislation did not result in an increase in youth use.[148,149] It was hypothesised this may be due to the majority of cannabis use in youth being recreational, rendering medical cannabis laws effectively redundant in this group (Quote 51).[149] Additionally, this was mainly seen in jurisdictions that already had a comparatively high youth use rate prior to the implementation of legislation (Quotes 52-54).[124,148] There was no consensus on the effect of use in youth following the introduction of recreational laws, which showed a range of results from no significant change (Quotes 55-57),[122,150,151] to an increase in youth use in some jurisdictions (Quote 58);[122] with variations in the way that youth perceive harms from cannabis. It was noted that both medical and recreational cannabis products were diverted for youth use (Quotes 59, 60),[123,152] and there was some concern that the increasing potency of products resulted in a potential for increased dependency in youth users (Quote 61).[123]

The effect of judicial change on disadvantaged groups, such as ethnic minorities and those with criminal convictions relating to cannabis possession was described. There was variation in the policing of cannabis legislation (Quote 62).[133,153] In some jurisdictions, cannabis related arrests may have decreased with the introduction of cannabis regulations, but the rate at which those arrests dropped varied significantly by ethnicity, despite cannabis use rates within ethnic groups being similar (Quote 63,64).[133,153,154] Minorities were more likely to have been affected by historical cannabis prohibition laws (Quote 65),[154] which in some jurisdictions limited their involvement in a legal cannabis market. Some jurisdictions allowed previous 'drug felons' to enter the legal market in a strictly controlled manner, while other jurisdictions determined that any drug misdemeanour excluded them from participation in the legal market (Quotes 66-68).[154] Jurisdictions also varied in the way they approached post-ameliorative relief within their legislation (Quote 69-71).[154,155]

Medical cannabis laws and recreational cannabis laws were both associated with an increase in positive cannabis tests in drivers and higher rates of traffic accidents in those jurisdictions (Quotes 72-76).[133,134,138,156–158] This was especially true if cannabis and alcohol were combined resulting in greater impairment (Quote 77).[133] While the literature did not identify the cause of the increasing rates, they surmised this might be due to increasing availability of increased testing, increased permissiveness and changing perceptions of safety.

Workplace impact is still yet to be determined. Some jurisdictions have had an increase in positive cannabis tests in the workplace following the implementation of recreational laws (Quote 78).[133] However, it was noted that the presence of a positive drug test does not correlate with the level of impairment, limiting the interpretation of such results (Quote 79).[133] There was an indication that

self-reported work absences due to health conditions decreased in jurisdictions with medical cannabis laws (Quote 80).[159]

Implementation of legislative change within one jurisdiction was not always geographically isolated, and could affect neighbouring jurisdictions. Those jurisdictions where cannabis remains illegal and which share a contiguous border with a jurisdiction that has undergone judicial change noted an increase in illegal cannabis products entering their jurisdiction, as well as increased cannabis related arrests at borders (Quotes 81-84).[133,134,160–162] This may be due to increased law enforcement in these areas, resulting in an over-inflation of the inter-jurisdictional impact (Quotes 85, 86).[160,161] Judicial change, local bylaws and zoning restrictions also affected community demographics with deliberate movement of families both into and out of legalisation zones (Quote 87),[163,164] and lower socio-economic areas having higher density of cannabis retailers (Quote 88).[165]

Modelling of major crime rates post medical legislation demonstrated no consistent effects on crime rates (Quote 89)[166] and post recreational legalisation modelling demonstrated an initial short term increase in crime that was not sustained in the long term (Quotes 90, 91),[167] as well as increased police clearance rates (Quote 92).[168]

2.4.2.5 Health

The impacts of cannabis legislation on both mental and physical related health outcomes have been one of the more significantly studied areas.

The mental health impacts of judicial change were seen in both the adult and adolescent population.[148,169] Residents of states with medical cannabis laws had higher levels of cannabis use, abuse and dependence (Quote 93).[170] Increasing cannabis use was reported in new adolescent patients presenting to mental health clinics following recreational legalisation (Quote 94).[169] There was a trend towards increased adult use of cannabis with a subsequent increase in cannabis use disorders (Quote 95).[148] In teens who were seen for cannabis use disorder the passing of cannabis laws increased legitimacy of use- which also contributes to the theme of normalisation (Quote 96).[123] Increasing potency of products was seen as a concern in regard to the development of cannabis use disorder in adolescents (Quotes 97, 98).[123] Health care workers engaged in the treatment of such disorders perceived that there was a lack of resources to cope with the increased demand on services following law changes (Quotes 99,100).[123] It was initially proposed that medical cannabis laws may have a protective effect on suicide risk, but this was not borne out with robust analysis (Quotes 101-104).[171]

An increase in drivers involved in fatal accidents who tested positive for cannabis was identified (Quote 105),[138] as was an increased cardiac mortality in those states with medical cannabis laws (Quotes 106,107).[172] There was also an increase in the rates of cannabis detected in trauma patients presenting to the emergency department and there were four case reports of fatalities relating to accidents/injuries following edible cannabis ingestion in jurisdictions with recreational cannabis laws (Quotes 108-110).[138,173,174]

The implementation of medical and recreational laws appears to have had a health impact in children, with unintentional ingestions of cannabinoid products resulting in increased emergency room visits and poison centre phone calls (Quotes 111, 112).[152,162] Lack of regulations around packaging of products that could appeal to children, such as edible candies, and the lack of need for child-proof containers in some jurisdictions is thought to have contributed to this (Quotes 113, 114).[152] The impact of laws in the use of cannabis in pregnancy is an emerging area of research, with a trend to increase use during pregnancy following legislative changes (Quote 115).[175]

Physical impacts included those resulting from the manufacture of cannabis products, such as the increase in burns as a result of making butane hash oil at home (Quotes 116-119)[133,140,176] and the risk of plant and product contamination during the growing and extraction process (Quotes 120-122).[133,135,136] Allowing home cultivation practices raised concerns that a lack of more stringent regulations may lead to more contamination in new growers, with increased risks particularly in the extraction processes (Quotes 123-126).[100,133]

There were also correlations drawn between legislative change allowing cannabis use and worsening disease states such as anxiety (Quote 127),[133] cannabis hyperemesis syndrome (Quote 128),[177] cognitive disturbance[133] and increased emergency department and hospital visits for cannabis related health problems (Quotes 129-130).[134,178] However, there have been some reductions in opioid use noted in specific groups (Quotes 131-133).[179,180]

2.4.2.6 Quality of Evidence

The results of the grading are included in the Appendix (7.6, Supplement 5). Papers varied widely in the quality of evidence seen across the assessed domains, with the ethics and bias domains showing the most disparate grading, likely a reflection of the range of literature included in the review. Over 80% of the papers were graded overall as fair or good (n=24 and n=53 respectively), with six papers graded as very poor. All graded papers were included within the data analysis and synthesis process.

2.5 Discussion

2.5.1 Main Finding

This review offers a meta-narrative approach to elicit major themes that emerged in the literature after cannabis regulation change, whether medical or recreational in nature. Despite the varying origins of the papers included for analysis (e.g. policy, public health, economics, social sciences, medicine) the same five themes emerged across the breadth of the literature: normalisation, economics, health, community and gatekeeping. This is regardless of the methodology of the papers, the focus or expertise of the specific authors, or the jurisdictions in which the regulations are developed.

Normalisation occurred mainly in the context of positive perception towards legislation enabling access to cannabis and a perceived reduction in the harms of using cannabis as a result of jurisdictional change irrespective of the specific legislative changes made. Economically, benefits generally accrued to governments that enacted legislative change, potentially at the expense of an unintended increase in the potency of legalised products, and not necessarily to the detriment of any pre-existing black market. Almost all legislative change required some kind of gatekeeper. Often this was the role of practitioners / prescribers in the context of medical cannabis legislation, but in the recreational context could involve a number of roles and bureaucratic processes that might be independent of the legislative changes made. In the community theme, the impact of increasing access to cannabis on youth is much explored, but by no means certain. Rather than increasing equity, policing of new regulations in some jurisdictions appeared to continue to apply criminality to some ethnicities and to be more forgiving to others, thereby actually increasing inequity. This was further exacerbated in legislative change that applied retrospective drug convictions to potential new market entrants preventing them from developing now legitimate businesses. Finally, in health, there were clear signals that legislatively enabling access to cannabis increased mental health and cannabis use disorders, may have contributed to higher driving fatality rates and almost certainly contributed to an increase in unintended childhood overdoses.

Many reviews of the outcomes of cannabis regulatory change are either quantitative in nature or contained within the breadth of author expertise.[114,181,182] As such, the primary focus has been on '*a priori*' outcomes of interest such as how such legalisation may affect health, safety and social-equity outcomes. The resulting outcomes have appropriately focused on very specific issues such as blurred boundaries between medical and non- medical use, lack of regulation in regards to potency

and difficulties in establishing the true public health effects.[114,182] A realist review, which aims to systematically investigate and synthesise programme theory related to complex social interactions, was undertaken by Stevens et al., 2019, and examined the alternatives to criminalisation for illicit drug possession, focussing on questions developed in discussion with policy stakeholders. They looked at contexts, mechanisms and outcomes of such alternatives and developed a realist program theory to guide such policy moving forward.[183] From this focus Stevens et al. established the outcomes of the review to be 'level and type of drug use', 'social integration of people who use drugs', 'other crime', 'health harms' and 'social costs' and were identified to be of interest to policy stakeholders .[183] This research was not specific to cannabis legislation, rather decriminalization in general, however it is of note that their outcomes map onto the themes that synthesised from this review, albeit with a different emphasis. Whilst also qualitative, this review used grounded theory approach to the broadest field of literature available and followed a formal synthesis approach to analysis, where the resulting themes are not pre-determined but are instead identified through the empirical coding of the papers. It is reassuring that the themes derived from this process are in keeping with the expert opinions, quantitative and realist reviews seen within the literature as it provides validity to the methodology undertaken.

2.5.2 How and why it is important

The emergent themes across the literature highlight the underlying commonalities across the broad range of disciplines examining the effect of cannabis legislation. Due to the overarching presence of these themes across all the literature, they may be used as a point of focus to compare and inform jurisdictional legislation. For example, in Nevada, the legalisation of recreational cannabis was proposed and passed with the intention of the scheme being regulated under the Department of Taxation, with excess revenue being placed in the State Distributive School account ,[184] suggesting that economic outcomes and community was of importance to that jurisdiction. Uruguay, which had a strong history of drug related crime, became the first country to legalise non-medical cannabis in 2013. Motivated by concerns about drug related crime, and despite wide-spread opposition, legislators provided for three access points to cannabis (home grown, cannabis social clubs and state-controlled pharmacy-only products) of which adults over the age of 18 must choose one and also prohibited advertising of pharmacy products.[185] Within this cultural context it could be argued that the government attributed weight not only to community (to decrease crime rates), but in developing their legislative solution gave weight to gatekeeping (controlling access within the

government framework) with less emphasis on economic benefit (by limiting the commercial market).

Through the lens of their own cultural contexts, jurisdictions developing or amending cannabis regulations may reflect on these five themes; normalisation, economics, gatekeeping, community and health, to focus discussions and reflect on gaps within the policy development. In NZ, the use of cannabis is already entrenched in society with a strong black market presence.[186,187] Already medical cannabis legislation has been enacted with prescribing practitioners as gatekeepers, however a government initiated public referendum to establish support for or against the proposed Cannabis Legislation and Control Bill undertaken in October 2020 failed to garner enough support to pass.[188,189] In this context it might be argued that initial weighting placed on health and gatekeeping relating to the medical cannabis laws in New Zealand are not yet outweighed in public opinion by the potential economic and community effects that have been considered overseas in the development of recreational legalisation. This in turn provides focus for future research to address these effects in the development of future legislation.

This is not to say that consideration of these themes from multidisciplinary angles will result in completely acceptable legislation, as cultural contexts may differ between legislators at a state or national level, professional and community bodies, ethnicities, religions and individuals. This has played out particularly in the domain of the investigators of this paper: health. In this review of the literature, the gatekeeping theme has emerged as a significant factor following the implementation of medical cannabis regulations. This seems unsurprising, but no evidence supports this notion prior to this review.[190] In jurisdictions with medical cannabis laws the role of 'approving' access to products has usually been attributed to the doctor or physician. However, following review of the literature it is apparent that is has not been universally successful, has been described as an impediment by many would-be cannabis users, and has not been the choice of doctors themselves. Doctors would be likely to argue that medical cannabis legislation gives an undue amount of weight to normalisation, and not enough to health and community. It may be argued that gatekeeping places a strain on patient-doctor relationships, the costs of consultation may increase inequity and that cannabis does not lie within the 'usual' professional construct of a 'medicine' with the clinical trial evidence and the good manufacturing practices that are inherent in other medicines they prescribe. They themselves may feel they will become complicit in normalisation by being required to prescribe it. Would-be patients might argue their needs are not being met, they are incurring additional expense to access cannabis, and that bureaucracy is driving them towards the black market.

Jurisdictions may better comprehend these views and develop responsive legislation by considering how each theme identified across a range of disciplines and cultural contexts may be used to assist in identifying both the intended and unintended consequences of cannabis reform.

2.5.3 Limitations of the study

A significant amount of the literature emerges from the USA where cannabis has an uneasy status, remaining illegal at the federal level with varying levels of regulatory approaches at the state level from illegality through to full legalisation. It was felt during analysis that this dichotomous approach would be detrimental to the narrative synthesis and, as such, each state was determined to be a separate jurisdiction for the purposes of the review. As such, papers that solely focused on the federal/state divide were excluded from the analysis. Whilst countries outside of the USA have also enacted primarily medical cannabis legislation, with the exception of Uruguay and Canada, there is somewhat limited research available about the effects in these jurisdictions which alters the base from which we were able to draw our analysis.

It is also acknowledged that the time since the enactment of legalisation affects the amount of research available to fully assess the impact of such changes. The purpose of the study was to be temporally broad and encompassing, however despite this most studies were relatively close to the time of change being implemented, even those in previous decades. As cannabis regulation becomes increasingly embedded (i.e. the research is temporally more distant from the regulatory or legislative change) the findings of work such as this may change. This issue is one, however, that limits all health research using a variety of methodologies and outcomes. In fact, for this sort of work the relative closeness of the research to the regulatory change potentially is beneficial, identifying early problems and allowing policy changes on this basis.

In regard to this review, unlike a traditional quantitative systematic review, much of the quality of the synthesis comes from the depth and breadth of papers that have been included. Whilst the literature search has been approached systematically, and reflexivity was in place, the synthesis process will in some form be shaped by the investigators' professional and personal background. This is true for any qualitative approach and the use of four investigators for triangulating of results helps counter this bias during the constant comparative phase. It is noted, however, that experts with a specific interest may consider other themes, subthemes or an emphasis on one of the themes identified as of particular importance. The added value of this formal qualitative approach is its

ability to provide a formal overview of a very wide range of disciplines and thereby offers additional points of reference to all experts.

Another of the limitations of an empirical approach is the data sources. Although a very broad systematic search of the literature was undertaken, using the advice and support of an IT expert, the search will never capture all that is written on the subject, resulting in omission of potential literature for review. Omissions such as this are akin to omission in other fields and identify an area where further empirical and published work would help the field to understand these interactions more fully.

This review was also limited by the type of research that has been undertaken and that is available within the body of literature. A strength of this 'bottom-up' empirical process is that it allows themes to be explored across the disciplines that previously may have been overlooked in studies that weight their reviews to what they believe researchers or policy makers find important.

Another common limitation of reviews of this nature is that once thematic saturation is reached, no further papers are reviewed. This may lead readers to believe that some sentinel papers have been omitted from the review or that more powerful supportive statements for the themes have been overlooked, whereas in fact the themes have become saturated, and it is anticipated that those papers not formally reviewed will in fact only provide further supportive evidence of the identified themes. This is an unavoidable limitation of all qualitative work and is minimised by qualitative techniques such as triangulation.

As papers are not weighted within a broad qualitative review framework, it is acknowledged that a thematic summary of results may appear softened compared to the literature as a whole. This is a reflection of the supporting evidence reviewed prior to the point of thematic saturation. However, this does not detract from the overall thematic analysis, as the themes do not change according to the strength of the supportive quotes.

2.5.4 Quality of Evidence

The grading of evidence within a qualitative review presents its own limitations. Commonly used assessment tools heavily weigh the methodological approach of RCTs as the gold standard for the grading of evidence, and as such, these tools are not appropriate to grading of literature that falls outside this approach. The use of the Hawker Assessment Tool was used to grade such disparate evidence.[109] It was not without its limitations, as we found that even within the tool were there were papers that were difficult to grade, as the way they were written or their field of study may not have

called for the assessed domains to be present. A further barrier was noted when trying to use the tool to appraise conference abstracts, which contain valuable information, but only fulfil one of the nine domains within the criteria. As such, these received an overall grade of Very Poor, despite receiving a Good score in the Abstract domain. It was therefore determined that all papers graded would be included within the synthesis due to the presence of only a small number of poor and very poor papers assessed.

2.5.5 Future Directions

From undertaking this review process, I found that there is much commentary and opinion about the effect of cannabis regulations, which creates a large amount of 'white noise' within the field and yet there is limited pre and post implementation data available. For those jurisdictions looking to implement a change in their regulatory process, such as introducing new legislation, it is imperative that prospective data is collected prior to the law change, rather than retrospectively. This will allow greater audit and robust data examining the impact of the effects of such law changes.

The approach that this study used, synthesizing themes from multiple disciplines in the literature using a single tool, may be applied to other areas of legislative change outside of cannabis that are considered 'wicked' problems, to empirically assess the impact of such changes and provide a thematic focus for future research and policy development.

2.6 Conclusion

This review provides a formal qualitative approach to the analysis of literature related to cannabis regulations that is in keeping with previous traditional systematic reviews and contributes to the literature in an area where discipline-specific expertise and comment dominates. By systematically searching a wide literature base and applying a formal social sciences technique to data synthesis, it moves the field of understanding forward in respect to the way cannabis regulation is changing the social landscape. This emphasises that the effect of cannabis legislation can be thematically synthesised into five themes across all disciplines, regardless of the source of the literature that may then be weighted according to the cultural context of the jurisdiction. Such consideration of the themes derived may support legislation and policy not only relating to cannabis, but possibly legislation relating to other broad-ranging areas such as social policy, welfare, education and health.

2.7 Implications for New Zealand

This review has highlighted the need for jurisdictions undergoing legislative change to ensure that they have a process set up to understand the effect of legislation on health, social and legal issues.

NZ has already implemented medicinal cannabis legislation, however there are currently no new products available through the Medicinal Cannabis Scheme. As these products become available there is an opportunity to develop research focussing on a cohort of patients prescribed products in the future to assess the impacts within NZ. The five identified themes from this review may be used as a reference point for consideration developing the research question and when interpreting the results. One area of particular interest may be the around the theme of Gatekeeping and the impact of the NZ access model on both patients and doctors.

When considering future recreational legalisation research, cohort studies, such as the Christchurch Health and Development Study and the Dunedin Multi-disciplinary Health and Development Study, which have explored the use of cannabis within their participants, provide a basis for pre-legalisation data. This may be combined with the Ministry of Health Survey 2012/2013 and the Youth Insights Survey which report on cannabis use within NZ.[83,191] There is an indication from these studies that cannabis use in NZ is already normalised with 80% of adults indicating that they have tried cannabis within their lifetimes, however youth use has recently been declining, despite no change in legal status.[84,191] Prior to the implementation of any law change, it is imperative that NZ continues to develop research related tools that allow for the impacts of legislative change to be measured, whenever that may be applied, which may then be mirrored following implementation. This will help inform accurately the effects of legislative change and contribute to a growing body of literature in this subject area.

It is also important that development of future legislation within the NZ context considers the impact that legislative change has through the community lens, especially in relation to ethnic disparities following the implementation of legalisation. NZ already has significant disparities in the impact that cannabis use has in health and justice outcomes for Māori, and this review demonstrated that despite legalisation for recreational use, this does not always result in reduction in inequitable treatment following such legal changes.

No matter what legal changes are made, there is need for transparent regulatory oversight and enforcement to ensure that guidelines are implemented correctly balance the effects on health and

society. This balance must be undertaken whilst supporting research and access to regulated medicinal cannabis products that have legitimate use in specific medical conditions.

Chapter 3 Non-pharmaceutical grade cannabis-based products for medicinal use in the regulated market

Study Two: A systematic review and meta-analysis using quantitative methodology examining the label accuracy and presence of contaminants in cannabinoid-based products in regulated markets

3.1 Background

As previously discussed in Chapter 1, four pharmaceutical grade medicinal cannabis products globally are available that have been through the traditional process of pharmaceutical development and clinical trials. These products have limited approved medical applications for which doctors may prescribe them, and as such, they are treated as any other medicine.

This does not apply to non-pharmaceutical grade products. Prior to the increasingly global trend for cannabis to be legalised the constituents of cannabis-based products existed in unknown proportions and quantities. As cannabis-based products for medical and recreational use have become more common, this situation is rapidly changing. Not only are producers identifying the quantities and proportions of cannabinoids but they are also often making efficacy claims. Such products vary widely, with the existence of many commercial preparations of cannabis for inhalation and oral consumption available, including dried raw plant material, oils, infusions, and pre-made edibles. Such variation in both the cannabinoid content of primary plant materials and eventual products is challenging from a regulatory perspective and may be complicated by the blurring of lines in products being used for both medicinal and recreational purposes. In 2019 alone, the Food and Drug administration (FDA) sent out 22 warning letters to Cannabidiol (CBD) manufacturers in the US due to health claims and misbranding and in 2015- 2016 they tested a variety of available CBD products where the cannabinoid content did not match the label.[192] Additionally, previous research has highlighted the issue of contaminated cannabis, primarily illicit, by heavy metals, pesticides, and microbes as well as contamination of other health supplements by undeclared pharmaceuticals.[193–195]

As stated in the introduction of this thesis, for a product to be prescribed as a medicine, clear international guidelines exist.[196] These vary by jurisdiction but have very similar principles. Prescribers need to know what is in the product (e.g. active ingredient and excipients) and the amount present (for dosing accuracy).[93] Consistency within products is essential so that prescribers

can be confident that patients receive the same dose each time. Prescribers also rely on clinical trials of products to support safety and efficacy claims. In the US, the use of cannabis may be recommended by a health care provider, however if the product has not met the jurisdictional requirements to be a medication it is not actually prescribed.[197] In Australia and NZ, regulations allow products that meet acceptable manufacturing quality standards as 'unapproved' prescription only medications without the need for clinical trials.[198,199] This approach is somewhat unusual, and has led to some concerns as to why cannabis-based products are in effect being treated differently from all other medicines.

The variations in regulatory approaches in regards to medicines and health supplements have led to concern about the labelling of cannabis-based products. Whether used recreationally or medicinally, it is important that prospective users can know what quantity of drug they are consuming so that they may ingest a dose that maximises the intended effect while minimising potential harms or impairment. There has been interest in the ratio of delta-9- tetrahydrocannabinol (THC) to cannabidiol (CBD) within such products as there is varying evidence that CBD may perhaps mitigate some of the adverse effects of THC alone.[5] In products that report to have only CBD it is important to know that what is written on the label accurately represents what is in the bottle, as the presence of THC may have both legal and health impacts.

To understand this from a global perspective I undertook a quantitative systematic review with meta-analysis exploring the accuracy of labelling and presence of contamination of products that were indicated as for medicinal use in overseas-regulated markets.

3.1.1 Note

This chapter is a modified version of Oldfield et al.'s. "A systematic review of the label accuracy of cannabinoid-based products in regulated markets: is what's on the label what's in the product?"[200] reproduced with permission of the SAGE publishing group. The background, method and discussion sections have been augmented for the purposes of this thesis. This study involved a team of six investigators. Dr John Ryan contributed to the duplicate title/abstract screening for inclusion and full-text review/data extraction/analysis. Dr Marjan Doppen and Dr Stacy Kung contributed to duplicate full-text review and data extraction/analysis. Associate-Professor Giles-Newton Howes and Professor Braithwaite contributed to dispute resolution. In addition, Ms Susan Hope, reference librarian, contributed to the development of the search strategies.

3.2 Aims and Objectives

The aim of this study was to review the current literature investigating the accuracy of cannabis-based product labelling. My primary outcome was the number of papers describing the label accuracy of cannabis-based products potentially used for medical purposes within regulated markets, exploring the reported label accuracy and reported cannabinoid content. My secondary outcome was papers discussing the detection of contaminants such as heavy metals, pesticides and moulds in cannabinoid-products within regulated markets.

3.3 Method

A systematic review of the literature was designed following the Preferred Reporting Items for Systematic Review (PRISMA) guidelines.[116] Due to the suspected heterogeneity and observational nature of the literature, I anticipated there would be limited scope for a meta-analysis to be undertaken; however, it was planned that in the case of papers being present with similar comparators this would be performed.

All types of study were eligible to be included in the review. Population inclusion criteria included any study looking at a cannabinoid product being produced for a perceived medicinal effect where a regulatory framework allows sale. Studies were excluded if they primarily included illegal or synthetic cannabinoid products, cannabis plant (material/extract) only, countries/jurisdictions with no regulatory frameworks, or those cannabinoid products that are already FDA or similarly approved (i.e. pharmaceutical grade products e.g. Sativex).

A search strategy was developed and refined in conjunction with an information technologist (IT)/librarian. The following electronic databases were used for the search: Ovid MEDLINE, EMBASE, PsycINFO, ProQuest, Web of Science and SCOPUS. Grey literature was sought through use of Food and Science Technology Abstracts and International Pharmaceutical Abstracts. The search terms used for each database can be found in the Appendix (7.7, Supplement 6).

Papers were entered in to the Covidence system for the purposes of the review. I undertook the primary title/abstract screening with one other investigator. The subsequent full text review for inclusion of papers involved four members of the study team, of which I reviewed all papers that were considered for inclusion. Two senior investigators were consulted for the purposes of resolving disagreements around the inclusion of the papers.

The data extraction worksheet can be found in the Appendix (7.8, Supplement 7). Data was extracted from the included papers by four investigators. All six investigators reviewed the final data analysis and included papers.

Papers were reviewed to determine the overall number of articles that were found that discussed label accuracy and the reported frequency of inaccuracies that were found (total amounts of cannabinoids, mean and standard deviations (SD) if provided) and description of contamination. Where possible data was assessed by a variety of sub-group analyses e.g. by country/state, product type, analysis method, regulatory process applied and ability to meta-analyse determined. Article authors were contacted for clarification of data where indicated.

Another investigator and I used the Hawker System for Qualitative Research tool to assess the included papers for quality of evidence.[121] This tool has been previously described in Chapter 2 and was used due to the range of study types that were anticipated to be included. Papers received an overall grading from very poor to good, based on assessment in nine domains. A full description of the grading process may be found in the Appendix (7.8, Supplement 7).

3.3.1 Statistical analysis

Results from studies with similar outcome measures were pooled. Due to reported study outcomes, meta-analysis was limited to proportions and 95% confidence intervals only. Heterogeneity between study outcomes was tested using the χ^2 test and the I^2 statistic with an I^2 value of greater than 50% indicative of substantial heterogeneity. Meta-analysis of proportions was undertaken using R Studio 4.0.1.

3.4 Results

Following the initial database search, 3009 records were identified, with 1942 records suitable for review following removals of duplicates. Following both title/abstract and full text review, nine records were included for analysis. The full PRISMA process may be seen in Figure 3.1.

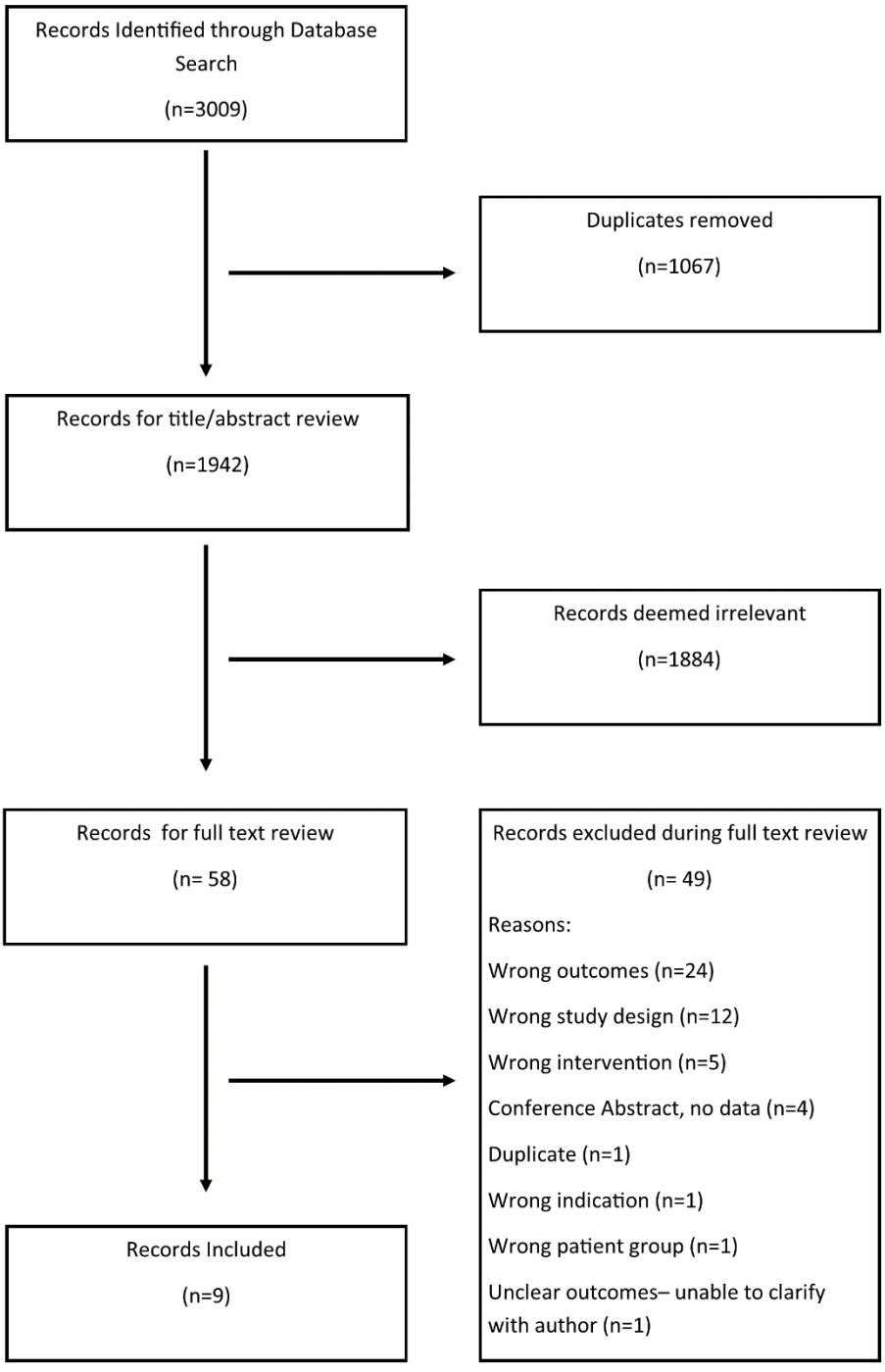

Figure 3.1. PRISMA diagram for selection of included papers

Six papers addressed the primary outcome variable of label accuracy and cannabinoid content and are summarised in Table 3.1. The cannabinoid-based products analysed were heterogeneous in nature, however all studies reported the observed cannabinoid content, primarily CBD and THC. Five of the six papers[201–205] identified the label accuracy of cannabinoid contents, results ranging from 17% to ~86% accurately labelled, with three[201,202,205] reporting some form of measured deviation from the label (Table 3.1). One paper provided approximate reports of inaccuracies whilst the other reported mean cannabinoid concentrations measured from pharmacy derived samples but did not comment overall on the label accuracy.[203,206] Due to heterogeneity of reporting units and product types, meta-analysis was unable to be performed.

Four papers[203,207–209] addressed the secondary outcome variable of contaminant presence. All studies identified varying levels of contaminants within the cannabis products tested (Table 3.2) ranging from microbes, solvents, pesticides and adulterants. Two studies, Raber et al. 2015 and Moulins et al., 2018, provided pesticide contamination proportions that could be meta-analysed, with the overall proportion of samples contaminated with pesticides being 0.25 (95% CI: 0.10 to 0.40), Heterogeneity: I^2=79%, Tau2= 0.0092, $\chi(1)^2$=4.74, p=0.03 (Figure 3.2).[207,208] One paper was excluded from the meta-analysis as absolute proportions were not reported.[203]

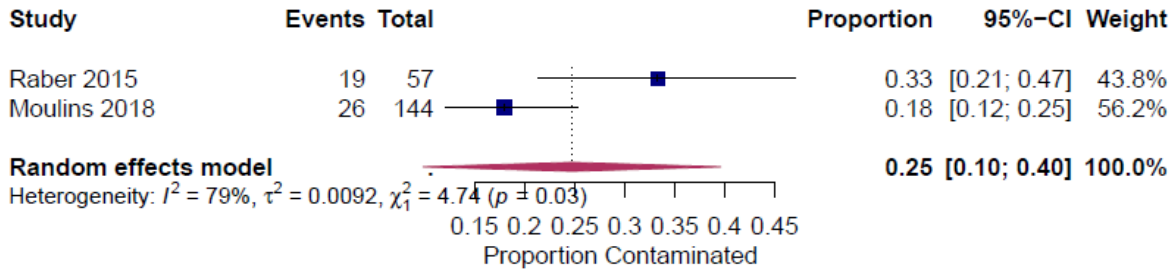

Figure **3.2**. Meta-analysis of the proportion of samples contaminated with Pesticides

The quality of evidence summary may be seen in Table 3.3. Overall the quality of the papers was rated as good.

Table 3.1. Primary outcome: labelling accuracy and deviation with cannabinoid content where described

Study ID	Country	Study Description	Analysis Method	Product Type (n)	Product Label Information	Observed Cannabinoid Content	Deviation from label	Samples accurately labelled (n, %) (unless otherwise specified)
Vandrey 2015[201]	USA	Observational Cross Sectional	HPLC	Edibles (all) (n=75)	-	THC (median, range) 54mg (<1-1236) CBD (median, range) 1mg (<1-20)	-	13 (17)
					Accurately labelled (range) 15 to 200mg Under labelled (range) 20-1000mg Over labelled (range) 2 to 325	Accurately labelled (range) 15-183mg Under labelled (range) 34 to 1236 mg Over labelled (range) <1 to 267	Accurately labelled (mean, SD) -3% (4) Under labelled (mean, SD) 28% (13) Over labelled (mean, SD) -47% (29)	-
				Baked (n=22)	-	-	-	2 (9)
				Beverage (n= 13)	-	-	-	3 (23)
				Chocolate/Candy (n= 40)	-	-	-	8 (20)
Bonn-Miller 2017[202]	USA	Observational Cross sectional	HPLC	Total (oils, tincture, vape) (n=84)	-	CBD mg/ml (mean, SD) 30.96 (80.86) THC mg/ml (mean, SD) 0.45 (1.18)	-	Accurately labelled (n, %, 95% CI) 26 (30.95) [22.08-41.49]
				Oil (n= 40)	Mean CBD mg/ml (95%CI) 56.15 (14.23 to 98.07)	-	Mean CBD mg/ml [95%CI] (mean % dev) 10.34 [4.95-15.7] (29.01)	Accurately labelled (n, %, 95% CI) 18 (45.00) [30.17-60.17]
				Tincture (n=20)	Mean CBD mg/ml (95%CI) 11.14 (5.60-16.60)	-	Mean CBD mg/ml [95%CI] (mean % dev) 3.94 [2.74-5.14] (220.62)	Accurately labelled (n, %, 95% CI) 5 (25.00) [11.19-46.87]
				Vape (n=24)	Mean CBD mg/ml (95%CI) 26.15 (12.50-39.74)	-	Mean CBD mg/ml [95%CI] (mean % dev) 11.52 [8.10-14.94] (1098.7)	Accurately labelled (n, %, 95% CI) 3 (12.50) [4.34-31.00]
Stevenson 2018[203]	USA	Editorial Report	Not specified	Not specified (n=5268)	Not specified	Not specified	Not specified	Approximately 86%[a]

Study ID	Country	Study Description	Analysis Method	Product Type (n)	Product Label Information	Observed Cannabinoid Content	Deviation from label	Samples accurately labelled (n, %) (unless otherwise specified)
Blebea 2019[204]	Romania Netherlands	Quantitative method analysis	UHPLC (-PDA)	CBD oil (n=3)	-	Content µg/ml	-	0 (0)[b]
				Sample # 174	1350 mg/100ml cannabinoids	CBD: 35.2245	Not specified	-
				Sample # 175	CBD: 2.50%	CBD: 48.3351	Not specified	-
				Sample # 181	CBD: 8% (4mg/drop)	CBD: 27.3011	Not specified	-
Deidda 2019[206]	Italy	Quantitative method analysis	Fast RP-HPLC/UV	Oil (n=459)		Mean mg/ml (SD)	Not specified	Not specified
				Bedrocan 100 mg/ml (n=95)	THC: 22% CBD <1%	THC: 16.6 (10.71) CBD: ND	-	-
				Bedrocan 70 mg/ml (n=98)	THC: 22% CBD <1%	THC: 12.7 (14.07) CBD: ND	-	-
				Bediol 100 mg/ml (n=51)	THC: 6.3% CBD: 8%	THC: 5.54 (13.98) CBD: 8.64 (14.60)	-	-
				Bediol 70 mg/ml (n=82)	THC: 6.3% CBD: 8%	THC: 3.98 (14.58) CBD: 6.55 (18.04)	-	-
				Bedrolite 100 mg/ml (n=17)	THC: <1% CBD: 9%	THC: ND CBD: 8.92 (10.02)	-	-
				Bedrolite 70 mg/ml (n=57)	THC: <1% CBD 9%	THC: ND CBD: 6.65 (18.81)	-	-
				FM2 100 mg/ml (n=12)	THC: 7.5-12% CBD: 5-8%	THC: 6.26 (12.43) CBD: 12.630 (12.04)	-	-
				FM2 70 mg/ml (n=47)	THC: 7.5-12% CBD: 5-8%	THC: 4.85 (14.42) CBD: 9.21 (14.81)	-	-
Herbst 2019[205]	USA	Case Report	Not specified	Oil (n=1)	Company analysis (mg/g) THC: 1.1 CBD: 24.5 CBN: 0.1 CBDA: 0.5	FDA analysis (mg/g) THC: 0.53 CBD: 15 CBN: 0.082 CBDA: 0.13	THC: -69.9% CBD: -48.1%	0 (0)

USA: United States of America, THC: Tetrahydrocannabinol, CBD: Cannabidiol, HPLC: High performance liquid chromatography, UHPLC (-PDA): Ultra high-performance liquid chromatography-photodiode assay, Fast RP-HPLC/UV: Fast Reverse phase-high performance liquid chromatography/ultraviolet detection, ND: Not detected

a: Derived from statement "68% of 20% failure rate for inaccurately labelled samples".
b: Discussion states "Of the three analysed samples: two samples were far below label claim and one sample was well above the label, up to 200%."
C: Discussion states "The values obtained highlighted the widely variable concentrations of the analytes between formulations."

Table 3.2. Secondary outcome: contaminant identification in cannabis-based products

Study ID	Country	Study type	Analysis method	Product	Types of Contaminants	Total Samples Contaminated n (%)
Raber 2015[207]	USA	Quantitative analysis	GM-CS	Total (Concentrates and hash) (n=57)	Solvents n % Isopentane 17 29.8% Present but proportion not specified: Butane, Heptane, Hexane, Isobutene, Isopropyl Alcohol, Neo-pentane, Pentane, Propane Pesticide n % Paclobutazorol 13 22.8 Bifenthrin 7 12.3 Myclobutanil 1 1.8	Solvents: 41 (71.9) Pesticides: 19 (33.3)
				Concentrate (solvent extract) (n=48)	Not specified	Solvents: 40 (83.3) Pesticides: 19 (39.6)
				Hash (water/dry extract) (n=9)	Nil identified	Solvent: 0 (0) Pesticides: 0 (0)
Moulins 2018[208]	Canada	Quantitative analysis	HPLC- MS/MS GCMS/MS GC-MS	Total (Oil, leaves, flowers) (n=144)	Pesticides	26 (18.06)
				Oil (n=36)	Pesticide (µg/g) n Conc range Myclobutanil 5 0.01-6 Boscalid 3 0.02-1 Bifenazate 2 0.02-2 Fludioxonil 2 0.01-0.02 Fluopyram 1 0.02 Tebuconazole 1 0.01	9 (25.00)
				Leaves (n= 45)	Myclobutanil 7 0.01-0.03 Pyraclostrobin 1 0.01 Boscalid 1 0.01 Piperonyl butoxide 1 0.8	9 (20.00)
				Flowers (n= 63)	Myclobutanil 8 0.03-20 Bifenazate 7 0.03-6	8 (12.70)
Stevenson 2018[203]	USA	Editorial Report	Not specified	Not specified (n=5268)	Pesticides, Microbial contamination, Solvents	Pesticides Approximately 4% Microbial Contamination Approximately 1.2% Solvents Approximately 1.0%
Rianprakaisang 2020[209]	USA	Case Report	LC-QTOF-MS	Oil (n=1)	AB-FUBINACA	1(100)

USA: United States of America, GC-MS: Gas chromatography-mass spectrometry, HPLC- MS/MS: High performance liquid chromatography-mass spectrometry, GCMS/MS: Gas chromatography-tandem mass spectrometry, LC-QTOF-MS: Liquid chromatography-quadrupole time of flight-mass spectrometry

Table 3.3. Hawker grading of domains for included papers

First Author	Publication Year	Title	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data Analysis	Ethics and Bias	Results	Transferability or Generalisability	Implications and usefulness	Overall Rating
Raber[207]	2015	Understanding dabs: contamination concerns of cannabis concentrates and cannabinoid transfer during the act of dabbing	Good	Good	Good	Fair	Good	Poor	Good	Fair	Good	32 (Good)
Vandrey[201]	2015	Cannabinoid Dose and Label Accuracy in Edible Medical Cannabis Products	Fair	Fair	Good	Poor	Good	Fair	Good	Poor	Good	29 (Good)
Bonn-Miller[202]	2017	Labelling Accuracy of Cannabidiol Extracts Sold Online	Fair	Fair	Good	Poor	Good	Fair	Good	Fair	Good	30 (Good)
Moulins[208]	2018	Multiresidue Method of Analysis of Pesticides in Medical Cannabis	Good	Good	Good	Good	Good	Very Poor	Good	Good	Fair	32 (Good)
Stevenson[203]	2018	Flash Report on Cannabis in California	Very Poor	Very Poor	Very Poor	Poor	Poor	Very Poor	Fair	Poor	Poor	15 (Poor)
Blebea[204]	2019	The Qualitative and Quantitative analysis of CBD in Hemp oils by UHPLC with PDA and applications	Fair	Fair	Fair	Poor	Poor	Very Poor	Poor	Poor	Fair	21 (Fair)
Deidda[206]	2019	Analytical quality by design: Development and control strategy for a LC method to evaluate the cannabinoids content in cannabis olive oil extracts	Good	Good	Good	Poor	Good	Poor	Good	Poor	Fair	29 (Good)
Herbst[205]	2020	Respiratory depression following an accidental overdose of a CBD-labelled product: A paediatric case report	Good	Good	Good	Good	Good	Good	Good	Good	Good	36 (Good)
Rianprakaisang[209]	2020	Commercial cannabidiol oil contaminated with the synthetic cannabinoid AB-FUBINACA given to a paediatric patient	Very Poor	Very Poor	Fair	Good	Good	Very Poor	Fair	Fair	Poor	22 (Fair)

3.5 Discussion

Legalisation of medical and recreational cannabis globally has led to an increase of cannabis-based products available for use. With the wide range of products available, the increasing growth of internet sales and varying regulatory inputs, there is reason for concern about the accuracy and contents of cannabis products on the market.

This review systematically examined the literature for research pertaining to the label accuracy and contamination of cannabinoid products. Nine papers were included within the analysis, six which examined the primary outcome of label accuracy and cannabinoid contents and four which examined the secondary outcome of product contamination. Included papers originated from the USA, Canada, Italy, Romania and the Netherlands. The papers reviewed were heterogeneous in nature, with small sample sizes resulting in limited scope for meta-analysis. Despite this, the review demonstrated that inaccurate labelling was a common finding and that contaminants and adulterants have also been found samples in regulated markets, particularly unapproved pesticides, solvents and microbes.

CBD extracts, which are easily accessible through the internet are commonly advertised as 'harmless'. In the USA, the FDA has recently approved Epidiolex, a pharmaceutical grade CBD medication, meaning other CBD containing products fall under the label 'unapproved new drugs'. This is then complicated by the many state level laws that allow the production and selling of CBD product. This permits regulatory loopholes to occur in establishing the quality, consistency and safety of such products being presented to the public. The outcomes of this study indicate that there is poor correlation in CBD products between what is written on the label and what is in the product. From a safety perspective, there may be some reassurance that the majority of products with labelling inaccuracies tended to be over-stated rather than under-stated cannabinoid content. Conversely, over-labelling is of concern if the result is sub-therapeutic dosing in indicated conditions.

Although many studies included in this review obtained their products through internet searches, the one study that visited medical dispensaries showed that consistency and accuracy in the labelling of products that include THC is also in question. The under-reporting of THC content in any cannabinoid-based product is of concern, as this creates a potential for increased psycho-active

adverse effects. There may be significant risks to children in the event of unintentional ingestion of THC where the label states a product is CBD only.

It is of interest that labelling inaccuracies are present across all modalities of drug delivery, including in-pharmacy compounded products. Due to these multiple modalities, a regulatory system becomes harder to implement. This study does not address reasons for label inaccuracy; however, there are multiple points within the manufacturing process that may contribute to this. Heterogeneity of the starting plant (material/extract) may contribute to intra and inter-batch variation. The excipient and/or processing may also affect the distribution of the cannabinoids within the product. The lack of standardisation across laboratories, as discussed by Jikomes and Zaroob, may also lead to label inaccuracies.[210] This can include a consistent skew in one direction across multiple samples, be it due to differences in testing methodology or otherwise. In markets with multiple competing laboratories, there may be a competitive advantage for those who find, on average, higher concentrations. This provides a strong argument for rigorous standardised and independent testing across the regulatory markets.

The paucity of literature regarding contaminants in cannabinoid-based products and their health effects has previously been highlighted by Dryburgh et al.,[193] and our findings support this view. Not only can contamination occur at any point in the production chain, one case study, Rianprakaisang et al., 2020, reported the presence of synthetic cannabinoids within a CBD product highlighting the wider risk of adulterants in products.[209] These findings and the lack of published material highlight the critical need to regulate standards for contents and testing across all aspects of the manufacturing, supply chain and testing of cannabinoid-based products.

Efficacy claims, ‘best before’ dates and shelf-life of cannabinoids were not explored in this review, however may also be of interest in future studies in this rapidly moving area of research.

3.5.1 Strengths and Limitations

The overall quality and quantity of the literature available within the searched databases limits the findings and provides an element of concern. Despite broad search terms that were redeveloped during the study process, it became apparent that cannabinoid-based outcomes are not published in the usual indexed databases. This highlights a gap within peer-reviewed indexed literature where further robust research should be undertaken, especially in new and emerging regulatory systems where testing regimes are yet to be implemented.

3.6 Conclusion

The literature reviewed shows that there is labelling inaccuracy and contaminants present across the spectrum of cannabinoid-based products in regulated markets, the breadth and depth of which cannot be discerned. To counter this, it is imperative that independent rigorous standardised testing and pharmacovigilance is undertaken to ensure that patient safety is not compromised as the demand for cannabinoid-based products grows.

3.7 Implications for New Zealand

The products that were included in this study were available for medicinal use in regulated markets, whether recommended or prescribed. Although only a small number of studies were found, the study findings have implications for NZ.

As has been stated previously, NZ only has one product, nabiximols, which has been approved by Medsafe, and no products that are currently on the Medicinal Cannabis Scheme (MCS). At present, unapproved cannabis-based products may be imported on prescription with Ministry of Health approval. These products fall under the remit of the review above. There is uncertainty for patients and doctors concerning these imported products, as there is potential for product contents to not be accurately reflected on the label.

The development of the MCS and the minimum quality standards provides a framework for the development of cannabis-based products in NZ. The majority of these products will not be of pharmaceutical grade and will not be approved by Medsafe unless they undergo traditional medicine developments with clinical trials. Therefore, these products will fall under the same umbrella as some of the products described in the review and will not be able to be sold under current regulations, unless they meet the minimum quality standards imposed by the MCS.

As discussed previously, the development of cannabis-based products for medicinal use have challenges in both inter and intra-batch consistency. This is due to the nature of the product itself, as in many plant-based products, where the expression of multiple active compounds is affected by the growing conditions, even if the seed stock is identical. This may be amplified during the product manufacturing process, resulting in diverse rather than consistent product. There is need for close monitoring by the Medical Cannabis Agency to ensure that those products that are accessed through the scheme undergo stringent post-market pharmacovigilance. This will reassure doctors that the

products that they are prescribing to patients are consistent with what is on the label, limiting the potential health harms from either receiving a sub or supra-therapeutic dose of the active ingredient and address concerns about potential contamination. As unapproved products will not be available for funding under the pharmaceutical agency (PHARMAC) there is also potential for financial harm to patients, especially if they receiving product that is of no benefit as it does not contain the active ingredient.

For doctors, good prescribing practice dictates that they know what is in the product that they are prescribing, as well as understanding the efficacy of the product and the potential side effects. As well as the products themselves being subject to ongoing testing, it would be of benefit to NZ to develop surveillance tools that examine the efficacy and side effects of such medications when prescribed. The development of a complete pharmacovigilance programme supports the doctors' ability to provide good and safe care to patients when considering the use of cannabis as a medicine.

There are further implications if NZ enacts legislation in the future allowing cannabis-products for recreational use. Overseas studies have shown that patients often choose to self-medicate with illicit products if barriers to medicinal products exist.[97,98,100] There is potential in NZ that this would extend to products legally available for recreational use, despite the fact that such products would not be produced to the same minimum quality standards as required to be listed as medicinal products by Medsafe. Therefore, when looking to create regulatory guidelines for recreational products, it is important that compliance with labelling in the recreational market be regularly monitored. This is not only for those people who are using cannabis recreationally but also for those who may choose to access these products for self-management of medical symptoms.

Product development, testing and labelling is one part of the complexities of using cannabis as a medicine. As previously discussed in Chapter 1, to access any cannabis-based product in NZ, a patient requires a doctor's prescription. These interactions may be complex in themselves, due to the knowledge and beliefs of both doctors and their patients. Understanding such interactions has the potential to provide empirical information to support the implementation of a successful medicinal cannabis scheme in NZ with these interactions explored in Chapters 4 and 5.

Chapter 4 NZ health-care practitioner's knowledge and experiences of the use of cannabis as a medicine

4.1 Background

As touched on in the previous chapter, the change to the Misuse of Drugs regulations in relation to CBD in 2017 and the passing of the Misuse of Drugs (Medicinal Cannabis) Act 2018 aimed to increase the access to quality medicinal cannabis products within NZ. This was followed by the implementation of the Medicinal Cannabis Scheme in April 2020, however as of December 2020, there are no products available, excluding nabiximols, which was already approved for use for spasticity in multiple sclerosis in NZ in 2010.

Whilst the law changes described have been primarily patient and access focused, it is important to reflect that these changes have an impact on the health care professionals who will be expected to prescribe the products as they become available through the scheme.

Research in countries with varying access to medicinal cannabis products provides an overseas perspective. A survey of Australian GPs in 2017 reported that over half of those surveyed had experienced patient enquiries about the use of cannabis-based products, with GPs expressing that they remain uncertain of efficacy and prescribing processes associated with the use of cannabis as a medicine.[211] Within other specialties studies have shown that doctors are likely to have lower levels of support for the use of medicinal cannabis than patients, depending on their specialty, with internal medicine and oncology-gynaecology specialists more likely to be supportive than psychiatrists and family medicine doctors.[212,213] In relation to neurologist's beliefs and support for the use of cannabis as a medicine, limited primary research exists, split between paediatric and adult neurologists. In a Canadian survey of twelve paediatric neurologists, some neurologists expressed concerns about insufficient evidence and lack of guidance for the use of cannabis as a medicine and that parents expectations may be overly optimistic and may not be consistent with their clinical determinations of effectiveness, leading to a need to combat 'false expectations'.[214] In a study of US based neurologists, nurse practitioners/nurses and pharmacists, 20-44% of participants indicated no knowledge of specific items relating to the content, effects and legality of CBD/medical cannabis.[215] The neurologist's attitudes towards CBD/medicinal cannabis were not as favourable as the nurse practitioners/nurses and pharmacists.[215] Oncologists also have expressed concern about the use of cannabis as a medicine with one study reporting only 30-36% of oncologists in the US

felt sufficiently informed to discuss the use of cannabis as a medicine with their patients, though approximately two thirds believe that it is effective for symptom control.[216,217] In Israel, where cannabis may be prescribed to patients with palliative diagnoses, 90% described a paucity of knowledge surrounding its use, instead relying on their own judgements as a guide for dosing.[218]

To understand what doctors in NZ have experienced through patient interactions as well as their knowledge surrounding the use of cannabis as a medicine during this period of legislative change a series of observational studies were undertaken.

I selected three health care practitioner groups to study. These were doctors working in general practice, neurology and oncology settings. General Practice was expected to have the greatest diversity of patients who may be expected to have queries from their patients about the use of cannabis as a medicine. The settings of neurology and oncology was selected as that is where there is evidence for use of cannabinoids (oncology- chemotherapy induced nausea and vomiting, neurology- multiple sclerosis, severe refractory epilepsy syndromes).

4.1.1 Note

This chapter contains excerpts from Oldfield et al's. "Medical cannabis: knowledge and expectations in a cohort of North Island New Zealand general practitioners"[219] and Oldfield et al.'s, "Experiences, patient interactions and knowledge regarding the use of cannabis as a medicine in a cohort of New Zealand doctors in an oncology setting"[220] and has been reproduced with permission from the New Zealand Medical Journal and BMJ publishing groups. Dr Jordan Tewhaiti-Smith assisted with data collection, Allie Eathorne assisted with statistical analysis, all other authors were involved in study planning and review of the final papers. The introductions have been edited and expanded, methods combined, and discussion of GP paper augmented to reflect the current literature.

4.2 Aims and Objectives

The aims of each of the studies were to understand what doctors had experienced with the use of cannabis as a medicine in the New Zealand context. This was achieved through using in-person surveys to assess doctor reported patient interactions and prescribing practices, indications for use, understanding of regulatory processes for obtaining prescribed products and knowledge of pharmaceutical grade products, future prescribing concerns and educational access regarding the

use of cannabis as a medicine. Due to the descriptive nature of the research undertaken, testable hypotheses were not able to be developed, however some consideration was given to anticipated responses from each of the participant groups, which are explained below.

4.2.1 Doctors in a General Practice setting

Study Three: An observational study of the knowledge and expectations regarding the use of cannabis as a medicine in General Practitioners

I anticipated that GPs in NZ would have limited knowledge around the use of cannabis as a medicine. This was due to the regulatory environment at the time of the survey. This included possible limited exposure to the management of patients with multiple sclerosis (the sole Medsafe approved indication for a cannabinoid-derived medication), the lack of funded products as well as well as potentially limited education about cannabis and the endocannabinoid system in both medical schools and vocational training schemes.

4.2.2 Doctors in a Neurology setting

Study Four: An observational study of the knowledge and expectations regarding the use of cannabis as a medicine in doctors in a neurology setting

Due to the Medsafe approval of nabiximols in NZ, and the international approvals of Epidiolex in neurological conditions, I anticipated that neurology-based doctors would have knowledge pertinent to prescribing for neurological conditions and experience with patients both requesting information about cannabis-based products and reporting self-management of conditions with illicit cannabis.

4.2.3 Doctors in an Oncology Setting

Study Five: An observational study of the knowledge and expectations regarding the use of cannabis as a medicine in doctors in an oncology setting

The historical use of dronabinol and nabilone for CINV overseas and relevant research in the literature led me to anticipate that oncology-based doctors were likely to have experienced patient interactions around the use of cannabis as a medicine regarding symptom control.) As such, it was expected that they would have some knowledge of cannabis-based products and their efficacy.

4.3 Methods

4.3.1 Study design

A prospective, observational, cross-sectional study design was used for all three settings.

4.3.2 Participants

Participants in each of the settings were eligible for inclusion if they were working in the specialty of interest at the time that I undertook the questionnaires. In the general practice setting, which was the first group to be completed, trainee intern medical students were included in the data analysis. The inclusion criteria were modified for the subsequent neurology and oncology-based questionnaires where medical students were excluded from the data analysis.

4.3.2.1 Doctors in a General Practice setting

GPs, GP registrars and Trainee Interns on GP attachments working in general practices throughout the North Island of NZ (Hutt Valley, Bay of Plenty, Wairarapa and Wellington) were recruited between June and October 2018 using a snowball technique,[221] useful in groups who rarely participate in research. Peer groups and continuing medical education (CME) sessions were the nidus for these snowballs with initial participants identified through the Medical Research Institute of NZ (MRINZ) GP research network. CME sessions were not associated with cannabis or substance abuse teaching. Specific GP caseloads or special interests e.g. chronic pain, were not established prior or during the recruitment period. A study investigator (primarily myself) then attended the CME meeting where attendees were asked to undertake the questionnaire, following a review of the participant information sheet (PIS).

4.3.2.2 Doctors in a Neurology setting

Doctors working in a neurology setting were recruited in three main NZ centres (Auckland, Wellington, Christchurch) between January 2019 and January 2020. Initial recruitment was through emails and phone calls to department senior medical officers (SMOs) in charge of organising CME meetings within hospitals. The PIS was circulated to attendees prior to the meetings. A study investigator (primarily myself) then attended the CME meeting where consultants, registrars and house surgeons working within respective neurology departments were asked to undertake the

questionnaire. If attendance at a CME meeting was not possible, the PIS and questionnaires were given to a SMO for distribution and return. Medical students present at meetings who chose to answer the questionnaire were excluded for the purpose of data analysis.

4.3.2.3 Doctors in an Oncology Setting

Doctors working in an oncology setting were recruited from oncology departments (medical and radiation oncology) in four NZ regional hospitals (Auckland, Wellington, Christchurch and Dunedin) between November 2019 and January 2020. Oncology consultants, trainees and house surgeons working in the departments were invited to participate. Contact was made with a senior oncologist in the department to arrange a time that an investigator (primarily myself) could attend local oncology CME sessions to discuss the research and collect questionnaires from those who wished to participate. A PIS was distributed to attendees prior to the meeting and those who were interested were invited to complete and return the paper-based questionnaires during the session. Where attendance at a CME meeting was not possible, the PIS and questionnaires were given to a SMO for distribution and return. Responses from medical students who were present at the meeting and chose to complete the questionnaire were excluded from the data analysis.

4.3.3 Questionnaires

A full copy of the health care practitioner questionnaires is provided in the Appendix (7.9). Examples of questions may be seen in Figure 4.1. The same questionnaire was used for all three participant groups, with a minor change when asking about other health care practitioners who had prescribed products for their patient (alternating the terms specialist or GP depending on the target population).

For the purposes of the questionnaire, medicinal cannabis was defined as “any use of cannabis plants and/or medications derived from cannabis used by a patient to treat a medical condition”.

Questionnaires were provided on paper and included the following domains (see Figure 4.1):

- Consultant GP/Specialist – Patient Interactions around the use of cannabis as a medicine
- Consultant GP/Specialist prescriptions of cannabinoid medications- facilitation and impediments
- Knowledge of conditions with evidence for or against the use of cannabis as a medicine

- Knowledge of the regulatory process for approvals, import and funding in relation cannabinoid medications
- Awareness of pharmaceutical cannabinoid medications worldwide

The original questionnaire was piloted on two Consultant GPs. Survey domains did not go through a validation process. Ideally, participants were asked to complete the questionnaire in the presence of a study investigator or SMO.

4.3.4 Data Entry and Analysis

All data was entered into REDCap (Research Electronic Data Capture).[222] All submitted questionnaires were included in the analysis. Partially completed questionnaires were included in the analysis to the point of completion. If questionnaires had single missing data points, such as a blank space in a table where other information had been input and it was clear that by leaving a question blank the participant did not know the answer it was analysed as such, otherwise this was recorded in the database as "No answer given".

Ethnicity data was prioritised according to the Health Information Standards Organisation.[223]

4.3.5 Statistics

A convenience sample was used for each of the participant groups. The sample size was developed considering the central limit theorem, which states that in sample sizes greater than 30, the studentised sampling distribution approximates the standard normal distribution.[224]

Proportions, percentages and 95% Confidence Intervals were calculated using Java Stat (General Practitioners), Microsoft Excel or SAS ® software, version 9.4.18 (Neurology and Oncology).[225,226] The proportion denominator was determined by the number of participants who answered that specific area of the questionnaire. Percentages are reported to zero decimal places, due to sample sizes less than 100. Free text answers were grouped for the purposes of reporting using NVivo. These groups are reported as frequencies in text and tables.

Post-hoc analyses comparing differences in proportions between the groups looking for significant associations were performed using the Chi squared test, with an alpha level of 0.05 (5%).

- "Have you been approached by patients seeking a prescription for medical cannabis products over the past 12 months?" Answers were categorised as none, 1-4, 5-10, 10+.
- "What impediments (if any) occurred when facilitating the request (for prescribed medical cannabis)" Categories for answers included cost, insufficient evidence base, side effects, insufficient understanding of process, and aware of process but benefit versus cost was inappropriate.
- "What conditions are you aware of that DO have Grade A/Level I RCT evidence for use of medical cannabis products" and "what conditions are you aware of in which there is substantive evidence of NO benefit to support the use of medical cannabis products but for which products may have been recommended?"
- Completion of a table identifying responsibilities' for approval, funding and import of CBD, Nabiximols and other medical cannabis products
- Of dronabinol, nabiximols, nabilone and Epidiolex, participants were asked to indicate awareness of the product, select primary constituents (THC and/or CBD), indicate if licensed in New Zealand, indicate formulation and estimate the annual cost to the patient for the product.

Figure 4.1. Examples of questions from each domain of the health care practitioners' questionnaire

4.4 Doctors in a general practice setting

4.4.1 Results

A total of 82 potential participants were approached, of which 76 agreed to take part (response rate 93%). Fifty-six questionnaires were completed in the presence of a study investigator (74%), with the remainder performed without supervision. Participant characteristics are shown in Table 4.1.

Table 4.1. GP participant characteristics (stratified by experience)

	Total (n)	**%**	**GP Consultant (n)**	**%**	**GP Registrar (n)**	**%**	**Trainee Intern (n)**	**%**	**Not Stated (n)**	**%**
Total Participants	76	100	67	88	3	4	2	3	4	5
Gender										
Male	45	59	42	55	1	1	1	1	-	-
Female	28	37	25	33	2	3	1	1	1	1
Not stated	3	4	-	-	-	-	-	-	3	4
Age Band										
20-29	3	4	-	-	2	3	1	1	-	-
30-39	11	15	10	13	1	1	1	1	-	-
40-49	18	24	17	22	-	-	-	-	-	-
50-49	18	24	18	24	-	-	-	-	-	-
60-69	21	28	18	24	-	-	-	-	3	4
70-79	3	4	3	4	-	-	-	-	-	-
Not stated	2	3	1	1	0	-	-	-	1	1
Ethnicity										
NZ European	53	70	49	65	1	1	2	3	1	1
Māori	3	4	3	4	-	-	-	-	-	-
Chinese	4	5	3	4	1	1	-	-	-	-
Indian	2	3	2	3	-	-	-	-	-	-
Other	11	15	10	13	1	1	-	-	-	-
Not stated	3	4	-	-	-	-	-	-	3	4

4.4.1.1 Patient interactions, prescribing practices and impediments

Of the GPs, 42/76 (55%) had at least one patient ask them for a medicinal cannabis prescription in the last 12 months (Table 4.2) most commonly for pain, cancer and palliative care. On request, 14/42 (33%) GPs attempted to prescribe, with 13 reporting impediments to prescribing and 7/13 reporting that the patient ultimately received their prescription (Table 4.2). Eight participants (8/73,

11%) reported they had patients who had been prescribed a medicinal cannabis product, with five reporting that this was specialist prescribed, however it was not established if this was prior to the GP request. There were 51/75 (68%) GPs with patients reporting using illicit/recreational cannabis in order to manage medical conditions, mainly for pain, anxiety/depression and cancer/palliative care. Smoking was reported by patients as the preferred form of use (Table 4.2).

4.4.1.2 Evidence for use of medicinal cannabis products

Out of 76 GPs, 33 (43%) considered there was at least one condition with Grade A/Level 1 RCT[227] for cannabis use in medical conditions; with the most commonly identified conditions listed in Table 4.3. A similar proportion (29/76, 38%) considered there were specific conditions for which there was clearly no evidence of benefit to support the use of medicinal cannabis products but that they were aware that these products might have been recommended or suggested outside evidence-based medicine, as listed in Table 4.3.

When asked about medicinal cannabis side effects, 49/76 (65%) GPs indicated at least one, with the most commonly stated side effects being drowsiness/sedation, psychosis/schizophrenia, nausea, and weight gain/increased appetite (n =25, 13, 13 and 9 respectively). Two of 76 (3%) GPs stated there were no side effects, 13/76 (17%) did not know and 12/76 (16%) did not answer.

4.4.1.3 Knowledge of pharmaceutical grade medicinal cannabis products

Just over half of GPs were aware of currently available pharmaceutical grade cannabinoid preparations (n=43/76, 57%). Of these, most were aware of nabiximols (n=37/43, 86%); 10/37 (27%) accurately described it constituents and 12/37 (32%) its formulation (Table 4.4). Of those aware of nabiximols 31/43 (72%) indicated they would prescribe it for at least one condition including pain syndromes (n=17), multiple sclerosis (spasticity/pain) (n=16) and epilepsy/seizures (n=11).

Table 4.2. GP-patient interactions relating to medicinal cannabis products and use of recreational/illicit cannabis for medicinal purposes.

	n	%	95% CI
Number of participants receiving patient requests for medicinal cannabis prescriptions	42/76	55	43 to 67
1 to 4 patients	38/42	91	77 to 97
5 to 10 patients	2/42	5	1 to 16
10+ patients	2/42	5	1 to 16
Number of participants attempting to prescribe	14/42	33	20 to 50
Number of participants with impediments (more than one answer could be given)	13/14	93	66 to 100
Specialist/Ministry approval needed	6/13	46	19 to 75
Cost prohibitive to patient	6/13	46	19 to 75
Lack of general knowledge/information	2/13	15	2 to 46
Put off by assuming responsibility of assuring CBD:THC ratio	1/13	7	0 to 36
Number of participants not prescribing at time of request	28/42	67	51 to 80
Reasons for not prescribing at time of request (more than one answer could be given)			
Insufficient Evidence Base	14/28	50	31 to 69
Cost	6/28	21	8 to 41
Insufficient Understanding of Process	4/28	14	4 to 33
Clinical Benefit vs logistics/cost inappropriate	3/28	11	2 to 28
Anticipated side effects	0/28	0	0 to 12
No answer given	8/28	29	13 to 49
Number of participants with patients reporting recreational/illicit cannabis use for medicinal purposes	51/75	68	56 to 78
1 to 4 patients	35/51	69	54 to 81
5 to 10 patients	9/51	18	8 to 31
10+ patients	6/51	12	4 to 24
No answer given	1/51	2	0 to 10
Preferred forms of use elicited from patients by participants (more than one answer could be given)			
Smoking	44/51	86	74 to 94
Edibles	19/51	34	24 to 52
Other (cannabis drops, oils, vaping, unknown)	8/51	16	7 to 29

Table 4.3. GP knowledge of evidence for medical cannabis use and future prescribing concerns

Response	Conditions with Grade A/Level 1 RCT evidence for use is available			Conditions with substantive evidence of no benefit for use but GP aware may have been suggested outside evidence-based medicine		
	n	**%**	**95% CI**	**n**	**%**	**95% CI**
None	17/76	22	14 to 33	5/76	7	2 to 15
Didn't know	13/76	17	9 to 27	15/76	20	11 to 30
Didn't supply an answer	13/76	17	9 to 27	27/76	36	25 to 47
At least one condition	33/76	43	32 to 55	29/76	38	27 to 50
Conditions cited	**n**			**n**		
Pain (all types)	19			15		
Epilepsy/seizure	16			7		
Multiple Sclerosis	15			0		
Nausea and Vomiting	8			1		
Psychological/Psychiatric illness	0			12[a]		
Cancer	0			3		
Other	10[b]			11[c]		
Concerns about future prescribing of medical cannabis products (more than one option could be given)				**n**	**%**	**95% CI**
Overall indicating concerns				59/75	79	68 to 87
Insufficient Evidence Base				39/59	66	53 to 78
Cost				19/59	32	21 to 46
Insufficient Understanding of Process				31/59	53	39 to 66
Clinical Benefit vs logistics/cost inappropriate				18/59	31	19 to 44
Side effects				12/59	20	11 to 33

a: Anxiety; n=5, post-traumatic stress disorder (PTSD); n=3, depression; n=3, psychiatric illnesses; n=1
b: Anxiety; n=2, Parkinson's disease; n=2, arthritis / rheumatological disorders; n=2, depression; n=1, dystonia; n=1, motor neurone disease; n=1, poor appetite; n=1.
c: Headache; n=2, dementia; n=2, cardiovascular disease; n=1, reduce adverse effects of antipsychotics; n=1, head injuries; n=1, autism spectrum disorder; n=1, HIV; n=1, rheumatological disorders; n=1, muscle spasms; n=1.

Table 4.4. GP knowledge of pharmaceutical grade medicinal cannabis products

Knowledge of any pharmaceutical grade cannabis-based product			
	n	**%**	**95% CI**
Able to cite at least one cannabis-based product	43/76	57	45 to 68
Nabiximols (Sativex)	37/43	86	72 to 95
Dronabinol (Marinol)	5/43	12	4 to 25
Nabilone (Cesamet)	2/43	5	1 to 16
Epidiolex	1/43	2	0 to 12
Knowledge of Nabiximols			
Primary constituents			
THC only	6/37	16	6 to 32
THC/CBD	10/37	27	14 to 44
CBD only	15/37	41	25 to 58
No answer given	6/37	16	6 to 32
Aware licensed in New Zealand	29/37	78	62 to 90
Formulation			
Capsule/Tablet	1/37	3	0 to 14
Buccal/Sublingual	12/37	32	18 to 50
Both	7/37	19	8 to 35
No answer given	17/37	46	29 to 63
Estimated cost per year to patient (NZ$)			
Less than $10000	11/37	30	16 to 47
Greater or equal to $10000	7/37	19	8 to 35
No answer given	19/37	51	34 to 68

4.4.1.4 Regulatory processes

Less than half of GPs responded to the regulatory section of the questionnaire, with 37/76 (49%) answering questions relating to nabiximols funding and 36/76 (47%) about its approval. Of those who supplied answers (for which more than one answer could be given), there were an equal number of responses indicating that specialist or MOH approval was needed for a nabiximols prescription (n= 21/36, 58%), with 20/37 (54%) indicating that they thought PHARMAC funding was available (Table 4.5).

Fifty-nine out of 75 (79%) GPs reported concerns about prescribing medical cannabis products in the future (Table 4.3). Sixty-three out of 75 GPs (84%) indicated that if there was a PHARMAC

funded, licensed product with good scientific evidence for specific conditions, they would be ‘somewhat’ or ‘very’ likely to prescribe this in their day-to-day practice.

4.4.1.5 Accessing information

When asked about education, 75 GPs responded, with 43/75 (57%) stating they had accessed one or more sources of information regarding cannabis use as a medicine. The educational sources accessed were journals (n=19/43, 44%), CME sessions (n=13/43, 30%), the Ministry of Health Website (n= 12/43, 28%) and other sources (n=15/43, 35%). Preferred educational methods were CME sessions (n=54/75, 72%), followed by CME online modules and information sheets (n=32/75, 43% and n=25/75, 33% respectively.

Table 4.5: GP knowledge of responsibility for the regulatory process relating to medical cannabis in NZ (more than one answer could be given)

	Nabiximols (n=36)			CBD (n=21)			Other cannabis products (n=9)		
Entity responsible for approval of medicinal cannabis products	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Total response rate (out of 76)	36	47	36 to 59	21	28	18 to 39	9	12	6 to 21
PHO	-	-	-	1	5	0 to 24	-	-	-
DHB	1	3	0 to 15	1	5	0 to 24	1	11	0 to 48
Specialist	21	58	41 to 75	8	38	18 to 62	2	22	3 to 60
MoH	21	58	41 to 75	12	57	34 to 78	6	67	30 to 93
PHARMAC	12	33	19 to 51	10	48	26 to 70	6	67	30 to 93
Entity responsible for funding of medicinal cannabis products	**Nabiximols (n=37)**			**CBD (n=25)**			**Other cannabis products (n=13)**		
	n	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Total response rate (out of 76)	37	49	37 to 60	25	33	23 to 45	13	17	9 to 28
PHO	-	-	-	-	-	-	-	-	-
DHB	3	8	2 to 22	3	12	3 to 31	-	-	-
Patient	16	43	27 to 61	12	48	28 to 69	7	54	25 to 81
MoH	6	16	6 to 32	1	4	0 to 20	-	-	-
PHARMAC	20	54	37 to 71	12	48	28 to 69	7	54	25 to 81
Entity responsible for the import of medical cannabis	**Nabiximols (n=32)**			**CBD (n=25)**			**Other cannabis products (n=11)**		
	n	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Total response rate (out of 76)	32	42	31 to 54	25	33	23 to 45	11	15	8 to 24
Prescribing Doctor	5	16	5 to 33	6	24	9 to 45	3	27	6 to 61
Pharmacy	10	31	16 to 50	9	36	18 to 58	3	27	6 to 61
Specialist	4	13	4 to 29	5	20	7 to 41	1	9	0 to 41
MoH	6	19	7 to 36	3	12	3 to 31	1	9	0 to 41
PHARMAC	11	34	19 to 53	9	36	18 to 58	5	46	17 to 77

*PHO: Primary Health Organisation, DHB: District Health Board, MoH: Ministry of Health, PHARMAC: Pharmaceutical Management Agency

4.4.2 Discussion

This study has identified that just over half of 76 GPs surveyed reported having patients ask about medicinal cannabis prescriptions in the past 12 months and two-thirds had patients discuss their use of illicit cannabis for medical reasons. Less than a third of GPs asked attempted to facilitate prescription requests citing cost and the need for Specialist/Ministerial approval as the largest impediments encountered. Just over half of the GPs were aware of pharmaceutical grade cannabinoid products, with the majority of them referencing nabiximols. Responses to the regulatory questions were limited and suggested uncertainty around the regulatory processes currently in place. Three quarters of participants expressed some concerns about prescribing medicinal cannabis in the future, however most (four in five) reported that they would be willing to prescribe a PHARMAC funded, prescription medication with Grade A/Level 1 RCT evidence in specific medical conditions. Half of the participants had accessed some educational (material/extract) about medicinal cannabis, with the majority preferring CME sessions as their future way of having information disseminated.

As previously described in Chapter 1, the Misuse of Drugs (Medicinal Cannabis) Amendment Act December 2018 allows for patients with any illness that requires palliation, as determined by a medical doctor or nurse practitioner, a defence against the charge of possession of a cannabis plant or preparation, pipe or utensil.[188] In addition, CBD products were removed from the Misuse of Drugs Regulations 1977, and it was required that the regulations for a Medical Cannabis Scheme to improve access to quality medicinal cannabis products be in place within one year of the law being implemented, which commenced in April 2020.[228]

Whilst this legal and regulatory environment for the use of cannabis as a medicine is changing, it does not necessarily follow that the medical profession are prepared for or support these changes. There is no conclusive definition as to what "medicinal cannabis" comprises; be it a pharmaceutical grade medicine that has undergone the scrutiny of drug development phases or a locally grown cannabis plant that is smoked or from which a preparation is made, with or without the presence of THC. From a prescriber perspective, any cannabis product that has not been developed to a pharmaceutical grade and approved by Medsafe is considered an unapproved medicine, and as such can only be prescribed under Section 25 of the Medicines Act 1981.[9] This means the prescriber assumes responsibility in regards to independently investigating and conveying risks, benefits and

contraindications related to the unapproved medication whilst providing appropriate follow up if they choose to prescribe it.[19,229]

Currently GPs that feel there is evidence for use of cannabis-based products for their patients and who attempt to facilitate a request find they are impeded by a confusing regulatory process and a high cost to the patient. They report some patients choose to self-manage using an unregulated illicit product, often delivered by smoking. This reported use of illicit cannabis to manage medical conditions is in agreement with the NZ Health Survey 2012/2013[83] suggesting that use of cannabis as a medicine has some currency in the eyes of the public.

There are varying levels of GP knowledge of the evidence for the use of cannabis as a medicine, with the same conditions being described in both the 'Grade A/Level 1 RCT evidence' and 'substantive evidence of no benefit of use' categories. Whilst there is a large amount of peer reviewed literature available, high quality randomised controlled trials remain limited. As previously stated, the National Academies of Science, Engineering and Medicine report into the Health Effects of Cannabis and Cannabinoids in 2017 found conclusive/substantial evidence for the use of cannabis-derived therapeutics in three areas. These were chemotherapy-induced nausea and vomiting, multiple sclerosis related spasticity and the treatment of chronic pain in adults. However they also specifically stated the need for further research.[4] More recent trials of Epidiolex in refractory childhood epilepsy syndromes have provided further evidence for use in specific medical conditions.[60–63,23054,218]

Almost half of GPs who participated in this study were aware of nabiximols, however the majority of those could not recall its constituents or its formulation. The majority of GPs were informed as to the potential side effects of using cannabis-based medications, likely reflecting knowledge of the adverse effects of recreational/illicit cannabis use. A minority were aware of the annual cost to patients (approximately $14,500) for the PHARMAC approved indication for prescribing. This is not unsurprising, as the prevalence of multiple sclerosis in NZ was most recently recorded as 73.1/100,000,[231] meaning many GPs may not have experience with patients who have multiple sclerosis and do not have experience prescribing nabiximols.

The majority of GPs expressed reservations about prescribing cannabis products in the future but indicated they would likely prescribe an approved medication that was PHARMAC funded and had Grade A/Level 1 RCT evidence for a specific medical condition.

The lack of substantial evidence for the use of cannabis as a medicine in many medical conditions and the relatively recent discovery of the endocannabinoid system is likely to have impacted the potential education that GPs have received. Overseas studies report that despite the legalisation of medical cannabis products in certain states of the United States of America, the training given at medical schools is limited, with 85% of residents and fellows reporting receiving no training about medical cannabis in medical school or residency and only 9% of medical schools having medical cannabis training in their curriculum.[232] This may reflect that although advocacy for use and legalisation of the products has occurred, the limited strength of evidence for the use of cannabis as a medicine precludes it from being included within the therapeutics section of medical school curricula. Current Australasian curricula concentrates on basic cannabinoid pharmacology; including receptors and signalling pathways, as well as cannabis related drug tolerance and harms, with discussions around therapeutics if and when substantial evidence for use is available.

There are a range of Australian resources available from the Therapeutics Goods Administration (TGA)[233] and ACRE[234] for practitioners to access about the use of cannabis as a medicine. However, with changing regulatory requirements, the addition of NZ-focussed education modules including regulatory processes involved, cannabinoid products available in NZ and supporting evidence for or against their use that is made available for post-graduate doctors, would add to the tools that health care professionals can use to have informed conversations with their patients.

4.4.2.1 Strengths and limitations

This study has limitations in its size, with 76 participants, however it has strengths in the fact that the majority of questionnaires (74%) were undertaken in the presence of a study investigator, rather than through an online portal, ensuring answers were based on immediate recall and therefore current knowledge. There is a likelihood that unanswered questions reflect areas that GPs have little or no knowledge, so the positive responses likely indicate the maximal current understanding in the GP community. There is a possibility of selection bias in that all participants were recruited through CME and peer group sessions, so only those doctors that attend these sessions would be approached, however it is a requirement of the Medical Council of NZ that all doctors undertake a CME programme. Due to the recruitment of an anonymous convenience sample, non-response bias was unable to be assessed. It is acknowledged specific GPs may have areas of special interest that mean they would receive a higher amount of interest in the use if medical cannabis as a medicine

and that this was not established at the time of the questionnaire being undertaken. The sample was small and skewed towards male GPs, which may limit the generalisability of the results. There were also a greater number of GPs from urban practices compared with rural practices involved in the study, which also has potential to limit the generalisability.

4.4.3 Conclusion

In conclusion, the Misuse of Drugs (Medicinal Cannabis) Amendment Act 2018, and subsequent implementation of the Medicinal Cannabis Scheme, has increased the likelihood that GPs will have patients wanting to discuss the use of cannabis as a medicine. Due to the issue of regulatory restrictions, ongoing limited pharmaceutical grade preparations available in NZ and the poor evidence base of efficacy in many conditions, individual GPs may feel the need to take on the responsibility of prescribing an unapproved medication under the Medicines Act. To counter this, it is essential that evidence-based, NZ-focused education modules are developed to allow GPs and their patients to have informed discussions around the legislative, evidential and practical elements of prescribing cannabis as a medicine.

4.5 Doctors in a neurology setting

4.5.1 Results

A total of 44 potential participants were approached, of whom 40 responded to the request (91% response rate). Participant characteristics are shown below in Table 4.6.

4.5.1.1 Reported patient interactions: requests for scripts, prescribing practices and illicit cannabis use

In total, 25/40 (63%) of doctors in a neurology setting had at least one patient request a prescription for cannabis-based medicine in the previous 12 months (Table 4.7), most commonly for epilepsy, pain and Parkinson's disease. Of these, 8/25 (32%) attempted to prescribe, with all reporting impediments. The primary reasons for non-prescription were insufficient evidence base and cost (Table 4.7). Illicit cannabis used to treat medical symptoms was reported to 38/40 (95%) doctors with patients citing pain syndromes, epilepsy and anxiety (n=23, n= 17, n=6 respectively) as the

reason for use. Smoking was reported to doctors as the preferred form of use by patients (Table 4.7).

Table 4.6. Participant characteristics of neurology-based doctors (stratified by experience)

	Total (n)	%	Consultant (n)	%	Registrar (n)	%	House Surgeon (n)	%
Total Participants	40	100	24	60	14	35	2	5
Gender								
Male	29	73	20	50	7	18	2	5
Female	11	28	4	10	7	18	-	-
Age Band								
20-29	6	15	-	-	4	10	2	5
30-39	15	38	5	13	10	25	-	-
40-49	6	15	6	15	-	-	-	-
50-59	4	10	4	10	-	-	-	-
60-69	6	15	6	15	-	-	-	-
70-79	2	5	2	5	-	-	-	-
Not stated	1	3	1	3	-	-	-	-
Ethnicity								
NZ European	26	65	19	48	6	15	1	3
Māori	1	3	-	-	1	3	-	-
Chinese	7	18	3	8	4	10	-	-
Other	6	15	2	5	3	8	1	3

4.5.1.2 Cannabis based products: Evidence of efficacy and side effects

With respect to evidence of efficacy, 31/40 (78%) of doctors cited at least one condition that they considered had Grade A/Level 1 RCT evidence for use (Table 4.8). For conditions without evidence of efficacy, but for which they were aware cannabis-based products may have been recommended, 20/40 (50%) listed at least one condition, with pain and epilepsy being the most commonly listed (Table 4.8).

When asked about side effects, 33/40 (83%) of doctors cited at least one side effect, with sedation, nausea and appetite changes (n=19, n=16, n= 6) being the most common. No answer was supplied by 6/40 (15%) and one participant was not sure.

Table 4.7. Neurology-based doctor-patient interactions relating to medicinal cannabis products and use of recreational/illicit cannabis for medicinal purposes

	n	%	95% CI
Number of neurologists receiving patient requests for medicinal cannabis prescriptions	25/40	63	46 to 77
1 to 4 patients	13/25	52	31 to 72
5 to 10 patients	10/25	40	21 to 61
10+ patients	2/25	8	1 to 26
Number of neurologists attempting to prescribe	8/25	32	15 to 54
Number of neurologists encountering impediments (more than one answer could be given)	8/8	100	-
Paperwork	3/8	38	9 to 76
Cost	6/8	75	35 to 97
Bureaucratic Issues/ Red Tape	2/8	25	3 to 65
Number of neurologists not prescribing at time of request	17/25	68	46 to 85
Reasons for not prescribing at time of request (more than one answer could be given)			
Insufficient Evidence Base	14/17	82	57 to 96
Cost	6/17	35	14 to 62
Insufficient Understanding of Process	4/17	24	7 to 50
Clinical Benefit vs logistics/cost inappropriate	2/17	12	2 to 36
Anticipated side effects	3/17	18	4 to 43
Number of neurologists with patients reporting illicit/recreational cannabis use for medical symptoms	38/40	95	83 to 99
1 to 4 patients	23/38	61	43 to 76
5 to 10 patients	8/38	21	10 to 37
10+ patients	6/38	16	6 to 31
No answer given	1/38	3	0 to 14
Preferred forms of use elicited from patients by neurologists (more than one answer could be given)			
Smoking	32/38	84	69 to 94
Edibles	14/38	37	22 to 54
Other (cannabis drops, oils, vaping, unknown)	10/38	26	13 to 43

Table 4.8. Neurology-based doctors' knowledge of efficacy of cannabis-based products as medicines and future prescribing concerns

Response	Conditions with Grade A/Level 1 RCT evidence for use is available			Conditions with substantive evidence of no benefit for use but participant aware may have been suggested outside evidence-based medicine		
	n	**%**	**95% CI**	**n**	**%**	**95% CI**
None	3/40	8	2 to 20	1/40	3	0 to 13
Didn't know	3/40	8	2 to 20	4/40	10	3 to 24
Didn't supply an answer	3/40	8	2 to 20	15/40	38	23 to 54
At least one condition	31/40	78	62 to 89	20/40	50	34 to 66

Conditions cited	**n**	**n**
Epilepsy (Paediatric Refractory Conditions)	25	-
Multiple Sclerosis (MS)/ Spasticity	11	2
MS excluding spasticity	3	2
Pain (all types)	10	11
Epilepsy (not specified)	5	9
Chemotherapy induced nausea and vomiting	2	0
Anorexia in oncology	1	1
Other	-	10[a]

Concerns about future prescribing of medical cannabis products (more than one option could be given)	**n**	**%**	**95% CI**
Insufficient Evidence Base	33/36	92	78 to 98
Cost	21/36	58	41 to 74
Insufficient Understanding of Process	12/36	33	19 to 51
Clinical Benefit vs logistics/cost inappropriate	5/36	14	5 to 29
Side effects	13/36	36	21 to 54

a: Parkinson's Disease n=3, Nausea n=2, Anxiety n=1, Cancer n=1, Dementia n=1, Depression n=1, IIH n=1, Many n=1, Most other neurological disorders n=1, Opioid sparing effect n=1

4.5.1.3 Knowledge of specific pharmaceutical grade product preparations

Of those doctors aware of pharmaceutical grade cannabis-based products, 36/38 (95%) of them were aware of nabiximols (Table 4.9). Of those, 9/36 (25%) knew that its constituent products were THC and CBD, 21/36 (58%) knew it was a buccal/sublingual formulation and 31/36 (86%) were aware that it was licenced in NZ. Just over a quarter indicated that the cost to patients was greater than $10,000 per year (Table 4.9). Reasons given for potential prescribing of nabiximols included

multiple sclerosis, pain syndromes and epilepsy (n= 14, n=7, n=5 respectively). Three neurologists indicated they would not prescribe nabiximols for any conditions.

For Epidiolex, 3/38 (8%) doctors indicated awareness of this product, with two aware it was a CBD only formulation. One participant indicated that they would prescribe this for Dravet syndrome.

Table 4.9. Neurology-based doctors' knowledge of pharmaceutical grade medicinal cannabis products

Knowledge of any pharmaceutical grade cannabis-based product			
	n	**%**	**95% CI**
Able to cite at least one cannabis-based product	38/40	95	83 to 99
Nabiximols (Sativex)	36/38	95	82 to 99
Dronabinol (Marinol)	5/38	13	4 to 28
Nabilone (Cesamet)	2/38	5	1 to 18
Epidiolex	3/38	8	2 to 21
Knowledge of Nabiximols			
Primary constituents			
THC only	3/36	8	2 to 23
THC/CBD	9/36	25	12 to 42
CBD only	17/36	47	30 to 65
No answer	7/36	19	8 to 36
Aware licensed in New Zealand (by Medsafe)	31/36	86	71 to 95
No answer	5/36	14	5 to 29
Formulation			
Capsule/Tablet	4/36	11	3 to 26
Buccal/Sublingual	21/36	58	41 to 74
Estimated cost per year to patient (NZ$)			
Less than $10000	6/36	17	6 to 33
Greater or equal to $10000	10/36	28	14 to 45
Unsure/indeterminate answer	8/36	22	10 to 39
No answer given	12/36	33	19 to 51

4.5.1.4 Understanding of the regulatory processes relating to patients obtaining cannabis-based products and future prescribing concerns

Of the doctors who replied to this section of the questionnaire, 24/34 (71%) indicated that specialists were responsible for approval of prescriptions for nabiximols, and 25/32 (78%) indicated that patients were responsible for meeting the cost of funding (Table 4.10). There was a spread of opinion amongst neurologists as to where responsibilities for importing nabiximols lie (Table 4.10).

Less than half of doctors responded to questions related to regulatory processes for CBD and other cannabis-based products (Table 4.10).

Most doctors (36/40, 90%) indicated that they had future prescribing reservations, mainly due to insufficient evidence of efficacy (n=33) and cost (n=21) (Table 4.8). Of 39 neurology-based doctors, 33 (85%) indicated that they would be ‘somewhat or very likely’ to prescribe a PHARMAC (Pharmaceutical Management Agency) funded, Medsafe approved product, four (10%) indicated they were ‘neutral’, and two (5%) indicated they would be ‘very unlikely’ to prescribe.

4.5.1.5 Accessing information about using cannabis-based products as medicine

Most doctors (32/40, 80 %) had accessed information about using cannabis-based products as medicines in the following ways; journals (27/40, 68%), CME sessions (21/40, 53%) and the Ministry of Health website (8/40, 20%). Greatest preferences for accessing information were CME sessions (26/40, 65%), information sheets (18/40, 45%) and podcasts (11/40, 28%).

Table 4.10. Neurology-based doctors' knowledge of responsibility for the regulatory process relating to medical cannabis in NZ (more than one answer could be given)

	Nabiximols (n=34)			CBD (n=20)			Other cannabis products (n=7)		
Entity responsible for approval of medicinal cannabis products	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Total response rate (out of 40)	34	85	70 to 94	20	50	34 to 66	7	18	7 to 33
PHO	1	3	0 to 15	2	10	1 to 32	-	-	-
DHB	-	-	-	-	-	-	-	-	-
Specialist	24	71	53 to 85	10	50	27 to 73	1	14	0 to 58
MoH	14	41	25 to 59	10	50	27 to 73	6	86	42 to 100
PHARMAC	9	27	13 to 44	1	5	0 to 25	-	-	-
Entity responsible for funding of medicinal cannabis products	**Nabiximols (n=32)**			**CBD (n=19)**			**Other cannabis products (n=7)**		
	n	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Total response rate (out of 40)	32	80	64 to 91	19	48	32 to 64	7	18	7 to 34
PHO	-	-	-	-	-	-	-	-	-
DHB	-	-	-	-	-	-	-	-	-
Patient	25	78	60 to 91	12	63	38 to 84	4	57	18 to 90
MoH	3	9	2 to 25	2	11	1 to 33	-	-	-
PHARMAC	7	22	9 to 40	6	32	13 to 57	3	43	10 to 82
Entity responsible for the import of medical cannabis	**Nabiximols (n=26)**			**CBD (n=17)**			**Other cannabis products (n=6)**		
	n	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Total response rate (out of 40)	26	65	48 to 79	17	43	27 to 59	6	15	5 to 30
Prescribing Physician	3	12	2 to 30	3	18	4 to 43	2	33	4 to 78
Pharmacy	12	46	27 to 67	6	35	14 to 62	2	33	4 to 78
Specialist	4	15	4 to 35	3	18	4 to 43	1	17	0 to 64
MoH	8	31	14 to 52	7	41	18 to 67	3	50	12 to 88
PHARMAC	8	31	14 to 52	2	12	2 to 36	1	16.7	0 to 64

*PHO: Primary Health Organisation, DHB: District Health Board, MoH: Ministry of Health, PHARMAC: Pharmaceutical Management Agency

4.5.2 Discussion

This study has shown that there is interest in the use of cannabis-based products as medicines within neurology. Approximately two-thirds of doctors working in a neurology setting reported that patients had asked them about a prescription for a medical cannabis product in the previous 12 months, with nearly all of them reporting that patients said they were using illicit cannabis for medical symptoms.

Over three quarters of doctors gave at least one medical condition that they felt had Grade A/Level I RCT evidence for use, whilst half expressed knowledge of conditions for which there was no evidence of benefit but for which they were aware it may have been recommended anyway. Nearly all were aware of nabiximols, with few aware of Epidiolex. Most doctors indicated that prescriptions required specialists' approval and patients' self-funding; however, there was a lack of consensus on responsibility for the import processes. Nearly all expressed concerns about future prescribing primarily citing lack of evidence for efficacy. The majority were open to prescribing a product that has traditional medical provenance. Most neurologists accessed information through medical journals and CME sessions; and expressed that CME sessions were their preferred form of education in the future.

Neurology has some of the highest level evidence of efficacy of cannabis products, and as a result, nabiximols and Epidiolex have been approved as medicines in a range of jurisdictions.[235–237] Therefore it is not unexpected that the majority of participating doctors were aware that cannabis-based products could be prescribed in their specialty area. What was surprising was that approximately half of those aware of nabiximols believed it contained CBD only. This may reflect both lack of training and lack of experience in prescribing within this group, where only one fifth of neurologists had attempted to prescribe any cannabis-based product, despite that fact that just under two-thirds had been approached for a prescription. Only a minority of the doctors surveyed were aware of Epidiolex, likely due to the fact that they are practicing within an adult neurology service, combined with a lack of Medsafe approval for use in NZ. Doctors working in paediatric neurology are likely to have a different level of knowledge and prescribing pattern of cannabis-based medicines. This has been seen in Europe, where 45% of doctors stated they are using CBD in childhood and adolescent epilepsy patients, with 48% of those exclusively using purified CBD products with no THC, though not specific commercial pharmaceutical grade preparations.[238]

Many doctors surveyed reported that patients were requesting prescriptions for cannabis-based products as well as reporting illicit cannabis use to treat medical symptoms, primarily epilepsy and pain syndromes. These findings are consistent with a 2017 Australian survey of patients with epilepsy that found 15% of adults surveyed had tried a cannabis-based product, often obtained illicitly, with good subjective success.[239] This is of concern, as while current evidence points towards efficacy of Epidiolex as adjunct therapy in severe refractory epilepsy syndromes, there is no current evidence that CBD products are effective in more generalised epilepsy syndromes.[4] Additionally, it is likely that illicit cannabis obtained by patients contains THC, potentially causing harm in those who choose to self-medicate with substances with unknown constituents and of unknown provenance. This highlights the need for both cannabis-based products to show traditional medical provenance and the need for strong and open doctor-patient relationships, as patient harm may result if cannabis is used without the doctor's knowledge.

Regarding pain syndrome requests, as previously noted in Chapter 1, a 2018 Cochrane review of the use of cannabis in chronic neuropathic pain found no high-quality evidence for its use, with low-moderate quality evidence showing that cannabis-based medicines may increase the number of people achieving pain relief.[54] This and Stockings et al.'s systematic review of cannabis use in chronic non-cancer pain syndromes concluded that the associated risks outweigh the potential benefits.[52,54] This limited evidence and potential for harm may contribute to neurologists reservations about future prescribing of cannabis-based products, where the guiding principle of using evidence-based medicine is to ensure that patients receive safe and appropriate management of their condition.[93] Where there is limited scientific evidence and lack of formal guidelines available for the use of cannabis as a medicine, it has been demonstrated that some health care providers, both licensed and unlicensed, may self-generate a community standard of practice where their observations drive recommendations for use.[240] This reinforces the need for ongoing high-quality research and easily accessible educational material, such as targeted CME sessions, that inform specialty clinical practice, decreasing the need for a patients to seek care through a 'cannabis specialist'.[145]

4.5.2.1 Strengths and limitations

Some methodological issues need to be considered in this study. The sample size is small, with 24 consultants, however this is a significant proportion of the full-time equivalent neurology consultant positions throughout NZ.[241] Due to the range of training levels surveyed it is acknowledged that level of clinical experience will likely impact the responses given.

As the questionnaire was administered in three main centres to maximise responses and to ensure the questionnaires were completed in person, these results may not be generalizable to the experience of those neurologists practicing in more remote locations. The distribution of the PIS to participants prior to the commencement of the meeting may have allowed participants to look up broad cannabis related literature prior to participating, however the presence of the study investigator at the CME meetings limited literature access during questionnaire completion. This does not limit recall bias, as those who have recently treated a patient with a medicinal cannabis product are more likely to remember and report this interaction. Due to the recruitment of an anonymous convenience sample, non-response bias was unable to be assessed. There was over representation of males in the group, however this is likely to be representative of this group as whole. The response rate of 91% indicates that the level of response bias was limited. It was felt that knowledge of pharmaceutical grade products was relevant to the NZ context, where access to products remains limited, however it is acknowledged that in other jurisdictions knowledge of THC and CBD may be of more relevance.

4.5.3 Conclusion

In conclusion, the evidence for efficacy of cannabis-based products in neurological conditions is niche. Doctors working in a neurology setting describe a lack of experience and information in both the niche and broader aspects of cannabis-based products in the practice of neurology. They are asking for educational opportunities that will allow them to have informed discussions with their patients. Positively for the doctor-patient relationship, in many outpatient consultations there are discussions with patients about cannabis-based products as medicines. Patients are telling their doctors that they are using illicit cannabis as a medicine for a range of medical problems beyond those indicated by clinical trials. In order for doctors to have informed discussions with their patients and to have their concerns around prescribing met, there must be ongoing high-quality research into the use of cannabis-based products as a medicine across the spectrum of neurological conditions combined with increased neurology focussed training about the use of cannabis as a medicine.

4.6 Doctors in an oncology setting

4.6.1 Results

A total 45 of 53 (response rate 85%) doctors who were approached to participate in the study completed the questionnaire, with 87% of questionnaires being completed in the presence of an investigator. One participant submitted a half-completed questionnaire, with their results analysed to the point of completion. Participant demographics may be seen in Table 4.11.

Table 4.11. Oncology-based doctors' participant characteristics (stratified by experience)

	Total (n)	%	Consultant (n)	%	Registrar/ MOSS [a] (n)	%	House Surgeon (n)	%	Not Stated (n)	%
Total Participants	45	100	27	60	15	33	2	4	1	2
Gender										
Male	20	44	13	29	7	16	-	-	-	-
Female	24	53	14	31	8	18	2	4	-	-
Not Stated	1	2	-	-	-	-	-	-	1	2
Age Band										
20-29	6	13	-	-	4	9	2	4	-	-
30-39	15	33	6	13	9	20	-	-	-	-
40-49	12	27	11	24	1	2	-	-	-	-
50-49	9	20	9	20	-	-	-	-	-	-
60-69	2	4	1	2	1	2	-	-	-	-
Not stated	1	2	-	-	-	-	-	-	1	2
Ethnicity										
NZ European	29	64	18	40	10	22	1	2	-	-
Māori	-	-	-	-	-	-	-	-	-	-
Chinese	2	4	1	2	-	-	1	2	-	-
Indian	5	11	5	11	-	-	-	-	-	-
Other[b]	8	18	3	7	5	11	-	-	-	-
Not stated	1	2	-	-	-	-	-	-	1	2

a: Medical Officer Special Scale (MOSS), b: Other: Irish (n=2), Malaysian (n=2), British (n=1), European (n=1), Sri Lankan (n=1), Not stated (n=1).

4.6.1.1 Patient interactions regarding cannabis-based products as a medicine

Table 4.12 summarises doctor-patient interactions regarding the use of cannabis as a medicine. Of the 44 doctors who replied to the patient interaction section, 37 (84%) reported at least one patient asking them to prescribe a cannabis-based product in the previous 12 months, with the most

common reasons reported for such prescription requests being pain, cancer treatment and nausea (n=19, 13 and 11 respectively).

Doctors (43/44, 98 %) stated that patients using illicit cannabis for medical reasons cited pain, nausea and cancer management/cure as their reason for use (n=20, 11 and 10 respectively).

Table 4.12. Oncology-based doctors' patient interactions relating to prescription of cannabis-based products and patient use of illicit/recreational cannabis for medical purposes

	n	%	95% CI
Received one or more requests from patients for cannabis prescriptions	37/44	84	70 to 93
Number of patients who requested medicinal cannabis prescriptions per doctor.			
1 to 4 patients	25/37	68	50 to 82
5 to 10 patients	8/37	22	10 to 38
10+ patients	4/37	11	3 to 25
Number attempting to prescribe	14/37	38	22 to 55
Number experiencing impediments to successful prescription (more than one answer could be given)	8/14	57	29 to 82
Paperwork required	3/8	38	9 to 76
Cost to patient	5/8	63	24 to 91
Asked to discuss with GP	2/8	25	3 to 65
Not in stock at the pharmacy	1/8	13	0 to 53
Number deciding not to prescribe at the time of request	23/37	62	45 to 78
Reasons for not prescribing at time of request (more than one answer could be given)			
Insufficient Evidence Base	9/23	39	20 to 61
Cost	2/23	9	1 to 28
Insufficient Understanding of Process	9/23	39	20 to 61
Clinical Benefit vs logistics/cost inappropriate	4/23	17	5 to 39
Anticipated side effects	-	-	-
Number with patients reporting illicit cannabis use for medical purposes	43/44	98	88 to 100
Number of patients who reported illicit cannabis use for medical purposes per doctor.			
1 to 4 patients	20/43	47	31 to 62
5 to 10 patients	12/43	28	15 to 44
10+ patients	9/43	21	10 to 36
Preferred forms of use elicited from patients (more than one answer could be given)			
Smoking	32/43	74	59 to 87
Edibles	28/43	65	49 to79
Other (cannabis drops, oils, vaping, unknown)	13/43	30	17 to 46

4.6.1.2 Prescribing cannabis-based products: Facilitation, impediments and concerns

A summary of doctors' facilitation of requests, impediments experienced and reasons for declining requests may be seen in Table 4.12. Of consultants reporting patient requests (24/27, 89%), 11/24 (46%) attempted to prescribe with 3/12 (25%) registrars approached attempting prescription. Overall, those who chose not to prescribe (23/37, 62%) indicated that an insufficient evidence base for use and insufficient understanding of the process informed their reason for declining.

Concerns surrounding prescribing are summarised in Table 4.13. Despite 82% expressing concerns, 23/44 (52%) would be 'very likely' to prescribe a cannabis product that was a pharmaceutical grade medication, had shown efficacy in clinical trials and was funded through the NZ funding agency (PHARMAC). Of the remaining doctors, 15/44 (34%) indicated they would be 'somewhat likely' to prescribe and the remaining six doctors (14%) indicated neutrality. There were no doctors indicating that they would be unlikely to prescribe such a pharmaceutical grade cannabis-based product.

4.6.1.3 Doctors' knowledge of the use of cannabis-based products in medical conditions

Responses to knowledge of efficacy in medical conditions is summarised in Table 4.13. Pain syndromes, nausea/vomiting and epilepsy were reported equally by doctors has having both Grade A/Level 1 RCT (Randomised Control Trial) evidence for use and no known evidence for use.

Regarding side effects (SEs), 43/45 (96%) of doctors cited at least one SE. The most commonly cited SEs were drowsiness (n=19), nausea (n=15) and psychotic symptoms (n=9).

4.6.1.4 Doctors' knowledge of pharmaceutical grade cannabis-based products

A total of 33/45 (73%) doctors cited at least one pharmaceutical grade cannabis-based product. Knowledge of nabiximols is summarised in Table 4.15. Of the three other currently available pharmaceutical grade cannabis-based products, seven (21%) and six (18%) doctors indicated awareness of dronabinol and nabilone respectively. No doctors indicated an awareness of Epidiolex.

Table 4.13. Oncology-based doctors' knowledge of evidence for medical cannabis use and future prescribing concerns

Concerns about future prescribing of medical cannabis products (more than one option could be selected)	n	%	95% CI
Insufficient Evidence Base	27/36	75	58 to 88
Cost	8/36	22	10 to 39
Insufficient Understanding of Process	20/36	56	38 to 72
Clinical Benefit vs logistics/cost inappropriate	13/36	36	21 to 54
Side effects	8/36	22	10 to 39

Response (N=45 unless indicated otherwise)	Conditions with Grade A/Level 1 RCT evidence for use is available			Conditions with substantive evidence of no benefit for use but participant aware may have been suggested outside evidence-based medicine		
	n	%	95% CI	n	%	95% CI
None	6	13	5 to 27	2	4	1 to 15
Did not know	1	2	0 to 12	2	4.4	1 to 15
Did not supply an answer	11	24	13 to 40	15	33	20 to 49
At least one condition	27	60	44 to 74	26	58	42 to 72
Conditions cited		**n**			**n**	
Multiple Sclerosis		12			-	
Nausea and Vomiting		7			6	
Epilepsy /Seizures NOS		5			4	
Epilepsy (Refractory syndromes)		4			-	
Cancer		-			12	
Pain Syndromes		10			10	
Other		7[a]			7[b]	

a: Muscle spasm=2, Dronabinol=1, Glioblastoma Multiforme=1, Loss of appetite=1, Movement Disorder=1, Neurologic spasm=1, Palliative care= 1
b: Anxiety=2, Depression=1, Glioblastoma Multiforme=1, Insomnia=1, Irritable Bowel=1, Lyme Disease=1., Movement Disorder=1

Table 4.15. Oncology-based doctors' knowledge of pharmaceutical grade cannabis-based products

Knowledge of any pharmaceutical grade cannabis-based product			
	n	**%**	**95% CI**
Able to cite at least one cannabis-based product	33/45	73	58 to 85
Nabiximols (Sativex)	27/33	82	65 to 93
Dronabinol (Marinol)	7/33	21	9 to 39
Nabilone (Cesamet)	6/33	18	7 to 35
Epidiolex	-	-	-
Knowledge of Nabiximols			
Primary constituents			
THC only	4/27	15	4 to 34
THC/CBD	9/27	33	17 to 54
CBD only	6/27	22	9 to 42
Aware licensed in New Zealand	21/27	78	58 to 91
Formulation			
Capsule/Tablet	4/27	15	4 to 34
Buccal/Sublingual	15/27	56	35 to 75
Estimated cost per year to patient (NZ$)			
Less than $10000	3/27	11	2 to 29
Greater or equal to $10000	10/27	37	19 to 58
Unsure/Indeterminate answer	5/27	19	6 to 38
No answer given	9/27	33	17 to 54

4.6.1.5 Doctor's knowledge of regulatory processes related to prescribing

Table 4.16 summarises the understanding of entities responsible for the regulatory processes related to prescribing. Response to this section was limited, with 67% of doctors responding to questions regarding the NZ regulatory processes in relation to nabiximols, 47% responding about CBD and 20% about other cannabis products.

Approval for nabiximols was thought to be performed by Specialists (50%) and the Ministry of Health (53%). Funding of nabiximols was thought to be patient responsibility by 69% of doctors, whilst 31% indicated that PHARMAC held some responsibility here. In regards to importing nabiximols, 50% felt the responsibility lay with the pharmacy.

4.6.1.6 Access to educational material relating to the use of cannabis as a medicine

When asked about educational material access over the 12 months prior to the questionnaire, 69% indicated that they had used at least one source (more than one could be chosen). Of all the doctors

surveyed, 29% accessed CME sessions, 29% accessed journals, 24% used the Ministry of Health website and 29% used other forms of information sources such as the internet and discussions with colleagues and pharmacists.

Regarding access to future educational material about the use of cannabis as a medicine, of which more than one source could be chosen, doctors indicated that CME sessions were their preferred form of education (64%), followed by information sheets (56%) and online CME modules (51%).

Table 4.16: Oncology-based doctors' knowledge of responsibility for the regulatory process relating to medical cannabis in NZ (more than one answer could be given)

	Nabiximols (n=30)			CBD (n=21)			Other cannabis products (n=9)		
Entity responsible for approval of medicinal cannabis products									
	n	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Total response rate (out of 45)	30	67	51 to 80	21	47	32 to 62	9	20	10 to 35
PHO	1	3	0 to 17	5	24	8 to 47	1	11	0 to 48
DHB	1	3	0 to 17	1	5	0 to 24	1	11	0 to 48
Specialist	15	50	31 to 69	8	38	18 to 62	3	33	7 to 70
MoH	16	53	34 to 72	8	38	18 to 62	6	67	30 to 93
PHARMAC	8	27	12 to 46	7	33	15 to 57	4	44	14 to 79
Entity responsible for funding of medicinal cannabis products									
	Nabiximols (n=26)			**CBD (n=23)**			**Other cannabis products (n=9)**		
	n	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Total response rate (out of 45)	26	58	42 to 72	23	51	36 to 66	9	20	10 to 35
PHO	1	4	0 to 20	1	4	0 to 22	1	11	0 to 48
DHB	1	4	0 to 20	3	13	3 to 34	1	11	0 to 48
Patient	18	69	48 to 86	16	70	47 to 87	6	67	30 to 93
MoH	3	12	2 to 30	1	4	0 to 22	-	-	-
PHARMAC	8	31	14 to 52	7	30	13 to 53	4	44	14 to 79
Entity responsible for the import of medical cannabis									
	Nabiximols (n=20)			**CBD (n=19)**			**Other cannabis products (n=9)**		
	n	**%**	**95% CI**	**n**	**%**	**95% CI**	**n**	**%**	**95% CI**
Total response rate (out of 45)	20	44	30 to 60	19	42	28 to 58	9	20	10 to 35
Prescribing Doctor	3	15	3 to 38	4	21	6 to 46	-	-	-
Pharmacy	10	50	27 to 73	9	47	24 to 71	5	56	21 to 86
Patient	3	15	3 to 38	6	32	13 to 57	3	33	7 to 70
MoH	5	25	9 to 49	5	26	9 to 51	3	33	7 to 70
PHARMAC	4	20	6 to 44	2	11	1 to 33	-	-	-

* PHO: Primary Health Organisation, DHB: District Health Board, MoH: Ministry of Health, PHARMAC: Pharmaceutical Management Agency

4.6.2 Discussion

Discussions about cannabis-based products between doctors in an oncology setting and their patients are common. Pain, nausea and the treatment or cure of cancer were the primary motivators of patients requesting prescriptions or using illicit cannabis. Despite the frequency of requests, two-thirds of doctors elected not to prescribe citing a lack of evidence and poor understanding of the prescribing process. Of those who did prescribe, just over half faced impediments to the process, including cost to the patient and paper work. The majority of doctors described concerns about prescribing cannabis-based products that did not have the provenance of a clear medicine development and clinical trials pathway, but were open to prescribing products that did meet these requirements. In the event of doctors actually having confidence in a cannabis-based *medicine*, less than two-thirds identified conditions which they thought there was good evidence for their prescription. There was good awareness of nabiximols as a product, with poor awareness of its constituents or formulation. Less than a quarter indicated knowledge of dronabinol and nabilone. The regulatory processes around accessing any of these products was poorly understood. Doctors identified a need for educational materials about the use of cannabis-based products as a medicine, preferring delivery through CME sessions and product information sheets.

It is reassuring that the majority of doctors are reporting that patients are enquiring about the use of cannabis as a medicine as this reflects a level of comfort within the patient-doctor relationship. Compared with the other health professional groups studied for this thesis, doctors in an oncology setting report a similar frequency of patient interactions concerning cannabis-based products (whether illicit or prescription based) for medical symptoms to neurology-based doctors (95%) and more interactions than GPs (68%).[219] This is likely reflective of changing patient expectations in regards to the use of cannabinoid-based products following the enactment of the Misuse of Drugs (Medicinal Cannabis) Amendment Act in 2018, which specifically accommodates those with a palliative diagnosis.

However, patients' expectations and doctor understanding of the efficacy of cannabis-based products do not always align. This research, like overseas studies,[216–218,242] demonstrates that doctors in an oncology setting understand there may be some evidence of efficacy for symptomatic relief in pain and nausea/vomiting, but little evidence for the curative properties of cannabis. Despite this, patients are asking for cannabis as part of their cancer management plan, which is consistent with overseas studies where 25-52% of oncology patients using cannabis as a medicine

stated that they believed it was efficacious or were using it in part for cancer treatment,[243,244] with further studies reporting patient discussions regarding this intent.[245,246] This disparate belief in efficacy is in part driven by patient access to curative claims made on the internet where patient testimonials and anecdotal evidence appears to support such claims.[247] Published case reports provide legitimacy,[248,249] while there are a lack of randomised controlled trials against which doctors can form evidence-based decisions. This lack of evidence inhibits evaluation of clinical equipoise and likely contributed to the decision not to prescribe by two-thirds of the doctors.

Regardless of whether or not doctors chose to prescribe, all indicated that they would be prepared to prescribe a product that had the provenance of a traditional medicine with safety and efficacy data specific to medical conditions, indicating they were not biased against the idea of using cannabis-based medicines in this clinical setting. This is not dissimilar to the previous findings seen within the GPs and neurology-based doctors involved in this thesis, who also had high levels of willingness to prescribe when provided with such provenance.[2192]

Of interest, cannabis-based medications such as dronabinol and nabilone, that have some evidence for the management of conditions like chemotherapy induced nausea and vomiting, were not well known by the doctors; instead, there was greater knowledge around nabiximols. Nabiximols has no current remit for use in oncology, but is the only cannabis-based product approved for use in any condition by the NZ medicines regulatory authority (Medsafe). Thus, when asked to prescribe for symptomatic relief, doctors are likely to turn to nabiximols in an off-label capacity as it is a pharmaceutical grade product already imported and available in NZ in preference to facilitating the import of a lesser known product.

4.6.2.1 Strengths and limitations

This survey had a high response rate. Due to the recruitment of an anonymous convenience sample, non-response bias was unable to be assessed. In 2009-2013, the full time equivalent (FTE) of oncology specialists (medical and radiation) in NZ was approximately 80,[250,251] so this study captures a third of this number with 27 specialists included. Just over half of the respondents were female, which is higher than the overall medical workforce in NZ, where they made up 45.4% in 2018, which has potential to limit the generalisability of the results, however the number of female doctors are currently predicted to outnumber males in NZ by 2025.[252]

One participant submitted a questionnaire that was only half completed, however as per the data analysis plan, the data was analysed for the questions that were completed and the numerator

reported in the results, allowing accurate question response rates to be gauged. The presence of a study investigator at the time of questionnaire completion was intended to help capture actual knowledge and decrease response bias. The sample population represents doctors who attended continuing medical education sessions within the hospital setting, which limits generalisability, however this offered an opportunity to reach doctors who may not otherwise answer questionnaires.

4.6.3 Conclusion

As in many other countries, doctors in the oncology setting in NZ are being asked by their patients about the use of cannabis-based products for treatment of both symptoms and possible curative effects. They are prepared to prescribe the use of cannabis-based medicines that have shown medical provenance, and as such schemes focussed on increasing access to medical cannabis products should also endorse and foster contemporaneous high-quality clinical research into targeted medical conditions. In the interim, it is of importance that clear and easily accessible clinical and regulatory guidelines are developed to support discussions and decision-making between doctors and their patients.

4.7 Comparison between healthcare practitioner groups

I undertook a post-hoc analysis for differences of proportions of responses between the three groups to look for significant associations, using the chi-squared test, which are reported below.

There was a difference in proportions of doctors in an oncology setting reporting patient requests for prescriptions when compared with GPs (χ^2 (1, N=120)=10.296, p=0.001) and doctors in a neurology setting (χ^2 (1, N=84)=5.0527, p=0.0249). The numbers of GPs reporting patients illicit cannabis use for medical symptoms was lower than both oncology (χ^2 (1, N=119)=14.767, p=0.0001) and neurology (χ^2 (1, N=115)=10.869, p=0.001) based doctors. Edibles were reported as preferred mode of patient use more often by oncology-based doctors than both GPs (χ^2 (1, N=94)=7.244, p=0.007) and neurology-based doctors (χ^2 (1, N=81)= 6.4596, p=0.01). There was no difference in proportions of doctors attempting to prescribe across all three groups (χ^2 (2, N=104)=0.27581, p=0.8712).

Future prescribing concerns were similar across all groups; however, reasons for this concern differed. A lower proportion of neurology-based doctors expressed concerns about costs compared with GPs (χ^2 (1, N=95)=6.263, p=0.012) and oncology-based doctors (χ^2 (1, N=72)=9.7578,

p=0.0018). A greater proportion of neurology-based doctors expressed concern about insufficient evidence for use compared with GPs (χ^2 (1, N=95)=7.9636, p=0.004), though this was not significant when compared with oncologists (χ^2 (1, N=72)=3.6, p=0.058).

4.8 Summary

All three studies demonstrated that doctors in NZ are experiencing patient enquiries about prescriptions for medicinal cannabis products. GP patient requests for medicinal cannabis products were similar in number to those seen by Karanges et al., who explored the knowledge and attitudes towards medical cannabis of general practitioners in Australia.[211] It was not unexpected that GPs had received less requests than both oncology and neurology-based doctors, as the majority of evidence for use of cannabinoid medications is in the neurology and oncology setting. Despite these enquiries, many doctors in all areas are not facilitating requests. This is primarily due to concerns about the level of evidence for use and a lack of understanding of the regulatory processes required for prescribing the products. Concern about prescribing is similar across all three groups, however GPs and oncology-based doctors were more likely to associate cost as an issue restricting their prescribing practices than neurology-based doctors, who had a greater association with concerns surrounding insufficient evidence for use. Since the completion of these questionnaires, the Medicinal Cannabis Scheme (MCS) has been introduced. The MCS provides a framework for the development of medicinal cannabis products and information for health care prescribers about the products available in NZ, which is currently only nabiximols. In regards to advice surrounding prescribing, there is not yet a formally produced guideline describing indications for use and dosage guidance for products. The development of such guidance is hampered by limited clinical evidence and ongoing lack of medicinal cannabis products.

It is apparent that patient desire for access to products is not necessarily in line with prescribing practices of the doctors involved. This has potential to place a strain on the patient doctor relationship. Increasing local clinical research in specific medical conditions is important to support the needs to doctors moving forward, in conjunction with a rigorous pharmacovigilance programme as more products become available through the MCS.

Chapter 5 NZ patient beliefs, experiences and knowledge of the use of cannabis as a medicine

5.1 Background

As described by the previous chapter, doctors are reporting that patients in NZ are requesting prescriptions for medicinal cannabis products, not only in the specialised areas of oncology and neurology but also in the general practice setting as well.

These requests may be bolstered by frequent media reports about the changes to local medicinal cannabis legislation. In addition, there has been ongoing media reporting about the referendum for the proposed Cannabis Legalisation and Control Bill, undertaken in October 2020. These reports may provide a catalyst in encouraging patients to talk to their doctors about cannabis and its use as a medicine.

It has previously been reported in the NZ Health Survey of 2012/2013 that 42% of those people who were using recreational/illicit cannabis stated that they were using it for a medical condition.[83] As previously mentioned in Chapter 1, Rychert et al., 2020, surveyed over 3000 medical cannabis users in NZ, and reported that 63.5% had discussed their self-management of medical symptoms using cannabis with their doctors.[99] However, only 14.5% had requested a prescription for a medical cannabis product, citing concerns about lack of faith in doctors prescribing, associated bureaucracy and cost.[99] Those patients surveyed perceived cannabis to be an effective therapy, with just over half experiencing side effects[99] Smoking was the most popular form of administration, consistent with my finding through surveying health-care practitioners in Chapter 4.

Overseas patient beliefs about the effectiveness of cannabis use in medical conditions tend to be greater than that found in randomised control trials. This is especially prominent in individuals who self-medicate their medical symptoms using recreational or illicit cannabis. A survey undertaken in the United Kingdom indicated that a third of patients with chronic illness had used for medical purposes, with over two-thirds reporting that is was effective.[253] Due to the psycho-active nature of cannabis, the ability to assess the actual effect on the symptom that a patient may be managing compared with the dissociative effect from ‘feeling high’ may be difficult to assess, further complicating the interpretation of subjective results. The use of cannabis as a medicine is complicated by the potential for abuse, especially in the light of limited efficacy in the current medical literature. This is compounded by beliefs that plant-based ‘natural’ products are not

harmful. In some areas, patients perceive 'medicinal cannabis' as not having the presence of THC, therefore they do not associate it with feeling high and the harms that are associated with its use.

Kruger et al., 2020, found that those patients who had discussed the use of cannabis as medicine with their primary care provider had better understanding of the subsequent effects and risks associated with cannabis use than those who had not undertaken such a discussion.[254] Such discussions are important as they bolster the patient-doctor relationship and allow an exchange of ideas to occur, ensuring that patients understand not only the benefits that may be associated with the use of cannabis as a medicine but also the risks.

As noted in Chapter 1, use of cannabis as a medicine has its greatest strength of evidence in the fields of neurology and oncology. Research of patient beliefs and use of cannabis as a medicine in these fields has been undertaken in many countries, including the US, Canada, Europe and Australia, however there is no research specifically in general practice patients as opposed to those patients who identify as medical cannabis users.

Specific to neurology, in Denmark, where there is limited access to cannabis-based products and no wider medicinal cannabis scheme, 49% of MS patients surveyed by Gustavsen et al., 2019, reported ever using cannabis, with 21% of current users and 5% of former users reporting having a prescription.[255] They reported that patients were primarily treating pain, spasticity and sleep disturbances, with the majority reporting a good to very good effect.[255] In Canada, which has an alternative medicinal cannabis scheme, 56.1% of MS patients surveyed by Banwell et al., 2016, reported life-time cannabis use, with 19.5% reporting current use.[256] Of current users, 41% had a prescription primarily treating sleep, pain and anxiety.[256] A study which surveyed epilepsy patients in Lithuania, where only recently limited medicinal cannabis laws have been passed, found 16.4% of participants reporting cannabis use for epilepsy symptoms, with a third expressing further interest in the use of cannabis as a medicine.[257] An Australian study by Suraev et al., 2017, reported that 15% of adults with epilepsy had ever used cannabis products for their epilepsy, with 90% reporting it effective.[239] In Germany, 28.4% of epilepsy patients surveyed by von Wrede et al., 2019, reported using cannabis, though only 12.8% of that group stated it was for medical reasons.[258] Research in other patient groups with neurology diagnoses provides further information. Finseth et al., 2015, reported 4.3% of Parkinson's disease patients surveyed about complementary and alternative medicine in Colorado reporting use of cannabis,[259] and Montagnese et al., 2019, reported 33% of US and 14% of German myotonic dystrophy patients surveyed indicated cannabis use, reporting effectiveness for myalgia and muscle stiffness as well as sleep and anxiety.[260]

Specific to the field of oncology, patient beliefs and use of cannabis are related to both symptom management, primarily pain and its potential for cancer cure. Macari et al., 2020, reported that medicinal cannabis users for oncology reasons cited that pain was the symptom with the highest frequency of improvement, followed by appetite and anxiety.[261] Singh et al., 2019, surveyed patients in a state (Georgia) with restrictive cannabis laws, with 95% of patients indicating that 'cannabis-related' products, whether illicit or licit, were important or extremely important in reducing pain.[262] In Italy, Cortellini et al., 2019, surveyed oncology patients about their beliefs surrounding medicinal cannabis use, of which 55% had considered use for pain.[263] Pergam et al., 2017, reported that active users reporting cannabis use were using it most frequently for pain.[243] From a cancer cure perspective, Pergam et al. found that 26% of participants believed that cannabis was helping to treat their cancer with Martell et al.'s 2018 study reporting that 16% of participants strongly agreed or agreed with the statement that cannabis helps cure cancer.[243,264] Braun et al., 2020, undertook a qualitative study of 24 cancer patients of which half of the sample indicated the use of cannabis as a way to treat their cancer, with eight hopeful about its efficacy.[265] Patients who are undergoing oncology care in the United States have expressed that they would like information from their oncology team about the use of cannabis as a medicine, however this is not always offered, therefore they seek information from friends, newspapers and websites.[243]

To understand how patients in NZ, who are not specifically medicinal cannabis users, interact with their doctors with respect to the use of cannabis as a medicine, I performed observational studies in the same three specialty areas as the health care practitioners involved in the earlier studies. I felt that these three areas remained most appropriate to investigate the beliefs and knowledge held by patients about the use of cannabis as a medicine.

5.1.1.1 Note

This chapter contains excerpts of a previously published article by Oldfield et al., "Knowledge and perspectives about the use of cannabis as a medicine: a mixed methods observational study in a cohort of New Zealand general practice patients"[266], and has been reproduced with permission from the New Zealand Medical Journal. Dr Ingrid Majers assisted with data collection, Allie Eathorne assisted with statistical analysis, all other authors were involved in study planning and review of the final papers. The introduction has been edited and expanded, methods combined and additional figures added for continuity within the thesis.

5.2 Aims and Objectives

The aim of the all three studies was to explore what patients attending their doctor (in the case of general practice) or those with specific diagnoses in two specialty areas (oncology and neurology) in NZ understood about the use of cannabis as a medicine. This was achieved by using questionnaires to more specifically investigate patient beliefs about the potential impact that medicinal cannabis products may have on their medical conditions, the proportions of participants that had undertaken discussions with a GP or specialist about medical cannabis products; if they had used medicinal or illicit cannabis for a medical condition in the past; what information patients wanted from their GP about the use of cannabis as a medicine and how they wished this to be communicated.

As previously acknowledged in Chapter 4, this research was descriptive in nature, and as such testable hypotheses could not be developed. Despite this, I considered responses may be expected from each patient group from my knowledge from review of the relevant literature, previous interactions with health care professionals and the status of medicinal cannabis in NZ at the time of developing the questionnaires. These considerations are indicated below.

5.2.1 Patients in a General Practice setting

Study Six: A mixed methods observational study in a cohort of NZ general practice patients regarding knowledge and beliefs about the use of cannabis as a medicine

I anticipated that patients would have expectations of cannabis-based products that exceed current scientific evidence, with limited knowledge about the specific cannabis-based products available. Since GPs generally see a wide spectrum of patients with a broad range of diagnoses, I thought that only a small proportion of patients would have discussed cannabis-based products with their GP or specialists.

5.2.2 Patients in a Neurology setting

Study Seven: A mixed methods observational study in a cohort of NZ neurology patients regarding knowledge and beliefs about the use of cannabis as a medicine

I anticipated that those patients with a neurology diagnosis would have expectations that medicinal cannabis products would be beneficial to their medical condition, as nabiximols is approved for use in NZ for the treatment of spasticity in multiple sclerosis and there has been recent discussion and evidence around the use of cannabidiol in severe epilepsy syndromes overseas. I thought that a significant number of patients with neurology diagnosis (primarily multiple sclerosis or epilepsy) would have discussed the use of cannabis as a medicine with their GP or specialist.

5.2.3 Patients in an Oncology Setting

Study Eight: A mixed methods observational study in a cohort of NZ oncology patients regarding knowledge and beliefs about the use of cannabis as a medicine

I thought that patients with an oncology diagnosis may have expectations that medicinal cannabis products may be useful for their medical condition. This was related to the fact that there are no approved cannabis-based products for symptomatic relief of cancer symptoms in NZ, despite these being available overseas. As such, I anticipated that only some patients may have discussed the use of cannabis as a medicine with their GP or specialist.

5.3 Methods

5.3.1 Study design

I used a mixed methods prospective observational study design for all three studies.

5.3.2 Participants

Eligibility and recruiting criteria for each of the participant groups are described below.

5.3.2.1 Patients in a General Practice setting

Recruitment was through four GP practices located within the North Island of NZ (Hutt Valley, Wellington, Wairarapa and Bay of Plenty) occurring between November 2018 and October 2019. GP Practices were included if they were part of the Medical Research Institute of New Zealand (MRINZ) GP Research Network, and the GPs themselves had participated in a related study of healthcare practitioners' knowledge of the use of cannabis as a medicine.[202]

Participants were eligible for inclusion if they attended the GP practice for an appointment on a day when the study investigator (primarily myself) was present in the practice and were 18 years or older. If the primary appointment holder was a child less than 18 then their parents or guardian were not eligible. Patients were not required to have a specific diagnosis to participate in the study.

Eligible patients were asked by the practice reception staff or attending GP if they were interested in completing a questionnaire and those expressing interest were given a participant information (PIS) sheet to read. Patients were then referred to the on-site study investigator, primarily myself, for full discussion of the study and answering of any questions. Participants were given the option to complete the questionnaire via iPad or paper. The on-site investigator was available during the completion of questionnaires to clarify any questions participants may have had. Implied consent was obtained by participants submitting the questionnaire.

5.3.2.2 Patients in a Neurology setting

Participants were eligible for recruitment if they had a neurology diagnosis, were over the age of 18 and were NZ residents. Parents and caregivers of children with neurology diagnoses were not able to answer questionnaires on behalf of their children, as this study was examining adult understanding of the use of cannabis as a medicine. For the purposes of the survey, the neurology diagnosis was patient reported and did not require a doctor's confirmation.

Initial recruitment was planned through the face-to-face visits at neurology outpatient clinics, however due to slow recruitment rates this was stopped and altered to online recruitment through patient advocacy groups and relevant research groups. Advocacy groups, such as Multiple Sclerosis (MS) NZ, Epilepsy NZ, Parkinson's NZ, Stroke NZ and Motor Neurone Disease NZ were approached with a request to distribute the questionnaire via a patient email database or post a link to the survey on their website, newsletter or Facebook page. Relevant research groups, such as the MRINZ, also posted advertising through Facebook and survey links through their email database to increase the population base reached. Images used in Facebook advertising may be seen in the Appendix (7.11).

Participants were able to directly access the PIS prior to undertaking the survey for a full explanation of the study. Participants were advised that they may stop the survey at any time and that data would only be analysed once they had submitted the questionnaire, indicating implied consent that they were happy for their data to be used. Participants also had the option to leave and return to the survey with a specific return code. As this was a public survey, participant responses

were not linked to a specific email to protect the privacy of the individuals involved. An email and phone number was supplied so that participants were able to contact me to clarify any information before or during taking the survey.

5.3.2.3 Patients in an Oncology Setting

Participants were eligible for this study if they had an oncology diagnosis, were over the age 18 years and were NZ residents. The oncology diagnosis was self-reported, and did not require confirmation from a doctor. Participants were eligible if they were in remission, as active management was not specified in the inclusion criteria, as an acknowledgement that historical experiences are relevant to patient experiences with the use of cannabis as a medicine. Parents and caregivers responding on behalf of their children were excluded from undertaking the questionnaire.

As with the neurology questionnaire, initial recruitment was planned through my attendance at oncology outpatient clinics, however due to the advent of COVID-19, this style of recruitment was no longer viable. Recruitment was then changed to an online model, where patient advocacy groups and relevant research groups were approached and asked to advertise the PIS and survey link through patient email databases, newsletters, websites and Facebook advertising. An example of the images used in Facebook advertising used may be seen in the Appendix (7.11). Some examples of advocacy groups approached were The Cancer Society, Bowel Cancer NZ, Brain Tumour Support NZ, Breast Cancer NZ, NZ Gynaecological Cancers, Prostate Cancer NZ, Māori Cancer Kaiarahi Service. The MRINZ also advertised the survey link through Facebook and their email database.

Participants were able to contact me via email or phone as required to clarify any questions that they may have. All survey responses were collected online, through REDCap (Research Electronic Data Capture), in the same manner as the neurology patient dataset. Participants were advised that they may stop the questionnaire at any time and that they answer would only be included for analysis once they had submitted the questionnaire. They were given the option to save and return to the survey using an individualised code, as the survey link was public and not linked to an email address. They were informed that once answers are submitted they would not be able to be removed from the dataset due to the anonymous nature of the survey, I would be unable to identify which answers were theirs.

5.3.3 Questionnaires

The questionnaire was developed with the assistance of a patient advocate and contained the following domains:

- Patient demographics
- Beliefs around the use of medicinal cannabis in relation to their medical conditions
- Patient knowledge of pharmaceutical grade medicinal cannabis products, particularly nabiximols (the only approved pharmaceutical grade medicinal cannabis product in New Zealand), including cost per year and availability in NZ
- Willingness to take a prescribed medicinal cannabis product
- Interactions with their GP and/or specialists about the use of medicinal cannabis
- Previous use of recreational/illicit cannabis to treat medical symptoms; perceived effectiveness of this treatment
- Information they would seek from a healthcare professional about the use of medicinal cannabis and preferred method of delivery of this information

For the purposes of the study, medicinal cannabis was defined as "any use of cannabis plants and/or medications derived from cannabis that have been used by a patient to treat a medical condition".

Questions allowed a mixture of Yes/No, Multiple choice and Free-text answers.

During the process of data collection through the GP Recruitment period, which was undertaken face to face, participant comments about the questionnaire structure were noted down. In order to increase the ease of responses, and to gather greater relevant data, I modified the neurology and oncology questionnaires prior to commencing data collection. The patient experience questionnaires used online for neurology and oncology patients were identical. A copy of these questionnaires may be found in the Appendix (7.12, 7.13).

5.3.4 Data Entry and Analysis

All data was entered into REDCap, either from paper source or directly by the participant through a direct survey link. Partially completed questionnaires that were submitted were included for analysis in the GP Patient study, as these were undertaken in the presence of a study investigator.

Within the neurology and oncology patient study, only survey responses that were indicated as 'complete' within REDCap were included, as this indicated that the participant had submitted their responses, however not all questions within the survey were marked as compulsory, meaning participants were still able to submit a partially completed questionnaire. Single missing data points such as a blank space in a table where all other information had been input were treated as a 'do not know' answer and contributed to the denominator. All other blank fields were treated as 'No answer given' and were removed from the analysis for that question.

Free-text answers relating to patient diagnoses and medications were grouped into related categories in NVivo[118] to be reported numerically, with supporting quotes used in the results as required. Free text answers in the neurology and oncology questionnaires that allowed the participant to freely comment on anything extra that they wished the study-investigator to know about the use of cannabis as a medicine were coded and analysed for emergent themes using the NVivo software and reported with supporting quotes. Word clouds were generated through NVivo for visual representation of word frequency in free-text responses. These word clouds were set to display the 1000 most common words over four letters in length, and grouped to included stemmed words. Ethnicity data was prioritised to level two and reported according to the Health Information Standards Organisation.[223]

5.3.5 Statistics

A convenience sample was used. The sample size was developed considering the central limit theorem, which states that in sample sizes greater than 30, the studentised sampling distribution approximates the standard normal distribution.[224]

Descriptive statistics were used to calculate proportions, percentages with 95% confidence intervals (CI) reported where appropriate. Percentages and CIs were calculated using Microsoft Excel and SAS® software, Version 9.4 Copyright © 2013. The proportion denominator was determined by the number of participants answering that specific question within the questionnaire. Percentages are reported to one decimal place, in accordance to sample sizes greater than 100.

Post-hoc analyses comparing differences in proportions between the groups looking for significant associations were performed using the Chi squared test, with an alpha level of 0.05 (5%).

5.4 Patients in a general practice setting

5.4.1 Results

Across the four practices, 360 potential participants were approached by receptionists to read the participant information sheet relating to the survey, of which 160 accepted (44.4%). Of these, 134 participants undertook the questionnaire (83.8%) with an overall response rate for the survey of 37.2%. Participant demographics are shown in Table 5.1. The median age-band was 50-59 years and the age-band distribution may be seen in Figure 5.1.

The most common reasons for GP attendance were hypertension (n=27), health check-ups (n=17), depression (n=15), anxiety (n=15) and musculoskeletal problems (n=11). The most commonly reported classes of patient medications were anti-hypertensives (n=45), anti-depressants and anti-anxiety medications (n=22), non-steroidal anti-inflammatories (NSAIDs) (n=19), cholesterol lowering agents (n=14) and proton pump inhibitors (n=10). Seven participants were taking opioid medications.

Table 5.1. GP patient demographics

	n	**%**
Gender		
Male	60	44.8
Female	74	55.2
Age		
<20	2	1.5
20-29	11	8.2
30-39	23	17.2
40-49	17	12.7
50-59	28	20.9
60-69	24	17.9
70-79	21	15.7
80+	8	6.0
Ethnicity		
NZ European	106	79.1
Māori	5	3.7
Pacific	3	2.2
Chinese	1	0.8
Indian	2	1.5
Other	17	12.7

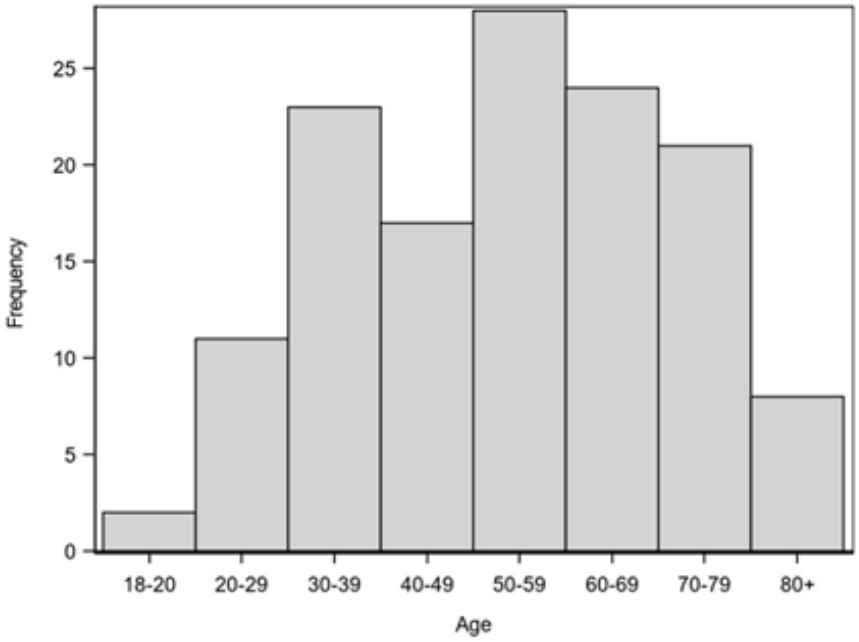

Figure 5.1. Age-band distribution of GP patient participants

5.4.1.1 Patient beliefs about medicinal cannabis products

Patient beliefs about medicinal cannabis products are shown in Table 5.2. When asked if they would take a prescribed medicinal cannabis product, 91.0% (95% CI: 84.8 to 95.3) reported 'Yes'. Most participants (71.2%) who thought their condition may be helped believed medicinal cannabis may be useful for pain relief. When participants considered symptom control, they primarily considered pain nausea and anxiety (Fig 5.2). Those participants who believed they would NOT benefit from medicinal cannabis products could be grouped into five categories: not relevant to current condition (n=26), belief that cannabis is useful for pain only (n=18), not knowing if it would help (n=15), satisfaction with current medication regime or not currently taking any medications (n=6), and belief that the mode of consumption, e.g. smoking, would exacerbate other problems (n=2).

Table 5.2. GP patient beliefs about medicinal cannabis products

	n	%	95% CI
Would you take a prescribed medicinal cannabis product?			
Yes	121/133	91.0	84.8 to 95.3
Do you believe a medicinal cannabis product would be helpful for your condition?			
Yes	59/131	45.0	36.3 to 54.0
No	72/131	55.0	46.0 to 63.7
If Yes, why? (more than one answer can be supplied)			
Symptom control[a]	14/59	23.7	13.6 to 36.6
Pain relief	42/59	71.2	57.9 to 82.2
Decrease anxiety	28/59	47.5	34.3 to 60.9
Cure my condition	5/59	8.5	2.8 to 18.7
Other reasons[b]	5/59	8.5	2.8 to 18.7

a: Nausea n=4, Fatigue n=2, Appetite n=1, Blood pressure n=1, Calmed state of mind n=1, Chemotherapy associated side effects n=1, Confusion n=1, Joint inflammation n=1, Muscle relaxant n=1, Sleep related disorders n=1, Spasticity n=1, Vomiting n=1.

b: Sleep related problems: n=3, Do not know n=2, General support of management n=1, Nausea n=1, Nutritional support n=1

5.4.1.2 Patient knowledge of medicinal cannabis products

Overall 43 participants (32.3%) stated awareness of at least one prescription medicinal cannabis product, though the majority of those were not aware of specific pharmaceutical grade products (Table 5.3). Of 38 participants who answered about specific products, eight were aware of nabiximols; with one participant aware it was combination of tetrahydrocannabinol and cannabidiol, five believing it to be a cannabidiol only product and two not supplying answers. Five participants estimated the annual cost to patients of nabiximols, with responses ranging from $1,600 to $1,000,000.

Table 5.3. GP patient knowledge of medicinal cannabis products

	n	%	95% CI
Total participants indicating awareness of prescribed products	43/133	32.3	24.5 to 41.0
Recognition of named products in those who indicated they were aware of prescribed products			
Nabiximols (Sativex)	8/38	21.1	9.6 to 37.3
Dronabinol (Marinol)	8/38	21.1	9.6 to 37.3
Nabilone (Cesamet)	3/38	7.9	1.7 to 21.4
Epidiolex	4/38	10.5	2.9 to 24.8

5.4.1.3 Interactions with health care professionals

Participants indicated they would be happy to discuss medicinal cannabis products with the health care professionals involved in their care; GP (91.7% (95% CI: 85.7 to 95.8)), Specialist (92.1% (95% CI: 83.6 to 97.0)), however less than 10% reported doing this (Table 5.4).

5.4.1.4 Use of recreational/illicit cannabis for medicinal symptoms

Recreational/illicit cannabis had been used for symptom relief of medicinal conditions by 15 (11.2%) participants, of whom the majority (80.0%) smoked cannabis (Table 5.5). Thirteen (86.7%) found it to be effective for their symptoms, with eight indicating they had reduced other regular medications. The primary symptoms that participants reported using recreational/illicit cannabis for were pain (n=8), insomnia (n=5) and anxiety (n=4).

5.4.1.5 Information communication from healthcare professionals

Participants wanted a wide range of information about medicinal cannabis from their healthcare professionals, with 82.8% (95% CI: 75.4 to 88.8) indicating that they would like further information. Emergent themes were benefits and side effects, efficacy in specific conditions and how that compared with other medications, dosage and administration- including long term use, addiction information, and impact on functioning, work and driving (Fig 5.3). Supporting quotes from participants are shown in Figure 5.4. The majority of participants wished to access information about medicinal cannabis from their provider through a website (68.7% (95 % CI: 60.1 to 76.4)) or a pamphlet (45.5% (95% CI: 36.9 to 54.4)).

Table 5.4: GP patient interactions with health care professionals about medicinal cannabis

	GP			Specialist		
	n	**%**	**95% CI**	**n**	**%**	**95%CI**
	Are you happy to discuss with your GP?			Are you happy to discuss with your Specialist?		
Yes	122/133	91.7	85.7 to 95.8	70/76	92.1	83.6 to 97.0
Do not have a specialist	-	-	-	57/133	42.9	34.3 to 51.7
If Yes, have you discussed medicinal cannabis products?	6/122	4.9	1.8 to 10.4	6/70	8.6	3.2 to 17.7
Did you feel informed?	2/6	33.3	4.3 to 77.7	3/5	60.0	14.7 to 94.7
Were you prescribed a product?	1/6	16.7	0.4 to 64.1	-	-	-
If not happy to discuss, why not?						
Stigma	-	-	-	1/6	16.7	0.4 to 64.1
Legal implications	5/11	45.5	16.8 to 76.6	2/6	33.3	4.3 to 77.7
Cost	2/11	18.2	2.3 to 51.8	-	-	-
Other[a]	5/11	45.5	16.8 to 76.6	3/6	50.0	11.8 to 88.2

a: GP: Dislike any type of drug n=2, Not aware of how it would help me n=1, Not interested n=1, No answer n=1

Specialist: No need n=1, Satisfied with condition currently n=1, No answer n=1.

Table 5.5. GP patient use of recreational/illicit cannabis for medicinal symptoms

	n	%	95%CI
Use of recreational/illicit cannabis to treat medicinal symptoms	15/134	11.2	6.4 to 17.8
Mode of consumption			
Smoking (pure)	12/15	80.0	51.9 to 95.7
Smoking (with tobacco)	2/15	13.3	1.7 to 40.5
Vaped	2/15	13.3	1.7 to 40.5
Oil	5/15	33.3	11.8 to 61.6
Edibles	1/15	6.7	0.2 to 32.0
Other	1/15	6.7	0.2 to 32.0
Did you find it effective?			
Yes	13/15	86.7	59.5 to 98.3
Did you reduce your prescribed medications?			
Yes	8/12	66.7	34.9 to 90.1

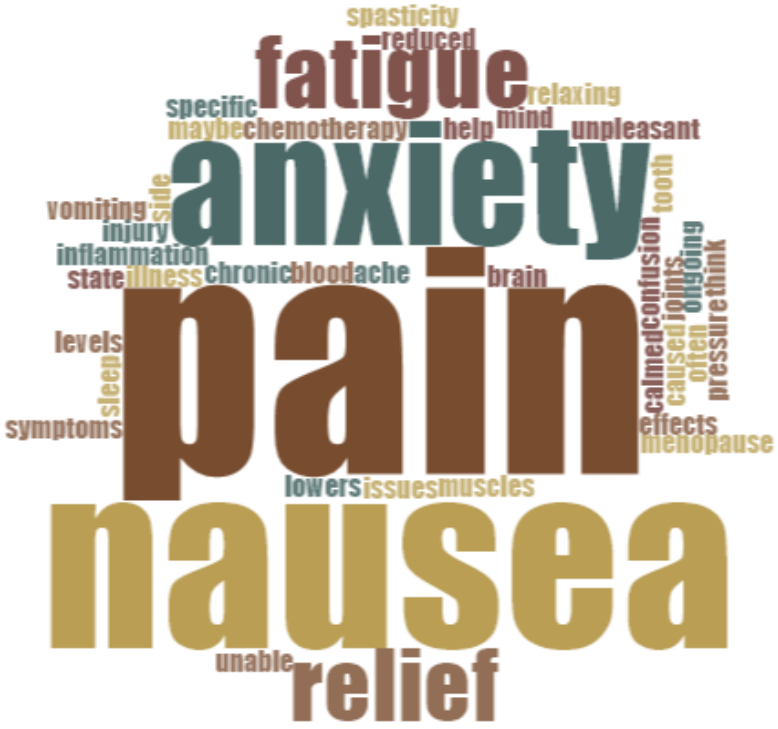

Figure 5.2 Word cloud showing responses to GP patient beliefs regarding symptom control

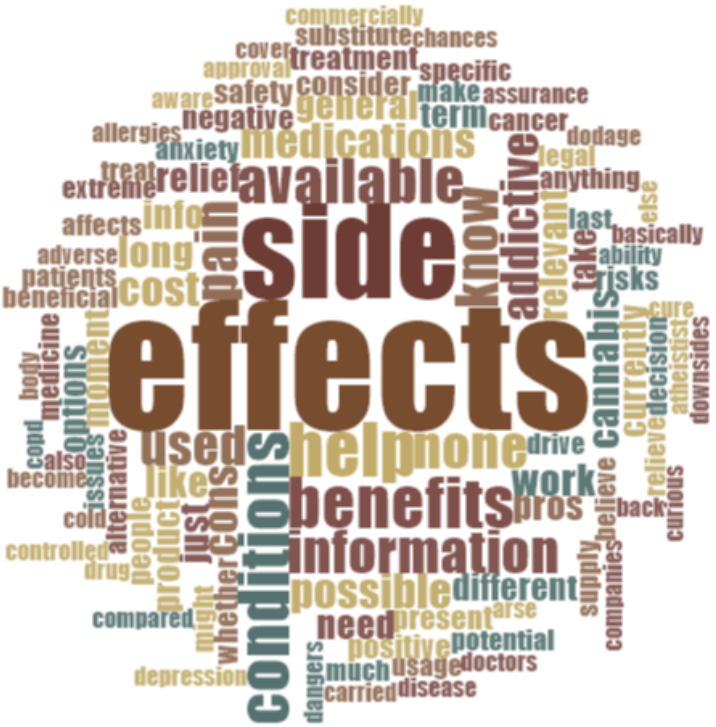

Figure 5.3. Word cloud showing the type of information GP patients want from health care professionals about the use of cannabis as a medicine

"If the product could potentially be useful for a condition I had I would like to know about it and the options I had and generally as much information about it as possible." Female, age 20-29

"What medications there are and how well users respond to them compared with other medication options?" Female, age 30-39

"Risks/Dangers/side effects of taking medical cannabis. What conditions etc the drug would be most suitable for etc?" Male, age 20-29

"Benefits of cannabis for me with my condition - side effects, reactions, negatives - long-term usage issues and guarantee of supply - costs and supply issues (legal; otherwise)." Male, age 60-69

"What it can help with? I am only aware of people needing to use it when they are extremely sick." Female, age 30-39

"Pro and cons, can you become addicted? Statistics of helping people with different conditions." Female, age 30-39

"Just if it would help any of my conditions basically, would it be beneficial, because I do believe that pharmaceutical companies need a kick up the arse." Male, age 50-59

"After effects at work, driving." Male, age 30-39

"I'd like to know its ingredients, its effects on nervous system, how it works and possible side effects." Female, 40-49

"What it helps for? The side effects - negative and positive. Cost. How you take it? How long you can take it for? Where to get it from?" Female, 40-49

Figure 5.4. What do GP patients want to know about the use of medicinal cannabis?

5.4.2 Discussion

In this study over 90% of patients would use medicinal cannabis products if prescribed by their GP or specialist and a similar proportion would be happy to discuss medicinal cannabis products with their practitioners. Most (70%) thought it would be best used for pain, and just under half thought it might be helpful for their specific condition. Despite this, awareness of approved medicinal cannabis products was low and less than 10% of patients had actually approached their doctor about medicinal cannabis. Those who did not want to discuss with their practitioners were concerned about legal implications and reported a dislike of 'drugs' in general. A small number of patients reported using recreational/illicit cannabis to treat medical symptoms, primarily through smoking, with the majority of these finding it effective, and two thirds indicating a reduction in use of other prescription medications. Less than half of this group stated that they had discussed medicinal cannabis with their doctor. The majority of patients wanted to know more about cannabis as a medicine from their doctor, either through accessing websites or being given pamphlets.

There are many possible reasons that may impact why patients display willingness to discuss cannabis products but do not follow through with it. These include being happy with their current treatment, concerns around stigma, cost, bureaucracy, lack of trust and the fact that patients rarely initiate treatment discussions.[99,267] Whilst a 'concordance' approach to undertaking a medical consultation,[267] where the patient and doctor have equal input into the discussion about medications is considered ideal, this does not always happen in practice, as patients may not be confident in asking about a treatment that the doctor has not suggested for fear of upsetting them.[100,268] Without this patient input, the limited evidence of efficacy combined with the current illicit status of recreational cannabis may make it less likely that a GP will bring cannabis-based products up in a consultation without a conscious plan to add this in to their usual practice.

There may also be an inherent appreciation of the apparent misalignment between progressive legislation and evidence-based medical practice. Patients expectations are that doctor prescribed medicinal cannabis products are effective, 'approved' and safe. The Medicinal Cannabis Scheme guidelines in NZ, where products may need to meet a minimum standard based on GMP, have no requirements for clinical trials prior to being available to doctors on prescription.[269] Such products will be 'unapproved' by Medsafe, NZ's regulatory authority, but will be able to be prescribed as an exception to the Medicine's Act.[9,19] The Medical Council of NZ's Good Prescribing Practice guidelines[93] which identify strict rules for when unapproved medications may be prescribed,

highlights the difficulties that doctors face if choosing to prescribe such medications.[19] Similar dichotomy is seen in the United Kingdom, where the NICE guidelines limit applications of the recent law changes[57,270] and Canada, where despite law changes, patients found it difficult to find physicians to support access of non-pharmaceutical medicinal cannabis due to lack of evidence for use compounded by its ongoing controversial status.[100,271,272]

It was expected that participants would not be aware of specific medicinal cannabis products. Although NZ is one of only two countries in the world that allows direct to consumer advertising of medications,[273] cannabis products are excluded. As a result, patients can only increase their awareness through media reporting, accessing internet fora and discussions with healthcare professionals. It is of interest that of those who stated they were aware of nabiximols, nearly all of them stated that they thought it was a CBD only medication, suggesting that the public perception may be that 'medicinal cannabis' is synonymous with cannabidiol and does not contain the perceived harmful substance delta-9-tetrahydocannbinol (THC).

It is of interest that the majority of the group who believed cannabis may be beneficial indicated that it is primarily helpful as a pain relief, with a number of whom believed it was *only* useful for pain, highlighting the widespread belief of its efficacy despite patchy medical evidence for this. Currently an internet search by a patient using the terms 'cannabis for pain relief' will provide over 13 million results, many of which extol its virtues through 'medicinal news' websites. However, there is no peer-reviewed evidence for the use of cannabis-based products in acute pain conditions with only low-moderate evidence of efficacy of cannabis on chronic neuropathic pain.[4,52] Despite this, ongoing patient belief in the efficacy of cannabis for pain management will likely result in GPs seeing increased patient enquiries and prescription requests as the use of cannabis as a medicine continues to be normalised.

Encouragingly, 83% of participants reported wanting information about the use of medicinal cannabis in the same way that their health care provider would recommend any medicine. This indicates that patients in NZ will be generally receptive to professional recommendations as to medicinal cannabis use as products become more widely available.

5.4.2.1 Strengths and limitations

The overall sample size provides reasonable confidence in the outcomes derived from questions with high response rates, with the quality of data enhanced by the availability of a study investigator

allowing for clarification of questions during survey completion. Two participants posted in their answers as they were unable to complete the questionnaire due time constraints, with 98.5% of responses recorded in the presence of an investigator. For the primary outcome, the proportions of participants amenable to use prescribed medicinal cannabis products and willing to discuss this with their GP or specialist were in excess of 90%, with lower confidence interval boundaries of 85% suggesting a relatively precise estimation of current opinion in a GP practice patient population.

There are also some methodological limitations. Time-pressured patients may be less likely to complete the questionnaire at the end of a consult, resulting in selection bias toward those who are time rich. Response rates varied depending on reception staffing levels on the days investigators were present and the limited geographical representation limits national generalisability. Despite this, the overall response rate of 37.2% is within the expected range when compared with GP patient surveys undertaken in NZ, the UK and Canada, which range from 19.8-55.9%.[274–276] Responder bias is likely in such a polarised topic, with those who have strong opinions about cannabis more likely to respond, and whilst comparative GP patient surveys regarding medicinal cannabis use in the general practice population were not identified, overseas studies in oncology patient populations have reported response rates of 27.4-63%.[244,261,264] Non-response bias was unable to be assessed due to the anonymous nature of initial recruitment for the survey. Whilst the availability of an investigator aimed to minimise confusion between medicinal cannabis use and the upcoming referendum about the legalisation of recreational cannabis, participant concerns around illegality of cannabis, distrust of cannabis companies, previous convictions and anti-drug sentiment may have negatively impacted the response rate. Due to the length of the recruitment period, it is acknowledged that attitudes towards medicinal cannabis may have altered, however this is unable to be tested.

Whilst the proportion of males in this sample was less than that of the general population, it is consistent with males attending GP consultations 30% less often than females.[277] There was overrepresentation of the elderly, which may be consistent with the population group who typically visit their GP.[278] In this sample Māori were under-represented (4%), where 8-11% of all consultations in targeted age ranges would be expected,[279] likely due to the geographic location of the general practices involved and the demographics of the practice population. This under-representation is in keeping with previous NZ research undertaken in the general practice population, where Māori were more likely to be under-represented in the initial recruitment and

subsequent completion of questionnaires.[274] This limits the generalisability of the results, and identifies an area in which future research could be undertaken.

5.4.2.2 Conclusion

This study suggests a not insignificant number of patients presenting to General Practice believe that medicinal cannabis may provide them clinical benefit; however, few have actively discussed this with their GP or specialist. The gap between those expressing a willingness to discuss medicinal cannabis with their healthcare professional and those who actually do is a concern and likely multi-factorial in nature. It is important that patients feel comfortable discussing cannabis in general, both illicit and medical use, with doctors facilitating these discussions. There is need for accurate and accessible information about the use of cannabis as a medicine to guide patient-doctor consultations in the context of the current evidence base and legislative status in NZ.

5.5 Patients in a neurology setting

5.5.1 Results

Across the period of online recruitment from June 2020 to October 2020, 325 online responses were commenced. Due to the nature of the recruiting style, response rates were not able to be calculated as the number of eligible participants who saw the link is unable to be verified. Of those who started the questionnaire, the completion rate was 54.5%. Following the review of completed responses, 24 were removed from the data analysis, as they did not have evidence of having a neurology diagnosis, leaving 153 completed responses suitable for inclusion. Participant demographics for eligible responses may be seen in Table 5.6. The median age band for respondents was 50-59 years, with a histogram showing age distributions in Figure 5.5. The majority (69.9%) of the sample surveyed identified as female, and the ethnicity of respondents was predominantly NZ European.

Table 5.6. Neurology patient demographics

	n	%
Gender		
Male	45	29.4
Female	107	69.9
Prefer not to disclose	1	0.7
Age		
<20	3	2.0
20-29	12	7.8
30-39	26	17.0
40-49	32	20.9
50-59	36	23.5
60-69	31	20.3
70-79	12	7.8
80+	1	0.7
Ethnicity		
NZ European	123	80.4
Māori	14	9.2
Pacific	0	0.0
Chinese	1	0.7
Indian	0	0.0
Other	15	9.8
Reported neurology diagnosis		
Multiple Sclerosis	43	28.1
Epilepsy	38	24.8
Dystonia	18	11.8
Motor Neurone Disease	13	8.5
Stroke	6	3.9
Other[a]	35	22.9

a: Fibromyalgia n=5, Migraine n=3, Brain tumour n=3, Neuralgia n=2, Vertigo n=2, Parkinson's Disease n=2, Sciatica n=2, Spinal stenosis/damage n=2, Blephorospasm n=1, Brachial plexus lesion n=1, Cauda Equina n=1, Cerebella ataxia n=1, Charcot Marie Tooth n=1, Chronic inflammatory demyelinating polyneuropathy n=1, Myalgic encephalomyelitis n=1, Neuropathy n=1, Organic solvent neurotoxicity n=1, Pigment dispersion syndrome n=1, Post encephalitis seizures n=1, Post viral meningitis damage n=1, Vagus nerve damage n=1, Tremor n=1

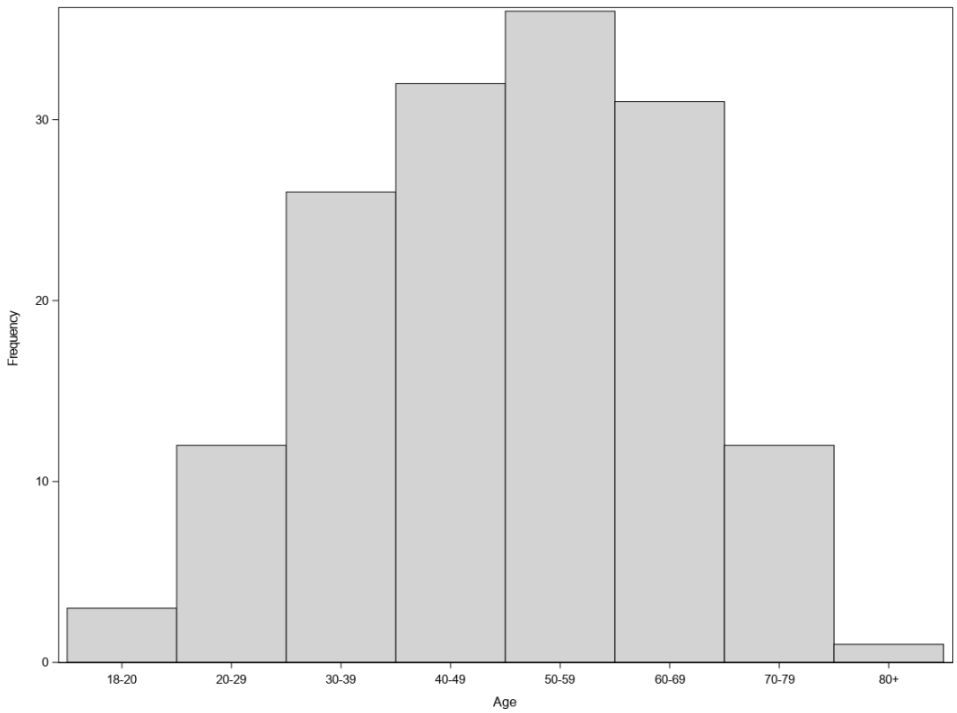

Figure 5.5. Age-band distribution of neurology patient participants

5.5.1.1 Patient beliefs about medicinal cannabis products

Table 5.7 summarises what neurology patients believe about the use of medical cannabis products. The majority (123/153, 81.7%) indicated that they would take a prescribed product, with only 2.6% (4/153) indicating that they would be unwilling to do so. In response to their beliefs surrounding benefits, 70.6% (108/153) indicated that they thought medical cannabis products may be helpful for their condition. Of those who indicated belief in benefits, 70.4% (76/108) indicated that symptom control had the greatest area of benefit, with participants expanding to indicate pain, sleep, seizures and spasticity as the symptoms most likely helped (n= 12, 11, 10 and 10 respectively) (Figure 5.6). Other benefits indicated by 25.9% (25/108) of participants included mental health effects (n=7) and relaxation (n=5). Few participants (5/108, 4.6%) indicated that they believed that cannabis-based products would be curative for their condition. Those who indicated that they did not know or did not believe that medicinal cannabis products would be helpful for their condition primarily cited lack of research and testing available for informed decisions (n=10), lack of experience with cannabis (n=6), and a general belief it would not help their condition (n=5). Other reasons given were that they consider it for pain only (n=4), their doctor had not suggested it (n=3), that their current medications were effective (n=3) and previous trials of cannabis-based products had made no change to their condition (n=3).

Table 5.7. Neurology patient beliefs about medical cannabis products

	n	%	95% CI
Would you take a prescribed medical cannabis product?			
Yes	123/153	81.7	74.7 to 87.5
No	4/153	2.6	0.7 to 6.7
Do not know	24/153	15.7	10.3 to 22.4
Do you believe a medical cannabis product would be helpful for your condition?			
Yes	108/153	70.6	62.7 to 77.7
No	10/153	6.5	3.2 to 11.7
Do not know	35/153	22.9	
If Yes, why? (more than one answer can be supplied)			
Symptom control[a]	76/108	70.4	60.8 to 78.8
Pain relief	72/108	66.7	57.0 to 75.5
Decrease anxiety	62/108	57.4	47.5 to 66.9
Cure my condition	5/108	4.6	1.5 to 10.5
Other reasons[b]	28/108	25.9	18.0 to 35.3

a: Pain n=12, Sleep n=11, Spasticity n=10, Seizure n=10, Muscle stiffness n=6, Mobility n=5, Depression n=4, Anxiety n=4, Bowel and bladder function n=4, Focus/brain fog n=3, Aura and tinnitus n=3, Cramping n=2, Fatigue n=2, Headache n=2, Nausea n=2, Tremor n=2, Hair thickener n=1, Energy n=1, Motivation n=1, Anti-inflammatory n=1, Aphasia n=1, PTSD n=1, Less side effects n=1

b: Mental health n=7, Sleep n=7, Relaxation n=5, Pain n=3, Cognitive function n=2, Bowel movements n=1, Neuroprotective effect n=1, Less side effects n=1, Tremors n=1, Foot spasms n=1, Increased quality of life n=1, Creativity n=1, Mobility n=1, Natural medicine n=1, Hearing loss due to usual medication n=1.

5.5.1.2 Patient knowledge of medicinal cannabis products

Nearly half of the neurology patients surveyed (74/153, 48.4%) indicated an awareness of prescription medicinal cannabis products, which is shown in Table 5.8. Of those indicating awareness of specific named pharmaceutical grade products, 64.9% (48/74) were aware of nabiximols, with 11/48 (22.9%) aware that it contained both THC and CBD, and 32/48 (66.7%) aware that it was available in NZ. Less than half of the participants answered knowledge questions about cost per year (19/48, 39.6%), with 9/19 (47.4%) indicating that the cost to patient per year was between $10,000 to $20,000 dollars. When asked if they were aware of any other cannabis-based products, 20/74 (27.0%) stated they were aware, with Tilray products being most commonly cited (n=9), with more recognition than the other pharmaceutical-grade products Epidiolex, dronabinol and nabilone.

Table 5.8. Neurology patient knowledge of medical cannabis products

	n	%	95% CI
Total	74/153	48.4	40.2 to 56.6
Recognition of named products in those who indicated they were aware of prescribed products			
Nabiximols (Sativex)	48/74	64.9	52.9 to 75.6
Dronabinol (Marinol)	3/74	4.1	0.8 to 11.4
Nabilone (Cesamet)	1/74	1.4	0.03 to 7.3
Epidiolex	6/74	8.1	3.0 to 16.9
Other named cannabis products not described above[a]	20/74	27.0	17.4 to 38.6

a: Tilray n=9, Medleaf n=4, Hemp Oil n=2, CBD Oil n=2, Miscellaneous n=4 (Activated Flower Oral Tincture, Activated Olive and Orange Tincture, Homemade CBD, "Something starting with T")

5.5.1.3 Interactions with health care professionals

Table 5.9 summarises patients' responses in regards to interactions with GPs and specialists. Of those who indicated they would be happy to discuss medical cannabis products with GPs (135/153, 88.2%), 33.3% (45/135) indicated that they had done so and 42.2% (19/45) felt they had been fully informed about medicinal cannabis. Of these, seven (15.6%) were prescribed a product of which six filled the prescription, with 50.0% (3/6) reporting they found it effective and that they had reduced other medications. When asked about interactions with specialists, 115/127 (90.6%) indicated they would be happy to discuss with their specialist, with 43/115 (37.4%) doing so and 37.4% (16/43) reporting they felt fully informed. Of those who received prescriptions (9/43, 20.9%) half who had filled the script stated it was effective. Stigma was the leading reason for unwillingness to discuss medicinal cannabis products with health care providers (GPs: 10/18, 55.6%, Specialists: 7/12, 58.3%) however other concerns included the perceived lack of support and understanding surrounding discussions from GPs (n=6) and specialists (n=4).

Table 5.9: Neurology patient interactions with health care professionals about medical cannabis

	GP			Specialist		
	n	**%**	**95% CI**	**n**	**%**	**95% CI**
	Are you happy to discuss with your GP?			Are you happy to discuss with your Specialist?		
Yes	135/153	88.2	82.1 to 92.9	115/127	90.6	84.1 to 95.0
If Yes:						
Have you discussed medical cannabis products?	45/135	33.3	25.5 to 42.0	43/115	37.4	23.6 to 46.9
Did you feel informed?	19/45	42.2	27.7 to 57.9	16/43	37.2	23.0 to 53.3
Were you prescribed a product?	7/45	15.6	6.5 to 29.5	9/43	20.9	10.0 to 36.4
Did you fill the prescription?	6/7	85.7	42.1 to 99.6	8/9	88.9	51.8 to 99.7
Did you find it effective?	3/6	50.0	11.8 to 88.2	4/8	50.0	15.7 to 84.3
Did you reduce other prescribed medications?	3/3	100.0	23.2 to 100.0	3/4	75	19.4 to 99.4
If No:						
Why not?						
Stigma	10/18	55.6	30.8 to 78.5	7/12	58.3	27.7 to 84.8
Legal implications	7/18	38.9	17.3 to 64.3	6/12	50.0	21.1 to 78.9
Cost	7/18	38.9	17.3 to 64.3	6/12	50.0	21.1 to 78.9
Other[a]	11/18	61.1	35.8 to 82.7	4/12	33.3	9.9 to 65.1

a: GP Worried about effects n=6, Perceived lack of support/understanding from GPs n=-6, Worried about doctor/patient relationship n=1, Lack confidence in discussing n=1, Not interested in medication just because it is getting publicity n=1 : Specialist: Perceived lack of support/understanding about cannabis from specialist n=4, Concerned about side effects n=1

5.5.1.4 Use of recreational/illicit cannabis for medicinal symptoms

Table 5.10 summarises how patients are using illicit/recreational cannabis to treat medical symptoms. Of those who reported using illicit/recreational cannabis (53/153, 34.6%), the majority reported smoking (42/53, 79.3%), with few combining this with tobacco (9/53, 17.0%). In those patients with multiple sclerosis, 21/43 (48.8%) reported illicit cannabis use for medicinal

symptoms. In patients with an epilepsy diagnosis, 9/38 (23.7%) reported illicit cannabis use for medicinal symptoms. The five most commonly reported symptoms/conditions that patients reported self-managing were pain (n=15), multiple sclerosis (n=12), anxiety (n=9), sleep (n=8) and epilepsy (n=7). Reported effectiveness of illicit cannabis products was high, with 88.7% (47/53) reporting effectiveness and nearly half (48.9%) stating they had decreased other prescribed medications. Patients frequently reported using more than one type of illicit cannabis-based products. When considering effectiveness, smoking was reported by 34/47 (72.3%) participants as being effective, with 18/47 (38.2%) reporting effectiveness with CBD oil, and 16/47 (34.0%) reporting effectiveness with edibles.

Table 5.10. Neurology patient use of illicit/recreational cannabis for medical symptoms

	n	%	95%CI
Use of recreational/illicit cannabis to treat medical symptoms	53/153	34.6	27.1 to 42.8
Mode of consumption			
Smoking (pure)	42/53	79.3	65.9 to 89.2
Smoking (with tobacco)	9/53	17.0	8.1 to 29.8
Vaped	7/53	13.2	5.5 to 25.3
Oil	26/53	49.1	35.1 to 63.2
Edibles	20/53	37.7	24.8 to 52.1
Other	4/53	7.6	2.1 to 18.2
Did you find it effective?			
Yes	47/53	88.7	77.0 to 95.7
Did you reduce your prescribed medications?			
Yes	23/47	48.9	82.1 to 92.9

5.5.1.5 Information communication from healthcare professionals

Patients were asked to indicate information that they would like from their health care professionals. The dominant emerging information requested was; side effects and safety when taking the medication (n=35), how the medications would specifically help or benefit with their own condition (n=27), the cost of products and how they are too expensive (n=23) and product safety and availability (n=18) (Figure 5.7). They indicated that they would like this information to

be delivered primarily though face-to-face conversations (116/153, 75.8%), website access (101/153, 66.0%) and pamphlets (77/153, 50.3%). Only 11/153 (7.2%) indicated that they did not want any further information.

5.5.1.6 Emerging themes from final comments regarding the use of cannabis-based products as a medicine

Patients were given the opportunity to express further comments to express thoughts about areas they felt had not been covered in the questionnaire, of which 62.8% (96/153) contributed. These responses were then synthesised into themes. Supporting quotes may be seen in Figure 5.8.

5.5.1.6.1 Access, availability and cost

Cost and access concerns remained prominent, not only access to products but also access to overall information, with patients expressing frustration in the process and wish for more open communication from their health care practitioners. Within access, some patients wished to have fully subsidised products available, whilst some wished to grow their own. Some of those who felt prescription products were too expensive expressed they would continue to access through 'green fairies' or other illegal means, whilst others found illegal cannabis too expensive and difficult to source. There was a lack of understanding as to why prescription cannabis-based products were so expensive. Legal concerns remained, with some patients expressing confusion around which medical cannabis products were legal to access.

Within this theme, there was a feeling that NZ based product development and to a lesser extent research should be undertaken to help increase product availability in the country.

Also, within the access theme, some patients acknowledged that although cannabis may not be useful for their own condition or that they may not have had a good response to cannabis-based products (illicit or prescribed) when previously trialled, they believed that it may be beneficial to others.

5.5.1.6.2 Knowledge and the doctor-patient relationship

Patients wanted their practitioners to have appropriate knowledge to discuss the use of cannabis as a medicine and felt that it needed increased awareness in the medical community. There was a feeling that doctors knew little about the effectiveness of medicinal cannabis products. Patients also expressed that doctors do not always listen when cannabis is brought up in a consultation. Some patients stated reluctance as a barrier to enquiring about use of cannabis as a medicine in case the

doctor declines the request. There was also a perception that doctors who may consider cannabis an appropriate option may treat it as an off the record conversation, leaving patients feeling their doctors lack transparency regarding these conversations.

5.5.1.6.3 Natural product benefits

A lesser theme to emerge was that of cannabis being a natural product that should be used either alongside or in place of 'pharmaceutical products', with a belief that it may have less side effects.

Those who expressed this also expressed that they did not necessarily need access to products produced under good manufacturing practice (GMP), just knowledge that the cannabis they used that was free of moulds and pesticides.

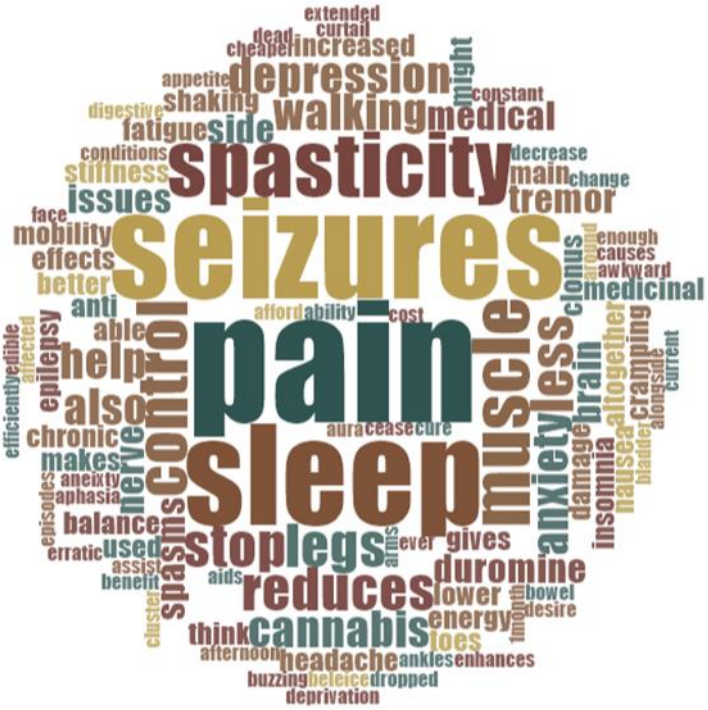

Figure 5.6. Word cloud showing responses to neurology patient beliefs regarding symptom control

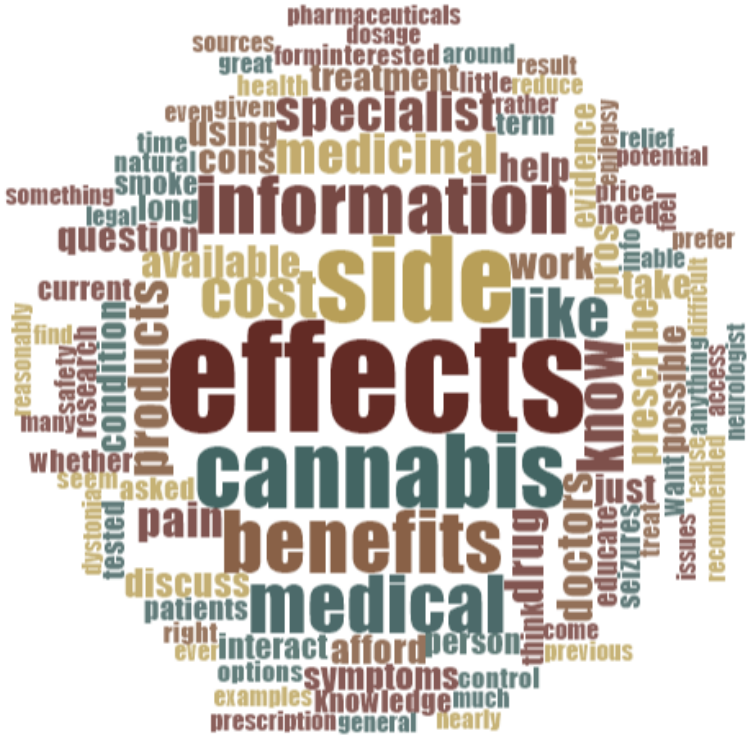

Figure 5.7. Word cloud showing type of information neurology patients want from health care professionals about the use of cannabis as a medicine

"It's frustrating not having access to low cost, high quality cannabis" Male, 50-59

"Ït is my fervent wish that an NZ grown & tested oil will become available at an affordable price." Female 50-59

"The biggest barrier for patients to access medicinal cannabis has been the cost for these products. Hopefully with NZ now able to produce regulated products we all hope that the prices will be more affordable. In an ideal world they should be partly or fully funded by Pharmac. Many of the patients most in need of this natural medicine are the least able to afford it due to living in poverty on a sickness benefit." Male 60-69

"Using illegal cannabis is cost prohibitive as well as difficult to source. I would like to use it to treat my symptoms, but the above means I just stick with prescription meds which I feel are worse for me." Female, 30-39

"The cost has been the biggest problem. I would like to be given the opportunity to see if it does help without any cost associated. I survive on a benefit that means I do not have the money." Female, 50-59

"I think there can be some real benefits to use in some cases but also risks with things like drug induced psychosis (a family member got this) so info needs to be balanced and non-judgemental." Female, 20-29

"I think it has a place as a useful medication for certain symptoms in selected patients." Female 60-69

"It seems that doctors know very little about the effectiveness of cannabis as a medicine." Male, 50-59

"It would be awesome if you could request cannabis and be referred to a clinic where they specialise in cannabis and they could carefully diagnose and decide what your dose rate should be and then monitor your progress. It feels like it is a bit of hit and miss at the moment." Female, 70-79

"I have been thinking of asking my doctor about it for over a year but am a bit shy in case they say no. For years people didn't believe me when I tried describing my symptoms so I lost a lot of confidence in trying to ask for help and think that doctors may not believe I should try it as they seem to only prescribe mainstream meds and have never offered it as an option for me so I just endure the pain and discomfort." Female, 30-39

"I believe health professions should get educated about cannabis as a real option towards better health. They often off the record discuss or encourage its usage and usually have story about a person they know that has benefited from it but don't want to be called on it." Male, 50-59

"Cannabis is a natural plant that should be made more available as medications that are given to treat conditions like epilepsy can do more harm as I have experienced." Male, 30-39

"I use a green fairy who I personally know... so am lucky that I know the plant is completely organic (even the soil is handmade with banana skins, molasses and worms etc) and the type of plant is more suitable for medical purposes - rather than for a 'high'." Female, 40-49

"I don't need GMP products, just well grown, known strains, preferably mould free, organic and vegan." Male, 50-59

Figure 5.8. Supporting quotes of final comments made by neurology patients regarding the use of cannabis as a medicine

5.5.2 Discussion

In this study, the majority of neurology patients indicated that they would be willing to take a cannabis-based product, with over two-thirds indicating that it may be useful for their medical condition. Within this group, symptom control was indicated as the primary reason given for potential benefit as well as a significant belief in cannabis working for pain relief; however, few indicated that it had curative properties. Nearly half of the group surveyed indicated knowledge of prescribed cannabis-based products, primarily nabiximols, with Tilray being the most commonly stated non-pharmaceutical grade product recalled. Despite recognition of nabiximols, less than a quarter were aware that it contained a combination of both THC and CBD. The majority of participants indicated they would be willing to discuss medicinal cannabis with their health care providers, and just over a third stated they had done so. Despite this, less than a half of them felt they were informed by their health care professional, and less than a quarter were prescribed a product. Of those who did receive and fill their prescription, half found it effective, with the majority reporting they had reduced other prescribed medications. Unlike the small numbers of patients receiving prescription products, over a third of participants reported using illicit or recreational cannabis for medicinal purpose, primarily by smoking. Pain was a primary reason for use, and the reported effectiveness of illicit cannabis for symptom management was high. The majority of patients wanted information from their health care providers, including side effects, safety, benefits for their own condition and product information, availability and cost. Face-to-face communication was indicated as the preferred way of receiving information. Emerging themes from overall comments included a focus on access and cost, the patient-doctor relationship and knowledge communication, as well as interest in cannabis as a natural health product compared with other pharmaceuticals.

The use of cannabis-based products within the neurology field has specific indications. As previously noted, use of nabiximols as an adjunct treatment for spasticity in multiple sclerosis and Epidiolex for severe refractory epilepsy syndromes of childhood has some evidence. However, access to these pharmaceutical-grade products remains limited in many jurisdictions, resulting in patients accessing non-pharmaceutical grade products through cannabis access schemes or alternatively illicit cannabis products. Overseas studies have demonstrated that patients with neurology diagnoses are accessing cannabis, whether licit or illicit to manage their symptoms, primarily sleep, pain, spasticity and epilepsy control.[255–258] Gustavesen et al. found that MS patients perceived illicit cannabis as being good to very good for symptom management and this was consistent with the findings of this study, where 89% of patients reported illicit cannabis effective

for their medical condition.[255] It is of interest that those studies of epilepsy patients[257,258] had similar findings to this study, where 23% of epilepsy patients reported using illicit cannabis for medical symptoms. Due to small numbers of patients receiving prescription cannabis-based medications, it is hard to draw conclusions about the effectiveness of such medication compared with illicit cannabis used for medical purposes. Half of those who filled prescriptions reported it effective, compared with almost 90% of those reporting effectiveness of illicit cannabis use. This is in contrast to an Australian survey of medicinal cannabis use (CAMS-18) that reported those users who accessed legally prescribed products who rated effectiveness preferred licit compared with illicit cannabis (44% vs. 24% respectively).[98]

In a New Zealand context, my survey results describing patient interactions are similar to that of Rychert et al., who reported that 63.5% of medicinal cannabis users surveyed stated they had discussed cannabis with their provider in the last year, with 14% requesting a product, but only 5% receiving a prescription.[99] Whereas Rychert et al. reported that patients had lack of faith in doctors prescribing a product impacting on discussions, those patients unwilling to discuss with their doctors in our survey reported concerns about stigma surrounding the use of cannabis and a perceived lack of understanding and support. These themes are also seen overseas, where the CAMS-18 survey reported similar findings, with participants not knowing a doctor willing to prescribe or believing that their doctor was not interested or unwilling to prescribe.[98] Bureaucracy surrounding access and cost were both cited as barriers for self-reported medicinal cannabis users, and this is reflected in the neurology patient population surveyed in this study. Cost of nabiximols was estimated at $10000 to $20000 per year, with patients reporting this to be prohibitive to access and encouraged them to continue to access cannabis-based products through illicit means. Such barriers to access have been seen in Australia and Canada, despite more established medicinal cannabis access schemes than currently seen in NZ.[97,98,100,128]

There is a lack of understanding as to why cannabis products are so expensive. Patients see cannabis as a plant, a natural substance, which they may consider to have less side effects than ‘pharmaceutical’ products. This belief, that cannabis is in some way different from other medications, contributes to the misalignment of how patients and doctors approach the use of cannabis as a medicine. Despite some patients who are willing to use cannabis no matter the source, the majority of patients have expressed they wish to know all the information about cannabis products, including side effects, risks, quality and safety information and effectiveness in their condition. This indicates that patients may not be aware of the processes required to obtain such information. By increasing legal access through alternative access schemes, the medical and

research community is in the unenviable position of discussing products for which basic dosage, safety and efficacy data does not exist. Whilst barriers to patient access may decrease through use of these schemes, there is no requirement for all the information that patients are seeking to be provided by producers, further pressuring the patient-doctor relationship.

5.5.2.1 Strengths and limitations

This study has some limitations. The combination of recruiting through both patient advocacy groups and Facebook allowed a wide range of potential participants to be reached. However, this is also a limitation in that patients who do not have internet access were unable to participate in this research. Participants were also required to self-identify as having a neurology diagnosis and could potentially fill out the survey more than once, however responses were reviewed for duplicates and none were found in the eligible responses. Response rate was unable to be calculated due to the lack of knowledge of number of potentially eligible participants who saw the link to the survey and this also meant non-response bias was unable to be assessed. It is acknowledged that cannabis is a polarising topic, and that those patients who have strong feelings for or against its use may be more likely to respond. There is also potential for recall bias, with those participants who have recently used cannabis or had doctor-patient interactions more likely to accurately recall their interactions.

An area of strength for this survey was the inclusion of full-text responses for qualitative responses, adding to the richness of quantitative data collected and allowing patient voices to be heard through the use of supporting quotes.

Whilst the age-bands of participants is normally distributed, more females than males participated, limiting generalisability. This gender response bias is in keeping with previous large surveys undertaken through Facebook, which demonstrated a predominantly female, non-Hispanic response group.[280] This is also seen in the ethnicity of participants, with 9.2% of the survey population identifying as Māori, significantly less than the normal population. One potential reason for this is that Māori are unlikely to have a diagnosis of MS,[231] which was the diagnosis group with the largest numbers of responses. Survey delivery style may also have impacted Māori response rate, as previous research reporting on Māori preferences for in person or phone surveys.[274] Subsequent surveys about the use of cannabis as medicine in patients with neurology diagnoses will require further collaboration with both neurology outpatient departments and Māori health-care providers to increase responses from under-represented groups.

5.5.2.2 Conclusion

Patients with a neurology diagnosis are interested in the use of cannabis as a medicine and wish to receive more information from their healthcare providers. Whilst some report discussions with their doctors, few patients report receiving a prescription for cannabis-based products, instead many report using illicit cannabis to self-manage their symptoms. Patients have identified cost and access as primary concerns relating to the use of medicinal cannabis products, combined with a belief that doctors are not willing to prescribe such products and are frustrated by the current processes in place. Due to the recent implementation of the Medicinal Cannabis Scheme, patient requests for medicinal cannabis are likely to increase, and without good clinical and regulatory guidance, will undoubtedly place a strain on the doctor-patient relationship.

5.6 Patients in an oncology setting

5.6.1 Results

During the three-month recruitment period (August 2020 to October 2020), 451 online responses were commenced. Of those who started the questionnaire, 201 completed it, giving a completion rate of 44.6%. Absolute response rate was unable to be calculated due to the inability to know the total number of eligible participants who were exposed to the survey link. Following review of the submitted responses, 60 were deemed ineligible due to no evidence of having an oncology diagnosis. This left 141 responses eligible for inclusion. Participant demographics for eligible responses may be seen in Table 5.11, with the median age band reported as 50-59 years, and the distribution of age-bands seen in Figure 5.9. The majority (74.5%) of the sample was female and 81.6% identified as being NZ European.

Table 5.11. Oncology patient demographics

	n	%
Gender		
Male	35/141	24.8
Female	105/141	74.5
Prefer not to disclose	1/141	0.7
Age		
<20	-	-
20-29	2/141	1.4
30-39	12/141	8.5
40-49	17/141	12.1
50-59	41/141	29.1
60-69	40/141	28.4
70-79	28/141	19.9
80+	1/141	0.7
Ethnicity		
NZ European	115	81.6
Māori	13	9.2
Pacific	1	0.7
Chinese	1	0.7
Indian	1	0.7
Other	10	7.1
Reported cancer site		
Breast	41	29.1
Haematological	37	26.2
Gastrointestinal	14	9.9
Prostate	8	5.7
Skin	7	5.0
Lung	6	4.3
Brain	6	4.3
Gynaecological	5	3.5
Endocrine	2	1.4
Unspecified	12	8.5

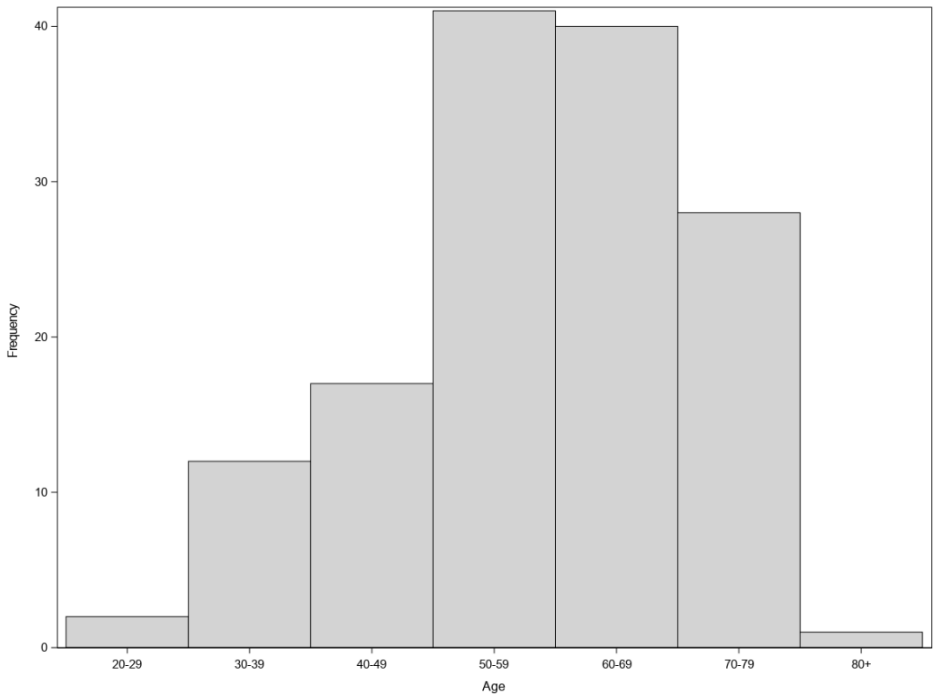

Figure 5.9. Age-band distribution of oncology patient participants

5.6.1.1 Patient beliefs about medicinal cannabis products

Table 5.12 summarises patient's willingness to take a prescribed cannabis-based product and their beliefs surrounding these products in relation to their own medical conditions. The majority of patients (127/141, 90.1%) stated they would be happy to take a prescribed product, 2.8% (4/141) indicating they would not be willing to do so. Considering their own medical conditions, 106/141 (75.2%) indicated a belief that it may be helpful for their medical condition (Figure 5.10). Pain relief was indicated by 87.7% (93/106) as most likely being helped by medicinal cannabis products. Patients who commented on symptom control (61.3%) cited pain (n=20), sleep (n=12), nausea (n=11) and anxiety (n=8) most commonly as symptoms they believed it could help. When asked about curative effects, 18/106 (17.0%) indicated that they believed it may cure their condition.

Those patients indicating that they did not believe or did not know about medicinal cannabis products being helpful primarily cited no need due to lack of pain (n=6) and lack of knowledge (n=6). Other reasons given were they were currently managing their own health and did not need it (n=5), lack of studies supporting use (n=4) and lack of belief of it being a cure (n=3).

Table 5.12. Oncology patient beliefs about medical cannabis products

	n	%	95% CI
Would you take a prescribed medical cannabis product?			
Yes	127/141	90.1	83.9 to 94.5
No	4/141	2.8	0.8 to 7.1
Do not know	10/141	7.1	
Do you believe a medical cannabis product would be helpful for your condition?			
Yes	106/141	75.2	67.2 to 82.1
No	11/141	7.8	4.0 to 13.5
Do not know	24/141	17.0	
If Yes, why? (more than one answer can be supplied)			
Symptom control[a]	65/106	61.3	51.4 to 70.6
Pain relief	93/106	87.7	79.9 to 93.3
Decrease anxiety	73/106	68.9	59.1 to 77.5
Cure my condition	18/106	17.0	10.4 to 25.5
Other reasons[b]	19/106	17.9	11.2 to 26.6

a: Pain (neuropathic, joint, visceral, bone, chronic, musculoskeletal, NOS) n=20, Sleep n=12, Nausea n=11, Anxiety n=8, Appetite/weight stimulant n=5, Mood related symptoms (exc anxiety) n=5, Bowel related symptoms n=5, Fatigue/exercise tolerance n=4, Thirst n=1, Hormonal changes n=1, Felling like dying n=1, Headaches n=1, None currently but think useful in the future n=1.

b: Sleeping habits n=8, Stress reduction n=3, Delaying/preventing cancer return n=2, Gut health n=2, Mood positivity n=2, Inflammation reduction n=1, Hormonal balance n=1, Chemotherapy symptoms assistance n=1, Appetite n=1

5.6.1.2 Patient knowledge of medicinal cannabis products

Table 5.13 summarises what oncology patients report knowing about prescribed cannabis-based products, with 38.8% (54/141) reporting any knowledge. Of those indicating any knowledge, 61.1% (33/54) indicated recognition of nabiximols, 24.2% (8/33) indicated that it contained both THC and CBD and 16/33 (48.5%) indicated awareness that it was available in NZ. Twelve participants estimated the cost to patients, with two patients indicating that the cost was greater than $10,000 per year, whilst the remainder indicated costs ranging from $120 to $5,000 per year, and $360 per bottle to “expensive”. Patients also reported ‘other’ cannabis products being used as a medicine in NZ (22/54, 46.3%), with Tilray brand being the most commonly cited (n=13).

Table 5.13. Oncology patient knowledge of medical cannabis products

	n	%	95% CI
Total	54/141	38.3	30.2 to 46.9
Recognition of named products in those who indicated they were aware of prescribed products			
Nabiximols (Sativex)	33/54	61.1	46.9 to 74.1
Dronabinol (Marinol)	3/54	5.6	1.2 to 15.4
Nabilone (Cesamet)	-	-	-
Epidiolex	-	-	-
Other named cannabis products not described above[a]	25/54	46.3	32.6 to 60.4

a: Tilray n=13, Medleaf n=3, Green fairy/illegal product n=3, Sativex n=2, Theraleaf n=1, CBD oil n=1, Cebimed n=1, Cannabis salve n=1, Hemp oil n=1, Rick Simpson Oil n=1, Charlotte's web n=1.

5.6.1.3 Interactions with health care professionals

Table 5.14 summarises patient reported comfort in discussing medicinal cannabis products with their GP and specialists, as well as interactions that they have already had. The majority of patients report willingness to discuss medicinal cannabis products with their GP (121/141, 85.8%) and their specialist (120/136, 88.2%). Of those who had actually discussed with their GP (44/141, 36.4%), eight were prescribed a product, with two prescriptions being made by specialists, where 43/120 (35.8%) reported discussions. Five patients reported filling prescriptions that the GP provided, with a cost of $120 to $398 per month, with four reporting it effective for a range of symptoms including sleep, mood/balance, pain relief, energy and belief in slowing of cancer growth, and one reporting a reduction in other prescribed medications. Both patients who were prescribed products from specialists reported filling their prescriptions, however, they did not comment on effectiveness.

A small number of participants (14.2%, 20/141) reported a range of reasons for not being comfortable discussing products with their GP. Concern around GPs being against it (n=3), uncertainty in the response they would receive from their GP to queries about it (n=1), GPs lack of knowledge (n=1) and lack of faith in GPs (n=1) were all cited as 'other reasons' for not discussing products. Participants not happy to discuss with their specialist (16/136, 11.2%) reported similar other concerns, with reports of previous negative reactions (n=3), uncertainty around reactions when raised (n=2), lack of interest from specialists (n=1) and concerns around specialists' lack of knowledge (n=1) all being cited.

5.6.1.4 Use of recreational/illicit cannabis for medicinal symptoms

Table 5.15 summarises patient reports of the use of recreational/illicit cannabis for medical symptoms. Patients (50/141, 35.5%) reported using illicitly obtained cannabis, primarily oils (34/50, 68.0%), followed by edibles (26/50, 52.0%) to manage symptoms. The symptoms that they reported self-managing were most commonly pain (n=20), cancer (n=13), anxiety (n=11), sleep (n=9) and nausea (n=7). The majority of patients using illicit cannabis reported that it was effective (47/50, 94.0%) for managing their symptoms, with 59.6% reporting a reduction in their other prescribed medications.

Table 5.14. Oncology patient interactions with health care professionals about medical cannabis

	n	**%**	**95% CI**	**n**	**%**	**95%CI**
	Are you happy to discuss with your GP?			Are you happy to discuss with your Specialist?		
Yes	121/141	85.8	78.9 to 91.1	120/136	88.2	81.6 to 93.1
If Yes:						
Have you discussed medical cannabis products?	44/121	36.4	27.8 to 45.6	43/120	35.8	27.3 to 45.1
Did you feel informed?	22/44	50.0	34.6 to 65.4	22/43	51.2	35.5 to 66.7
Were you prescribed a product?	8/44	18.2	8.2 to 32.7	2/43	4.7	0.6 to 15.8
Did you fill the prescription?	5/8	62.5	24.5 to 91.5	2/2	100.0	15.8 to 100.0
Did you find it effective?	4/5	80.0	28.4 to 99.5	-	-	-
Did you reduce other prescribed medications?	1/4	25.0	0.6 to 80.6	-	-	-
If No:						
Why not?						
Stigma	8/20	40.0	19.1 to 63.9	7/16	43.8	19.8 to 70.1
Legal implications	9/20	45.0	23.1 to 68.5	8/16	50.0	24.7 to 75.3
Cost	8/20	40.0	19.1 to 63.9	4/16	25.0	7.3 to 52.4
Other[a,b]	9/20	45.0	23.1 to 68.5	7/16	43.8	19.8 to 70.1

a: GP: GPs against it n=3, Not needed n=2, Lack of faith in GPs n=1, Not sure of GPs reaction n=1, GPs lack knowledge n=1, Do not like taking drugs n=1, Concerned about side effects n=1, Prefer advice from fellow sufferers who are using cannabis already n=1

b: Specialist: Negative reaction from specialists previously n=3, Not sure of specialists' reaction n=2, Do not feel they are interested n=1, Specialists lack of knowledge n=1, Prefer to talk to someone who specialises in the area n=1

Table 5.15. Oncology patient use of recreational/illicit cannabis for medical symptoms

	n	%	95%CI
Use of recreational/illicit cannabis to treat medical symptoms	50/141	35.5	27.6 to 44.0
Mode of consumption			
Smoking (pure)	23/50	46.0	31.8 to 60.7
Smoking (with tobacco)	3/50	6.0	1.3 to 16.5
Vaped	12/50	24.0	13.1 to 38.2
Oil	34/50	68.0	53.3 to 80.5
Edibles	26/50	52.0	37.4 to 66.3
Other	8/50	16.0	7.2 to 29.1
Did you find it effective?			
Yes	47/50	94.0	83.5 to 98.7
Did you reduce your prescribed medications?			
Yes	28/47	59.6	44.3 to 73.6

5.6.1.5 Information communication from healthcare professionals

Patients were asked what information they would like from their health care professionals. The most commonly cited information that patients wanted was relating to the effects of cannabis-based medicines (including side effects and long-term effects) (n=43), information about availability of products (n=19), dosage and administration (n=18) the conditions and symptoms it can help with (n=17) and proposed benefits, cost and safety information (n=16 respectively) (Figure 5.11).

Patient reported wanting this information communicated through face-to-face consultations (112/141, 79.4%), websites (87/141, 61.7%) and pamphlets (80/141, 56.7%). Only 3.5% (5/141) reported not wanting any further information from health care professionals.

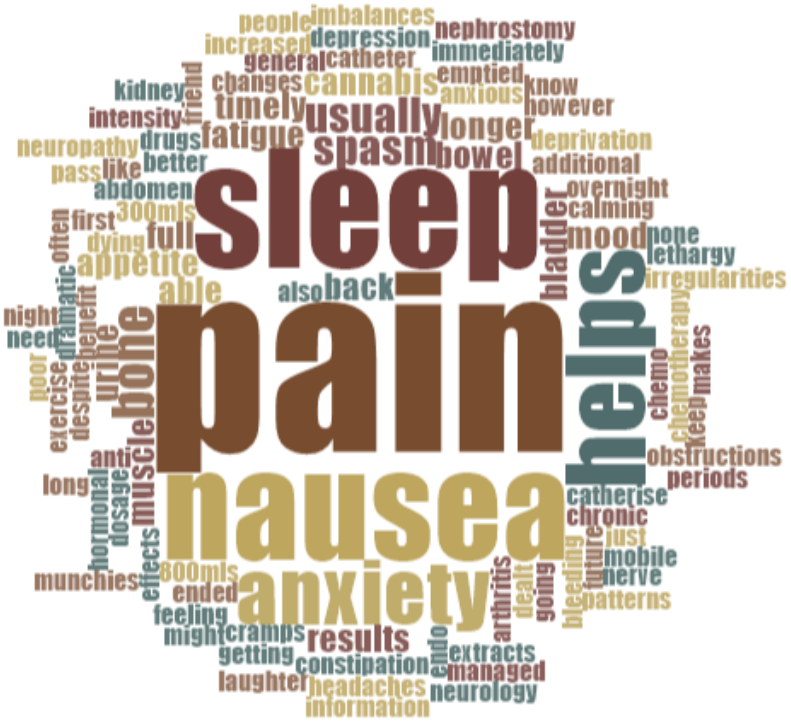

Figure 5.10. Word cloud demonstrating oncology patient beliefs of the benefits of medical cannabis for symptom control

Figure 5.11. Word cloud showing type of information wanted by oncology patients from health-care professionals regarding the use of cannabis as a medicine

5.6.1.6 Emerging themes from final comments regarding the use of cannabis-based products as a medicine

Patients were asked to give their thoughts about the use of cannabis as a medicine that they felt had not been covered completely in the previous questions. Responses were given by 94/141 (66.7%) participants. These were then synthesised into themes. Supporting quotes are seen in Figure 5.12.

5.6.1.6.1 Expense and access

The predominant theme emerging from the comments were the cost to the patient and how it is prohibitive, not only the product cost but the cost of visiting the doctor as well for the prescription. Access was seen as extremely difficult, despite the fact that medicinal cannabis products are technically legal. It was felt that this forced patients to access cannabis products through the illegal market. There were concerns that if only medicinal cannabis remained legal then the cost would remain prohibitive.

5.6.1.6.2 Doctor-patient relationship

Patients expressed concerns surrounding the patient doctor relationship, where some patients felt that there was a stigma attached to them asking about the use of cannabis as a medicine, with one patient expressing that using medicinal cannabis does not make them a drug addict. There was a feeling that doctors are not interested in discussing medicinal cannabis. Patients felt that doctors should be knowledgeable or be willing to refer to a doctor who does have an interest in the field if they did not want to discuss medicinal cannabis. Others felt that their specialists were interested in the idea of medicinal cannabis but were unsure of how to go about prescribing.

5.6.1.6.3 Belief in efficacy

Patients indicated that cannabis-based products were efficacious to their own health, especially in pain relief, and that it ‘was known’ that it was effective in other health conditions. Some credited the use of cannabis and cannabis-based products with the ability to live normal lives, improving their mental health and keeping them alive. Cannabis was attributed to being able to be used for many different conditions, and proposed to replace other prescription medicines in this case. There was also acknowledgement that if you are in a situation where you have a terminal illness you are willing to try anything that might help your situation, regardless of evidence.

5.6.1.6.4 Natural medicine

The theme of cannabis being a natural medicine also emerged. Cannabis was seen as different from ‘chemical medicine’. There was a perception that it may have less side effects and be less toxic than ‘mainstream’ medicine.

5.6.1.6.5 Concern

A theme of concern emerged. Some was from patients who had used cannabis and recalled negative experiences. Although some wished more funding to be given to cannabis for use in cancer management, others were worried that the publicity and pressure would divert funding away from treatments with better curative results. There was concern about the negative effects that people had seen cannabis have on their family members, primarily the psychoactive effects. When considering products, there was concern about what people are actually accessing through ‘green fairies’ and that patients are merely guessing the CBD/THC content of these illicitly accessed products.

"Approved cannabis medicines are too expensive and too hard to get hold of - the recreational cannabis bill is our only hope in the face of such GP\specialist hostility." Female, 50-59

"The only reason that I am not continuing using Medleaf is the cost of the drug and the specialist consultation" Male 70-79

"The cost of prescriptions is incredibly high. NZ products are the most expensive. CBD with THC is only available through ministry of health approval." Female, 50-59

"As I understand it, currently the cost of cannabis-based products for medicinal use are very, very expensive. That would exclude me from accessing a treatment that could be beneficial. This reinforces the two-tiered medication system oncology patients face on a daily basis. Sigh." Female, 60-69

"Make it legal but teach doctors that using it doesn't mean we are drug addicts" Undisclosed, 60-69

"I believe that the majority of people [are] Uneducated especially those who are unable to differentiate between CBD products and those containing THC, also the mythology surrounding cannabis use which has largely been discredited. My specialist and members of a multidisciplinary team declined by request for a script and were ignorant of any positive research and held the view that it would lead to addiction etc even though the request was for CBD." Female, 60-69

"I was very disappointed that when I was very sick that this was not suggested to me by medical professionals and the whole attitude in New Zealand about cannabis is antiquated." Female 30-39

"The huge cost of CBD oil and the unwillingness of normal GPs to prescribe or admit that it might be as helpful as some of the medicines that they are prescribing is hugely unhelpful for many patients. It may not work for all, but neither do current medicines." Female, 50-59

"I don't think many GPs and specialists support the use of medicinal cannabis and neither do they go out and find out more about it - not good enough." Female, 50-59

"I would like the doctors to discuss all options to anybody that it could benefit and not have to make people ask about it as it makes some people very uncomfortable to broach it first so like me I don't want to ask it makes me feel like a doctor may judge me." Female, 30-39

"My doctors are unsure about prescribing, but seem to be interested. Specialist has referred me to Hospice people I suspect he thinks they will be more familiar. Haven't seen them yet but will raise it with them." Male, 60-69

"I believe the cancer was stopped in my head due to the use of cbd and I also believe if it was at a more affordable product and I was taking a larger amount the cancer would of not existed." Male, 30-39

"I believe that research has proven that cannabis has a major role to play in treatment of diseases such as PTSD cancer and epilepsy with minimal side effects. I believe that cannabis is less toxic than many main stream pharmaceuticals." Female, 60-69

"We know its good for stopping epileptic seizures, curing cancer, and many, many others." Male, 70-79

"I believe Cannabis is a potent pain reliever and should be used instead of morphine in severe/terminally ill persons as it does not cause the patient to be drowsy/sleeping etc." Female, 70-79

"It doesn't matter what the condition is this could replace many prescriptions and with a lot less side effects." Male, 30-39

"I like the idea of cannabis being a natural medicine as opposed to chemical medicine." Female, 60-69

"Currently most taking oil are guessing as to the suitability of CBD vs THC and what they are actually taking due to getting from a "green fairy"." Female, 50-59

"I am concerned that drugs that are proven to cure or alleviate conditions will have reduced funding because of the inevitable uptick in demands for cannabis" Female, 60-69

Figure 5.12. Supporting quotes of final thoughts by oncology patients about the use of cannabis as a medicine

5.6.2 Discussion

The results of this study indicate that oncology patients are interested in the use of cannabis as a medicine, primarily for symptomatic control in the form of pain relief. Few patients indicated that they would not take a prescribed cannabis-based product, with three-quarters believing that such products would be helpful for their medical condition, and 17% indicting that it may cure their condition. Just over two-thirds were aware of medicinal cannabis products being prescribed in NZ, with nabiximols and Tilray being most commonly cited. Only a quarter of respondents were aware that nabiximols contained both THC and CBD, and less than half were aware it was available in NZ. Whilst the majority of participants reported comfort in discussing medicinal cannabis with their GPs and specialists, those who were not comfortable were equally concerned about legal implications, stigma and possible negative interactions with their health care providers. Over a third of participants reported use of illicit cannabis for medicinal symptom management, with the preferred mode of consumption in oil or edible form. Nearly all participants who reported illicit use stated that it was effective, with over half decreasing their other prescribed medications. Patients reported wanting their doctors to know what the effects of cannabis-based medicines were, how they could access these products and how to dose and administer them and they preferred that this information was delivered face to face. Less than five percent indicated they did not want further information. Cost and access were a major driver in the final comments about cannabis-based products, with participants indicating despite being legally available they found the process difficult. There was significant belief in the efficacy of medicinal cannabis products, not only for symptomatic control but also for ability to help with their quality of life. Despite this, a small subset of patients expressed concerns, not only around their own perception of negative experiences, but also concerns around what was in the products that patients accessed through the illicit market.

It is not unexpected that oncology patients have considered the use of cannabis-based products for symptomatic relief. Dronabinol and nabilone, both synthetic THC analogues, have been available in the US since the late 1980s for use for chemotherapy-induced nausea and vomiting, however they are not available in NZ. Somewhat unusually, nausea and vomiting, though mentioned by the oncology patients surveyed, was not the primary reason for which they believed that cannabis would help. Instead, the primary reason indicated was pain. This finding is similar to overseas studies with Marcari et al., Singh et al., Cortellini et al. and Pergam et al. all indicating pain as one of their most common reasons for using cannabis.[243,261–263]

Whilst pain management seems to be of most interest to the patients in our survey, it is of interest that 17% of participants indicated they believed that cannabis may be able to cure their condition. Despite a lack of clinical trials providing evidence to support this position,[4] similar levels of belief have been found in other studies, ranging from 16% to 26%.[243,264,265] There is research investigating patient access to information that may reinforce their belief about the curative properties of cannabis. Shi et al., 2019, reviewed internet search activity using Google trends surrounding cannabis and cancer cure.[281] They found that the use of cannabis for cancer cure was present in 23.5% of high impact articles on alternative cancer treatments, and that the top false news story claiming cannabis as a cure generated 4.26 million engagements, compared with 36,000 engagements with the top accurate news story debunking false news.[281] This pervasive belief in cannabis being able to cure cancer is a complex area that requires clear doctor-patient communication during the patient journey, allowing acknowledgement of patient beliefs whilst challenging them with current scientific evidence. This is most significant in those patients for which there is currently a recognised evidence-based cure due to the potential harms that may be faced if patients forgo more mainstream treatment early in their cancer diagnosis in lieu of self-management using cannabis.

Access to medicinal cannabis was cited as a primary concern for patients in this study. It is of interest that even in jurisdictions that have a broad range of access to medicinal cannabis products through medical cannabis card schemes and dispensaries, patients are still accessing cannabis illicitly. Martell et al. reported, that of lifetime cannabis users with an oncology diagnosis, 14% had an authorisation to use, whereas 80% reported accessing through friends or other means (though this is not necessarily related to symptomatic treatment), with 9% reporting that they had accessed cannabis through a medical dispensary.[264] Within the state of Georgia, Singh reported that 32% of patients accessed their cannabis products from a private supplier and 57% shipped it from out of state, whilst 10% reported using a medical cannabis dispensary.[262] As with my study, cost and access regarding cannabis-related products rated highly as a concern in multiple studies, regardless of diagnosis.[97–100,262]

Whilst a recent study of NZ medicinal cannabis users, regardless of diagnosis, indicated that smoking was the primary mode of administration,[99] this study indicated that oncology patients were just as likely to use oils and edibles. This is in keeping with an Australian study by Luckett et al., where in oncology patients who were surveyed about cannabis and possible participation in a clinical trial for anorexia and appetite loss indicated a preference for oral administration of medicinal cannabis products (71%).[282] Singh et al. reported that more than 50% of participants were

using oil of some type, compared with 20% indicating 'other use'.[262] Pergam et al. reported equal numbers of active users who smoked and used edible/oral administration.[243] This may be taken into consideration when reviewing the types of medicinal cannabis products offered through medicinal cannabis schemes.

Patients favoured face-to-face interactions for communication of information about the use of cannabis as a medicine in cancer, followed by websites and pamphlets, with few (3.5%) not wanting further information. This is similar to Pergam et al., who reported that 74% wished to receive information from their cancer team, followed by other cancer patients, websites, family members and pamphlets, with 8% not wanting any further information.[243] When considering comfort in discussing cannabis use with their oncologists, Martell et al. reported that only 5% did not feel comfortable discussing current or previous cannabis use, with 27% unsure or did not complete the question, compared with 11.2% of participants in our study who indicated lack of comfort.[264] This supports the integration of discussion about cannabis use into oncology patients' care early in their cancer journey, emphasising that patients' preference for face-to-face consultations is only likely to foster the patient-doctor relationship.

5.6.2.1 Strengths and limitations

The involvement of patient advocacy groups allowed a wide recruitment pool, most groups preferred advertising on their Facebook page, which limited the number of times the link to the survey was viewed. Patients had a self-identified oncology diagnosis, and due to the nature of a public survey link, could potentially fill out the survey more than once. To limit this, responses were examined for signs of duplication as well as obvious report of an oncology diagnosis and those without such information were removed from the eligible group. No duplicates were found in the completed responses. Due to the polarising views surrounding cannabis, this may have affected responses, with those who have had previous experience with cannabis or hold particular views, whether for or against, more likely to respond. Due to the nature of the anonymous survey, non-response bias was unable to be assessed. Despite these limitations, it is of interest and reassuring that in general our responses are similar to oncology patient groups who have been surveyed in overseas studies.

The sample population was overwhelmingly female and European, in keeping with other online surveys predominantly undertaken through Facebook.[280] The age distribution was skewed to an older population, however this is in keeping with reported rates of cancer diagnoses in NZ.[283] Māori were under represented, at 9.2%, possibly reflecting the style of survey recruitment and

administration undertaken. Whilst Māori health providers were approached to assist with recruitment via Facebook, it has been previously reported that Māori are more likely to undertake research that is conducted face to face or via phone.[274] To counter this, future research in NZ surrounding this topic could focus on both oncology outpatient clinics and Māori health care providers to ensure that there is increased representation of Māori views. The sample was heterogeneous for oncology diagnoses, however more patients with a diagnosis of breast cancer and blood cancer responded to the survey than other groups and may be in part due to the engagement level of patient advocacy groups in reaching their members. This somewhat limits overall generalisability, and future studies involving specific subsets of oncological diagnoses may be indicated for comparison between different subgroups.

5.6.2.2 Conclusion

Oncology patients are expressing a wish to know more about the use of cannabis-based products for symptom management, with a subset believing that cannabis may be curative for their condition. Whilst they express comfort in discussing the use of cannabis with the health care professionals involved in their care and would like information delivered face-to-face, few have received prescriptions and instead report using cannabis obtained illicitly to manage their symptoms. This has identified a gap in access that should be addressed, not only through careful management of the medicinal cannabis scheme in NZ, but also through the development of clear and concise clinical and regulatory guidelines to assist health care professionals in this space.

5.7 Comparison between groups

I undertook a post-hoc analysis for differences of proportions of responses between the three groups to look for significant associations, using the chi-squared test.

Patients with an oncology (χ^2 (1, N=272)=25.85, p<0.0001) or neurology (χ^2 (1, N=284)=19.018, p<0.0001) diagnosis had a significant association with believing that medicinal cannabis may be helpful for their condition when compared with GP patients. A difference in association was noted in belief in cannabis curative properties between oncology patients and neurology patients (χ^2 (1, N=214)=8.5079, p=0.003536), but not between either group and GP patients. A greater proportion of oncology (χ^2 (1, N=92)=14.488, p=0.00014) and neurology (χ^2 (1, N=112)=19.277, p<0.0001) patients were aware of nabiximols compared with GP patients. Oncology (χ^2 (1, N=276)= 22.712, p<0.0001) and neurology (χ^2 (1, N=288)=22.014, p<0.0001) patients were more likely to report use

of illicit cannabis for medical symptoms than GP patients. When comparing mode of consumption between just oncology and neurology patient groups, a greater proportion of neurology patients reported smoking pure cannabis (χ^2 (1, N=103)=12.214, p=0.0004744), with similar proportions reporting edible use (χ^2 (1, N=103)=2.1181, p=0.1456).

5.8 Summary

These studies have shown that there is interest in the use of cannabis as a medicine across a wide range of patient groups, in general practice, neurology and oncology. The majority of all three patient groups have indicated willingness to take prescribed cannabis-based products, and indicated comfort in discussing cannabis as a medicine with both their GPs and secondary care specialists. Despite this, in all groups, less than half of those who have discussed cannabis felt informed about the use of cannabis as a medicine and less than a fifth reported being given a prescription for a cannabis-based product. Patient wishes across all groups were similar, with a wish for increased communication regarding side effects, benefits, cost and availability of cannabis-based products. The information sought from patients is similar to other prescribed medications. Concerns surrounding access to products were highlighted in the oncology and neurology patient groups who reported more interactions with their GPs and specialists than the GP patient group.

Not unexpectedly, few patients in the GP patient group reported using illicit cannabis to self-manage their symptoms. Reported self-management with illicit cannabis was much higher in both the neurology and oncology patient groups. Of interest, all three groups indicated pain as a primary reason for this use, likely reflecting on the common narrative seen through internet searches and on the media that it is an effective pain relief, combined with personal experience.

This combination of low prescription rates and high self-management with illicit cannabis for symptoms that have limited high quality evidence poses a conundrum. Of most impact to NZ, the access of quality medicinal cannabis products at an affordable price combined with a robust education process for patients and health care professionals with ongoing investment into appropriate clinical trials would be best for both doctors and patients. In the interim, patients have indicated that they will continue to access illicit cannabis to self-manage their symptoms, so supporting the patient-doctor relationship to empower both patients and doctors to discuss the clinical impact of cannabis use on individual conditions is imperative. Health literacy concerning the use of cannabis in medical conditions is based on low-moderate quality evidence, anecdote and

personal experience. To counter this, doctors must not be afraid of acknowledging these challenges and engage with patients moving forward.

Chapter 6 Conclusion

6.1 Framing the use of cannabis as a medicine

The aim of this thesis was to frame the use of cannabis as a medicine in NZ, informing ongoing discourse surrounding the future medical applications of cannabis. I achieved this in three ways. First, I reviewed the outcomes of legislative change surrounding cannabis for both recreational and medicinal use. Second, I reviewed the literature to see if cannabis-based products produced in jurisdictions that have implemented such legislation contain active ingredients that match their label. Finally, I surveyed selected cohorts of both doctors and patients in the NZ setting to understand their knowledge and beliefs regarding the use of cannabis as a medicine.

To gain an understanding of the effects of legislation, I undertook a systematic review of the literature and thematic analysis using novel methodology. The outcomes of this analysis indicate an intertwining of medicinal cannabis laws and recreational cannabis laws across jurisdictions. The review ultimately resulted in the synthesis of five super-ordinate themes that cover social, health and political domains. These themes were named normalisation, gatekeeping, community, health and economics. Having identified these themes, I will now apply them as a reflexive lens to frame the outcomes of the other studies I undertook.

6.1.1 Normalisation

The indications by doctors that patients are both requesting cannabis products and reporting recreational/illicit use for medical purposes demonstrates that use has become normalised. This is reflected by patients expressing the wish that medicinal cannabis should be treated like any other medication that they would expect to be prescribed by their doctors. The number of patients expressing the belief that cannabis may help their condition further backs this up. Patients have also expressed a belief that cannabis is natural and some hold beliefs of its overall health benefits. This further supports normalisation of its use. However, patient beliefs in the normalisation of cannabis as a medicine are not in line with doctors. It has emerged that there is a lack of patient understanding as to the availability of the information that may be imparted about specific cannabis-based products that have not gone through the usual framework applied to testing traditional medications.

Normalisation of cannabis use as a medicine is perpetuated by the way it has been treated differently from other medications that are traditionally covered under the Medicines Act 1981.

The enactment of the Misuse of Drugs (Medicinal Cannabis) Amendment Act at the end of 2018 and subsequent Medicinal Cannabis Scheme enforces those differences, by allowing unapproved products that meet minimum quality standards but that have not gone through clinical trials to be prescribed by doctors. Whilst this may meet patients' needs by increasing access, it does not meet the needs of the doctors who are being asked to prescribe such medications. As such, doctors have expressed concerns around this prescribing practice, as can be seen from the studies undertaken in this thesis.

6.1.2 Gatekeeping

The theme of gatekeeping is prominent within these studies and is multifaceted in nature; be it perceived gatekeeping of knowledge relating to the use of cannabis as a medicine or access to the actual products themselves. There is a perception from some patients that doctors are not interested and are biased against the use of cannabis as a medicine. This is not necessarily the case; rather the majority of health care professionals wish to have it treated like any other medicine, where they know that what they are prescribing is consistent in nature, has safety data and evidence of efficacy in the clinical indication for which it is being prescribed. Unfortunately, the push for access to medicinal cannabis products has outpaced the traditional development of medications, not only in NZ. As such, the medical profession is faced with a 'wicked problem' of balancing patient and public expectations against the quality of evidence for use versus the potential health harms associated with cannabis and cannabis-based products. The lack of high-quality evidence for efficacy overall in specific medical conditions and the lack of product specific information means that doctors do not necessarily have the tools to be able to navigate the role of gatekeeper successfully. This impacts on the patient-doctor relationship, where patient expectations do not always align with doctors' expectations.

It is reassuring that the MCS has guidelines for what the minimum quality standards are, however it is important that the actual implementation of the law is undertaken to the highest quality. From the systematic review examining labelling of cannabis products that are being used for medicinal purposes in markets where they are permitted, it is apparent that there is variation in product quality, even where there are regulations in place for such use. This again feeds back into the concerns that health care practitioners have when prescribing products, the need for knowledge that

the product they are prescribing contains the correct amount of the active ingredient. From a NZ perspective, this highlights that merely having regulations in place does not necessarily reflect that products will meet these standards, and demonstrated the need for implementing a strong pharmacovigilance process to ensure that such problems encountered overseas are not found in products imported or developed in NZ.

As of December 2020, there are no NZ based products on the scheme, and whilst licenses to produce products that may be accessed under the scheme have been granted, there is currently no timeline given as to when these NZ products will be available.

There was hope within the patient community that legalisation would mean increased access to lower cost medicinal cannabis products, despite insistence by the government that these legislative processes were completely separate. Following the referendum in October 2020, which did not receive enough support to approve the draft of the Cannabis Legalisation and Control Bill, there will be further pressure to increase availability and access to products through the medical cannabis scheme.

It is apparent from the patient observational studies that lack of engagement with health-care professionals may result in them bypassing these ‘gatekeepers’ in a search for illicitly obtained cannabis. Even those that are prescribed cannabis-based products in NZ express that it is too expensive, effectively making price another gatekeeper in the process. Those with money are more likely to be able to access prescribed cannabis-based products reinforcing inequities in the country, which in turn is likely to disparately affect those in lower socio-economic regions, particularly Māori and Pasifika patients.

6.1.3 Community

When considering the theme of community, the observational studies demonstrated concerns from some patients perceiving stigma from both friends and doctors when discussing the use of cannabis-based products for medical purposes. Some patients were concerned around the effect that prescribed cannabis may have on their ability to work, workplace drug testing and the effect that it may have on their driving. Knowledge of the active product ingredients is essential to allow doctors to have conversations about the potential effects that the products they are prescribing may have. From a legal perspective, the fact that over 30% of both neurology and oncology patients stated that they have used illicit cannabis for medical purposes, and intend to do so whilst there is minimal

access to expensive prescribed products demonstrates that other patients feel the benefit of possession and use outweighs the legal risks associated with such access.

6.1.4 Health

Health effects of cannabis use as a medicine may also be seen if patients accessing illicit cannabis for medical use. Some patients in the observational studies expressed uncertainty about what is contained in the product that they have accessed. This gives potential for patients to be exposed to differing levels of cannabinoids, contaminants and adulterants. With the blurring of lines of how patients define use for both medical and recreational reasons, if the use of cannabis-based products for medicinal purposes continues there will be need to ensure access to good support services to address associated health harms. This is significant for cannabis use disorder, which would be expected to develop in ten percent of regular cannabis users.

Another health effect explored in the course of this thesis was patient beliefs regarding efficacy of cannabis as a medicine, especially those who believed that cannabis may cure their condition. This has potential to have negative outcomes if patients choose to forgo medications with known provenance and use cannabis as a medicine instead. This belief in curative properties was primarily noted in a small sub-group of oncology patients. This may be termed a ‘false expectation’, and is likely to apply pressure to the patient-doctor relationship. Doctors require research and training to be able to confidently address and discuss such beliefs with their patients.

6.1.5 Economics

Concern surrounding the cost of products emphasises how the theme of economics plays a part in access within the NZ context. In the light of prescribing cannabis-based products for patients where there is believed to be evidence for use, both doctors and patients expressed concerns about the cost of such products. These costs may be seen at a patient and government level. There is a cost to patients in form of paying for products and accessing doctor’s appointments. The cost to the health care system may be seen with the subsequent support services potentially required with increased use of such products. This in turn reflects on the aim of the Medicinal Cannabis Scheme, which is to allow access to lower cost products meeting minimum quality standards. There is pressure on the government to ensure that products developed in NZ are economically viable for both patients and the producers; considering how products will be licensed, tested and taxed.

Reflecting on the observational studies of both patients and doctors and what they wish to know about the specific cannabis-based products, those product developers who use a traditional medical approach may be at an advantage if they are able to offer even basic safety and tolerability information relating to their specific products. This information may be gathered in the form of Phase I clinical trials. These examine the pharmacokinetic and pharmacodynamics of medications when applied to humans, and gauge the safety and tolerability through collection of associated adverse events and identification of the maximum tolerated dose. Such trials, which typically have six to twelve participants per cohort, may be undertaken over a six to nine-month period and have the potential to offer some reassurance to prescribers and patients who are accessing such products. To facilitate such studies moving forward, an example of a protocol developed during my thesis for this type of trial of cannabis-based products may be seen in the Appendix (7.12). Ultimately, larger scale, Phase II and III clinical trials of these products in specific medical conditions to establish efficacy should be pursued and would be of most benefit to patients and their doctors, however it is acknowledged that this is a costly process, both in terms of time and money.

6.2 Recommendations for applying research findings

Reviewing my research in light of the synthesised themes made me consider how I might approach the complex problem of the use of cannabis as a medicine in New Zealand.

Being a health care professional, a consultant general practitioner, I am aware of the complexities of the patient-doctor relationship and the discussions of treatments and management plans. I am also aware that this provides my own internal bias that must be challenged when considering the research. As a practicing doctor, prior to starting this thesis, I knew little about the use of cannabis as a medicine, and would have felt out of my depth and challenged when answering my own questionnaire. It did not come as a surprise to me that many doctors express lack of knowledge and concerns regarding the use of cannabis as a medicine as this reflects my own experience.

As has been expressed earlier, doctors are the gatekeepers to medicinal cannabis products under the MCS. At present, they do not have the required tools to fulfil this responsibility under the good prescribing practice guidelines outlined in Chapter 1. These tools include knowing the safety AND efficacy data that is associated with each medication, rather than just one or the other. This is also reflected in what patients have expressed that they want to know about the use of cannabis a medicine. Whilst Medsafe approved medications may be used in an off-label or experimental situation where there is minimal efficacy data, doctors have the added reassurance that the specific

medication they are prescribing has both met GMP standards indicating that what they are prescribing has the same formulation and ingredients each time and that it undergone clinical trials to establish its safety. This reassurance may not be extended to unapproved products on the MCS.

In order to address this, I would suggest that certain measures be put in place to ensure the best outcome for patients and doctors. There is need at a government level to have an ongoing advisory group that represents all stakeholders within the medicinal cannabis field, which are involved in the ongoing administration of the MCS. This advisory group may then consider using the emergent themes that have developed as focus points for review of the current integration of the scheme.

From a healthcare practitioner perspective, those unapproved products that have met the minimal quality standard and are placed on the MCS should be required to go through a clinical trials process, at a minimum to establish the safety and tolerability of each specific product. Ideally this framework would be developed independent of industry and grant funding, and be integrated into the ongoing development of the MCS. This would address some of the concerns held by prescribers.

In addition, interim access to pharmaceutical grade medications such as dronabinol, nabilone and Epidiolex, could be established, with a cap applied to the amount that can be charged under the medicinal cannabis scheme. This would help address the access concerns described by patients during the course of this research.

From an education perspective, the development of a 'living' educational module should be established, with patient and doctor focused information. This module could also be incorporated into the MCS, with quarterly reviews and updates to inform recent significant changes in the literature and supporting evidence for the use of cannabis as medicine.

I think it is also important to acknowledge that some patients have indicated that they may still be unable to access prescribed medicinal cannabis products or may choose to use non-approved or illegal products. From a health harm reduction perspective, I would also suggest that an easily accessible product testing service be established through the MCS, where patients could submit samples of their product for analysis with no penalties, so they could have some reassurance that what they are using is safe. Within this harm reduction framework of testing non-approved products, continuing discussion about mode of administration should be encouraged, with patients advised against smoking cannabis products as their primary mode of administration.

6.3 Future research opportunities

There are many avenues of future research that have arisen following completion of this thesis. Despite their being no current need for clinical trials for products that meet the minimum quality standards of the MCS, there is still interest in undertaking early phase trials of these products. As previously stated, I have written a protocol aimed at establishing the safety and tolerability of cannabis-based products, and hope to have the opportunity to undertake this research in the future.

Within NZ, research of medicinal cannabis users has primarily been cross sectional in nature. In order to continue informing doctors and patients about the use of cannabis as a medicine, there is need for the development of long-term cohort studies within the field. One such study would be to examine the prescribing process of medicinal cannabis products in NZ, exploring patient, doctor and pharmacy outcomes. Another involves following medicinal cannabis users and characterising the products they are using- whether prescribed products or illegally obtained- to establish pragmatic outcomes of current patients in NZ. I am currently a named investigator on both grant applications and research projects that aim to address these research questions.

There is also room for future research regarding the development of an educational module for patients and doctors. This needs to be addressed in conjunction with the introduction of the MCS.

6.4 Closing statement

Understanding the complexities involved in the use of cannabis as a medicine is essential to developing appropriate strategies to manage the process moving forward. It has already been normalised in the eyes of patients, and science must now balance the benefits versus the harms to allow ongoing communication about its use. I have demonstrated that the use of cannabis as a medicine is indeed a 'wicked problem' and must be viewed through a multi-faceted lens. Enacted legislation must constantly be revisited in a timely fashion ensuring successful implementation of processes. This is supported by the review I undertook examining product label accuracy and contaminants, which demonstrated that even with implementation of processes, there must be continuing oversight to allow delivery of safe products to patients. Doctors identified that their greatest need is for clear clinical and prescribing guidelines that are NZ specific, with ongoing high-quality research into cannabis-based products and their use in medical conditions. Patients identified that access and low-cost products are their greatest needs. Balancing their needs against a need for evidence for use is particularly difficult, as demand for prescription medications is not

typically part of the doctor-patient relationship. One aspect that may assist both doctors and patients is the development of high-quality clinical trials, with increased involvement of patients in trial design as well as including a combination of both objective measurements and validated subjective scales to assess patient response.

Demand for cannabis-based products is not going to go away and as it has been deemed by government that this is to be medicinal in nature, there needs to be investment in the process at multiple levels. These levels include government, industry, medicine and academia. Collaboration starts at the highest levels, with review of cannabis related legislation performed by not only government officials, but also health care providers, industry stakeholders and patient advocates. Following such review, changes made must be clearly communicated to the health-care professionals and patients ensuring informed discussions. They may then discuss the benefits and risks of cannabis-based medicines in their conditions and if deemed appropriate following these discussions, seek access to quality cannabinoid products through the government mandated Medicinal Cannabis Scheme. Use of this scheme may then provide an opportunity to collect and review data around the ongoing use of cannabis-based products as a medicine in NZ, including safety, benefits and harms. This will provide further information that may then be drawn back up to the government level for ongoing review of the ‘wicked problem’ of medical cannabis legislation.

Chapter 7 Appendices

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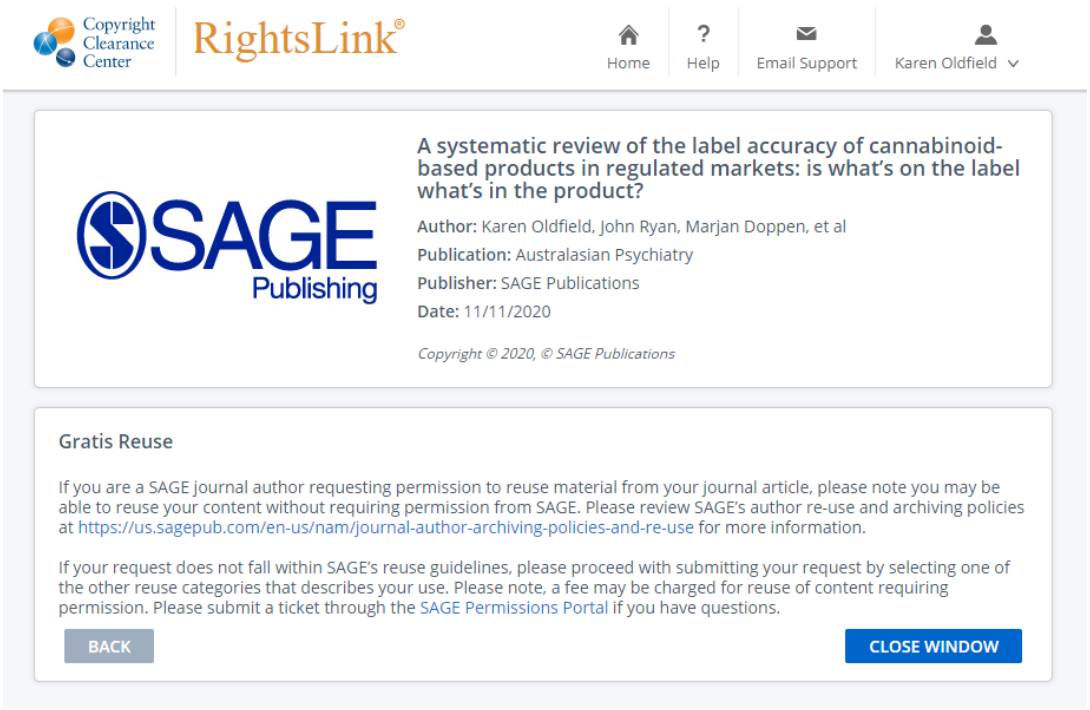

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Platform or provider used:	Ovid SP
Date of coverage:	1946 to Nov 22 2019
Date Search undertaken:	25 Nov 2019

#	Searches
1	Cannabis/
2	exp Cannabinoids/
3	(marijuana or marihuana or cannabi* or "delta-9-tetrahydrocannibinol" or "Δ-9-tetrahydrocannabinol" or "Δ-9-THC").ti,kf.
4	1 or 2 or 3
5	exp Social Control, Formal/
6	lj.fs.
7	(regulat* or legislat* or jurisdiction or "law change*" or legali* or decriminali* or control polic*).ti,ab,kf. not (regulat* adj3 (cell* or receptor*)).ti,kf.
8	5 or 6 or 7
9	4 and 8
10	limit 9 to humans
11	limit 9 to animals
12	9 and (rat or rats or rodent* or mouse or mice or murine).ti.
13	(9 not (11 or 12)) or 10

EMBASE

Database searched: EMBASE- All years

Platform or provider used: Ovid SP

Date of coverage: 1947 to present with Daily Update

Date Search undertaken: 25 Nov 2019

#	Searches
1	exp cannabinoid/
2	exp “cannabis (genus)’/
3	exp “cannabis use”/
4	(marijuana or marihuana or cannabi* or “delta-9-tetrahydrocannbinol’ or “Δ-9-tetrahydrocannabinol” or “Δ-9-THC”).ti,kw.
5	(13956-29-1 or 89958-21-4 or 8063-14-7 or 1972-08-3).rn.
6	or/1-5
7	exp drug control/
8	(regulat* or legislat* or jurisdictions or “law change*” or legali* or decriminali* or control polic*).ti,ab,kw. not (regulat* adj3 (cell* or receptor*)).ti,kw.
9	7 or 8
10	6 and 9
11	limit 10 to human
12	limit 10 to (animals and animal studies)
13	10 and (rat or rats or rodent* or mouse or mice or murine).ti.
14	(10 not (12 or 13)) or 11
15	limit 14 to medline
16	14 and (1* or 2* or 3* or 4* or 5* or 6* or 7* or 8* or 9*).pm.
17	14 not (15 or 16)

PsycINFO

Database searched: PsycINFO

Platform or provider used: Ovid SP

Date of coverage: 1806 to November Week 3 2019

Date Search undertaken: 25 Nov 2019

1 exp cannabis/

2 exp cannabinoids/

3 (marijuana or marihuana or cannabi* or "delta-9-tetrahydrocannbinol' or "Δ-9-tetrahydrocannabinol" or "Δ-9-THC").ti,id.

4 1 or 2 or 3

5 exp drug legalisation/

6 exp drug laws/

7 (regulat* or legislat* or jurisdiction or "law change*" or legali* or decriminali* or control polic*).ti,ab,id. not (regulat* adj3 (cell* or receptor*)).ti,id.

8 5 or 6 or 7

9 4 an 8

10 limit 9 to human

11 limit 9 to animal

12 9 and (rat or rats or rodent* or mouse or mice or murine).ti.

13 (9 not (11 or 12)) or 10

14 (1* or 2* or 3* or 4* or 5* or 6* or 7* or 8* or 9*).pm.

15 13 not 14

EBSCO

Databases searched:

Academic Search Complete, Australia/New Zealand Reference Centre, Business Source Complete, CINAHL, Communication & Mass Media Complete, Education Research Complete, GreenFILE, Health Business Elite, Health Source - Consumer Edition, Health Source: Nursing/Academic Edition, Hospitality & Tourism Complete, Humanities International Complete, MAS Ultra - School Edition, MasterFILE Premier, Psychology and Behavioral Sciences Collection, SPORTDiscus with Full Text, Wildlife & Ecology Studies Worldwide

Platform or provider used: EBSCO

Date of coverage: To 25 Nov 2019

Date Search undertaken: 25 Nov 2019

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S2 TI (regulat* OR legislat* OR jurisdiction OR "law change*" OR legali* OR decriminali* OR (control N/1 (polic* OR drug* OR cannabi* OR marijuana))) OR SU (regulat* OR legislat* OR jurisdiction OR "law change*" OR legali* OR decriminali* OR (control N/1 (polic* OR drug* OR cannabi* OR marijuana))) OR AB (regulat* OR legislat* OR jurisdiction OR "law change*" OR legali* OR decriminali* OR (control N/1 (polic* OR drug* OR cannabi* OR marijuana))
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S3 S1 AND S2

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Date of coverage: To Nov 25 2019

Date Search undertaken: 25 Nov 2019

S1 (((ti(marijuana OR marihuana OR cannabi* OR “delta-9-tetrahydrocannbinol’ OR “Δ-9-tetrahydrocannabinol” OR “Δ-9-THC”) OR su(marijuana OR marihuana OR cannabi* OR “delta-9-tetrahydrocannbinol” OR “Δ-9-tetrahydrocannabinol” OR “Δ-9-THC”)) AND (ti(regulat* OR legislat* OR jurisdiction OR “law change*” OR legali* OR decriminali* OR (control NEAR/1 (polic* OR drug* OR cannabi* OR marijuana))) OR su(regulat* OR legislat* OR jurisdiction OR “law change*” OR legali* OR decriminali* OR (control NEAR/1 (polic* OR drug* OR cannabi* OR marijuana)))) AND stype.exact(“Scholarly Journals”))) NOT ti(ecstasy)

Web of Science

Databases searched: Web of Science

Platform or provider used: Web of Science

Date of coverage: To Nov 21 2019

Date Search undertaken: 21 Nov 2019

S1 TS=(marijuana OR marihuana OR cannabi* OR "delta-9-tetrahydrocannibinol" OR "Δ-9-tetrahydrocannabinol" OR "Δ-9-THC") AND TS= (regulat* OR legislat* OR jurisdiction OR "law change*" OR legali* OR decriminali* OR (control NEAR/1 (polic* OR drug* OR cannabi* OR marijuana))) NOT PMID=(1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9)

Scopus

Databases searched: Scopus

Platform or provider used: Scopus

Date of coverage: To Nov 21 2019

Date Search undertaken: 21 Nov 2019

S1 (TITLE (marijuana OR marihuana OR cannabi* OR "delta-9-tetrahydrocannibinol" OR "Δ-9-tetrahydrocannabinol" OR "Δ-9-THC") OR AUTHKEY (marijuana OR marihuana OR cannabi* OR "delta-9-tetrahydrocannibinol" OR "Δ-9-tetrahydrocannabinol" OR "Δ-9-THC") OR CASREGNUMBER (13956-29-1) OR CASREGNUMBER (89958-21-4) OR CASREGNUMBER (8063-14-7) OR CASREGNUMBER (1972-08-3)) AND (TITLE (regulat* OR legislat* OR jurisdiction OR "law change*" OR legali* OR decriminali* OR "control polic*") OR AUTHKEY (regulat* OR legislat* OR jurisdiction OR "law change" OR legali* OR decriminali* OR "control polic*")) AND NOT (PMID (1*) OR PMID (2*) OR PMID (3*) OR PMID (4*) OR PMID (5*) OR PMID (6*) OR PMID (7*) OR PMID (8*) OR PMID (9*)) AND (LIMIT-TO (DOCTYPE , "ar") OR LIMIT-TO (DOCTYPE , "re") OR LIMIT-TO (DOCTYPE , "ch") OR LIMIT-TO (DOCTYPE , "ip") OR LIMIT-TO (DOCTYPE , "sh") OR LIMIT-TO (DOCTYPE , "bk")) AND (LIMIT-TO (LANGUAGE , "English"))

7.3 Supplement 2: Descriptive data extraction

Descriptive data was extracted using the following headings:

Type of study; Country and state of study; Study Population; Dates of legislations/guidelines being reviewed (if present); Medical or recreational use legislation/guideline (if described); Description of legislation/guideline being reviewed; Intended outcomes of guidelines/laws (if present); Outcomes of guidelines/laws (if present); Cultural or socio-economic status of country (if present). Investigators could also provide comments to ensure other potential areas of interest were not missed.

7.4 Supplement 3: Included papers for data synthesis (Legislative review)

Author	Publication Year	Title	Countries Involved	Participants (if relevant)	Medical/Recreational/Both Legislation (if described)
Maloff[141]	1981	A review of the effects of the decriminalisation of marijuana	USA	Data from state surveys, numbers not given	Decriminalisation
Suggs[284]	1981	A qualitative and quantitative analysis of the impact of Nebraska's decriminalisation of marijuana	USA	108 police officers, 135 students	Recreational
Abel[186]	1997	Cannabis policy in Australia and New Zealand	NZ/AUS	Not applicable	Recreational
MacCoun & Reuter[285]	2001	Evaluating alternative cannabis regimes	Multiple		Recreational
Garmaise[144]	2002	Canadian News. Physicians dislike new medical marijuana regulations	Canada		Medical
Khatapoush & Hallfors[149]	2004	Sending the wrong message: Did medical marijuana legalisation in California change attitudes about use of Marijuana	USA	15,567	Medical
Belle-Isle & Hathaway[128]	2007	Barriers to access to medical cannabis for Canadians living with HIV/AIDS	Canada	197 Participants with HIV/AIDs	Medical
Nussbaum & Thurstone[146]	2011	Mile high macaroons: The medicalization of marijuana in Colorado	USA		Medical
Wall et al.[124]	2011	Adolescent marijuana use from 2002 to 2008: Higher in states with medical marijuana laws, cause still unclear	USA	23,300	Medical
Caplan[145]	2012	Medical marijuana: A study of unintended consequences	USA		
Cerdá et al.[170]	2012	Medical marijuana laws in 50 states: Investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence	USA	34653	Both

Author	Publication Year	Title	Countries Involved	Participants (if relevant)	Medical/Recreational/Both Legislation (if described)
Adda et al.[286]	2014	Crime and the depenalization of cannabis possession: Evidence from a policing experiment	UK		
Belle-Isle et al.[100]	2014	Barriers to access for Canadians who use cannabis for therapeutic purposes	Canada	628 CTP users	Medical
Boyle[176]	2014	Butane hash oil manufacturing related burn injury: A disturbing trend	USA	11 cases	Recreational
Couper & Peterson, 2014[156]	2014	The prevalence of marijuana in suspected impaired driving cases in Washington State	USA		Both
Wang et al.[152]	2014	Association of unintentional paediatric exposures with decriminalisation of marijuana in the United States	USA	985 cases	Non-legal vs transitional vs decriminalised
Williams & Bretteville-Jensen [287]	2014	Does liberalizing cannabis laws increase cannabis use?	Australia	NDSHS survey, 1998, 2001, 2004, 2007, 2010	Decriminalisation
Běláčková et al.[143]	2015	"Should I buy or should I grow?" How drug policy institutions and drug market transaction costs shape the decision to self-supply…	NED/Czech	Secondary analysis data	Personal use
Bell et al.[140]	2015	Butane hash oil burns associated with marijuana liberalization in Colorado	USA	29 cases	Recreational
D'Amico et al. [129]	2015	Gateway to curiosity: Medical marijuana ads and intention and use during middle school	USA		Both
Grucza[171]	2015	A re-examination of medical marijuana policies in relation to suicide risk	USA	662,993 COD files	Medical
Hall & Weier[127]	2015	Assessing the public health impacts of legalizing recreational cannabis use in the USA	USA		Both
Kim et al. [177]	2015	Cyclic vomiting presentations following marijuana liberalization in Colorado	USA		Both
Pacula et al[288]	2015	Assessing the effects of medical marijuana laws on marijuana use: The devil is in the details	USA	21 states	Medical

Author	Publication Year	Title	Countries Involved	Participants (if relevant)	Medical/Recreational/Both Legislation (if described)
Sznitman & Zolotov[289]	2015	Cannabis for Therapeutic Purposes and public health and safety: A systematic and critical review	Multiple		Medical
Barry & Glantz[132]	2016	A public health framework for legalized retail marijuana based on the US experience: Avoiding a new tobacco industry	USA	Not applicable	Recreational
Boidi et al.[147]	2016	Cannabis consumption patterns among frequent consumers in Uruguay	Uruguay	294 frequent cannabis users	
Caulkins & Kilmer[290]	2016	Considering marijuana legalization carefully: insights for other jurisdictions from analysis for Vermont	USA	Not applicable	Recreational
Davis et al.[291]	2016	Public health effects of medical marijuana legalization in Colorado	USA		Both
Estoup et al.t[292]	2016	The impact of marijuana legalization on adolescent use, consequences, and perceived risk	USA	262 students in school-based drug use intervention programmes	Recreational
Freisthler et al.[293]	2016	A micro-temporal geospatial analysis or medical marijuana dispensaries and crime in Long Beach, California	USA	7992 space time settings	Medical
Huber, Newman, & Lafave[294]	2016	Cannabis control and rime: Medicinal use, depenalization and the war on drugs	USA	State level data	Medical and Depenalisation
Jensen & Roussell[155]	2016	Field observations of the developing legal recreational cannabis economy in Washington State	USA	Not applicable	Recreational
Keyes et al.[295]	2016	How does state marijuana policy affect US youth? Medical marijuana laws, marijuana use and perceived harmfulness: 1991-2014	USA	1,134,734 adolescents in 8th, 10th and 12th grades	Medical
Kim & Monte [296]	2016	Colorado cannabis legalization and its effect on emergency care	USA	Not applicable	Both
Onders et al.[297]	2016	Marijuana exposure among United States children younger than six years old	USA	1969 cases	Medical

Author	Publication Year	Title	Countries Involved	Participants (if relevant)	Medical/Recreational/Both Legislation (if described)
Schmidt et al.[298]	2016	Young people's more permissive views about marijuana: Local impact of State laws or national trend?	USA	Middle school–aged youths (aged 12–14 years, rounded n=111 100), high school–aged youths (aged 5–17 years, rounded n=114 000), and young adults (aged 18–25 years, rounded n=225 200)	Medical
Sobesky & Gorgens[123]	2016	Cannabis and adolescents: Exploring the substance misuse treatment provider experience in a climate of legalisation	USA	11 substance abuse treatment providers	Recreational
Ullman[159]	2016	The effect of medical marijuana on sickness absence	USA		Medical
Adam & Raschzok[299]	2017	Cannabis policy and the uptake of treatment for cannabis-related problems	Belgium, Finland, France, Portugal	EMCDDA indicator data	Recreational
Al-Shammari et al.[300]	2017	Effects of the 2009 medical cannabinoid legalisation policy on the hospital use for cannabinoid dependency and persistent vomiting	USA		Medical
Al-Shammari et al.[301]	2017	US national trend analysis of cyclic vomiting incidence with liberalisation of cannabis use	USA		Both
Baggio & Choi[163]	2017	Is access to marijuana a disamenity?	USA	Data from state surveys, numbers not given	Medical
Banerji & Hoyte[302]	2017	Marijuana and synthetic cannabinoid patterns in a US state with legalized marijuana: a 5-year NPDS review	USA	National poison data system	Recreational
Běláčková et al.[303]	2017	Assessing the concordance between illicit drug laws on the books and drug law enforcement: Comparison of three states on the continuum form "decriminalised" to "punitive"	USA, Czech Republic, Australia	3 states/countries	Recreational
Carliner et al.[148]	2017	Cannabis use, attitudes and legal status in the US. A review	USA		Both
Carnevale et al.[134]	2017	A practical framework for regulating for-profit recreational marijuana in US states: Lessons from Colorado and Washington	USA	Not applicable	Recreational

Author	Publication Year	Title	Countries Involved	Participants (if relevant)	Medical/Recreational/Both Legislation (if described)
Cerdá et al.[122]	2017	Association of state recreational marijuana laws with adolescent marijuana use	USA	253,902 students (USA wide)	Recreational
Červený et al.[304]	2017	Cannabis decriminalisation and the age of onset of cannabis use	Czech republic	In 2008 n=1086, in 2012 n=438	Decriminalisation
Chhabra & Leikin[142]	2017	Analysis of medical marijuana laws in states transitioning to recreational marijuana- a gateway drug policy?	USA	42/50 states laws	Both
Daniulaityte et al.[305]	2017	Retweet to pass the blunt: Analyzing geographic and content features of cannabis-related tweeting across the United States	USA	13,233,837 cannabis related tweets	Comparison of all types
Dilley et al. [164]	2017	Community-level policy responses to state marijuana legalization in Washington State	USA		Both
Ellison & Spohn [160]	2017	Borders up in smoke: Marijuana enforcement in Nebraska after Colorado's legalization of medical marijuana	USA		Medical
Ghosh et al.[138]	2017	Lessons learned after three years of legalized, recreational marijuana: the Colorado experience	USA		Both
Thompson[154]	2017	"Good moral characters:" how drug felons are impacted under state marijuana legalization laws	USA	Not applicable	Recreational
Zhang et al.[137]	2017	A review of the impact of marijuana's legalization on Colorado's industrial warehouse lease rates: how high is high?	USA		Recreational
Abouk & Adams[172]	2018	Examining the relationship between medical cannabis laws and cardiovascular deaths in the US	USA		Medical strict versus medical lax
Bradford & Bradford[179]	2018	The impact of medical cannabis legalization on prescription medication use and costs under Medicare Part D	USA		Medical
Calcaterra et al.[178]	2018	The impact of legalisation of recreational marijuana on a safety-net health system	USA	Data from hospital systems	Recreational

Author	Publication Year	Title	Countries Involved	Participants (if relevant)	Medical/Recreational/Both Legislation (if described)
Caulkins et al.[136]	2018	Big data on a big new market: Insights from a Washington State's legal cannabis market	USA	35 million transactions	Recreational
Cruz et al.[139]	2018	The status of support for cannabis regulation in Uruguay 4 years after reform: Evidence from public opinion surveys	Uruguay	3005	Both
D'Amico et al.[130]	2018	Planting the seed for marijuana use: Changes in exposure to medical marijuana advertising and subsequent adolescent marijuana use, cognitions, and consequences over seven years	USA		Both
Daniulaityte et al.[135]	2018	A Twitter-based survey on marijuana concentrate use	USA	687 cannabis users	Both
Grucza et al.[306]	2018	Cannabis decriminalisation- A study of recent policy change in five US states	USA	2007 -2015	Decriminalisation
Harpin et al.[131]	2018	Adolescent marijuana use and perceived ease of access before and after recreational marijuana implementation in Colorado	USA	2013 n=12,240 2014 n=11,931	Recreational
Jones et al.[307]	2018	The impact of the legalisation of recreational marijuana on college students	USA	1413	Recreational
Parnes et al.[133]	2018	A burning problem: cannabis lessons learned from Colorado	USA	Not applicable	Recreational
Amiri et al.[165]	2019	Availability of licensed cannabis businesses in relation to area deprivation in Washington State: A spatiotemporal analysis of cannabis business presence between 2014 and 2017.	USA		Recreational
Anderson et al.[308]	2019	Association of marijuana laws with teen marijuana use: New estimates from the Youth Risk Behaviour Surveys.	USA		Both
Aydelotte et al.[309]	2019	Fatal crashes in the 5 years after recreational marijuana legalization in Colorado and Washington	USA	11.3 million	Recreational

Author	Publication Year	Title	Countries Involved	Participants (if relevant)	Medical/Recreational/Both Legislation (if described)
Chu & Townsend[166]	2019	Joint culpability: The effects of medical marijuana laws on crime	USA	Population	Recreational
Chung et al.[173]	2019	The impact of recreational marijuana commercialization on traumatic injury	USA	40951	Recreational
Eichelberger[157]	2019	Marijuana use and driving in Washington State Risk perceptions and behaviours before and after implementation of retail sale	USA	2355 drivers	Recreational
Everson et al.[310]	2019	Post-legalization opening of retail cannabis stores and adult cannabis use in Washington State, 2009-2016.	USA		Recreational
Firth et al.[153]	2019	Did marijuana legalization in Washington State reduce racial disparities in adult marijuana arrests?	USA	National Incident Based Reporting System data	Recreational
Garcia-Ramirez et al.[311]	2019	Retail availability of marijuana in Oregon counties and co-use of alcohol and marijuana and related beliefs among adolescents	USA		Recreational
Gnofam et al.[175]	2019	Impact of legalization on prevalence of maternal marijuana use and obstetrical outcomes	USA	2392	Recreational
Hao & Cowan[161]	2019	The cross-border spill over effects of recreational marijuana legalization	USA	The whole state and surrounding areas	Recreational
Jones et al.[158]	2019	Marijuana and alcohol use among injured drivers evaluated at level I trauma centres in Arizona, 2008–2014	USA	30,083 Drivers	Medical
Klassen, & Anthony[312]	2019	The effects of recreational cannabis legalization on forest management and conservation efforts in U.S. national forests in the Pacific Northwest	USA		Recreational
Levine et al.[174]	2019	Prevalence of marijuana use among trauma patients before and after medical marijuana became legal	USA	n=5573	Medical

Author	Publication Year	Title	Countries Involved	Participants (if relevant)	Medical/Recreational/Both Legislation (if described)
Lo et al.[180]	2019	Cannabis legalization does not influence patient compliance with opioid therapy	USA	"High-risk," chronic pain drug testing panel that was completed with pathologist interpretation and consultation.	Recreational
Lu et al.[167]	2019	The cannabis effect on crime: Time-series analysis of crime in Colorado and Washington State	USA		Recreational
Makin et al.[168]	2019	Marijuana legalization and crime clearance rates: Testing proponent assertions in Colorado and Washington State.	USA		Recreational
Melchior et al.[150]	2019	Does liberalisation of cannabis policy influence levels of use in adolescents and young adults? A systematic review and meta-analysis.	USA	n=336 to n>11,703,100	Both
Nelson & Tarshis[169]	2019	Legalized marijuana in California: Prevalence of cannabis use in new patients now that cannabis is legal	USA	Not stated	Recreational
Nemer et al.[313]	2019	Severe acute pancreatitis incidence and outcomes after cannabis legalization in two states	USA		Recreational
Nicksic et al.[314]	2019	Cannabis legalization, tobacco prevention policies, and Cannabis use in E-cigarettes among youth	USA	2016 and 2017 National Youth Tobacco Survey	Both
Stormshak et al.[151]	2019	The impact of recreational marijuana legalization on rates of use and behaviour: A 10-year comparison of two cohorts from high school to young adulthood.	USA	1468	Recreational
Ward et al.[162]	2019	The impact of marijuana legalization on law enforcement in States surrounding Colorado	USA	228 police departments (33% response rate)	Recreational
Wen et al.[125]	2019	The effect of medical marijuana laws on marijuana-related attitude and perception among US adolescents and young adults	USA		Medical
Wen et al.[126]	2019	Addendum to "The effect of medical marijuana laws on marijuana-related attitude and perception among US adolescents and young adults"	USA		Medical

7.5 Supplement 4: Examples of supporting quotes for each domain (Legislative review)

7.5.1 Normalisation

1. *"Within Washington, the rate of perceived harmfulness of marijuana use decreased and the rate of past-month use increased among eighth and 10th graders following passage of RML…"*[122(p146)]

2. *"We also found that the implementation of MMLs was associated with an increase in the probability that young adults perceived no/low health risk related to marijuana use from 41.20% to 45.92% points."*[125(p221)]

3. *"In contrast, Colorado did not exhibit any change in perceived harmfulness or past-month adolescent marijuana use following RML enactment."* [122(p146)]

4. *"They found no differences in rates of change in cannabis use, or in the perceived risks of cannabis use, between states that allowed medical marijuana and those that did not."*[127(p609)]

5. *"Perceived riskiness of marijuana use in states in the years prior to passing MML was 30.5%, not significantly different than states that already passed laws (30.9%, p= 0.58) but significantly lower than states without MML (35.7%, p < .0001)."*[124(p715)]

6. *"Providers observed that legalization has validated cannabis use, encouraged its consumption, and reinforced misperceptions in both adolescents and other members of the community about the potential dangers of the substance."*[123(p69)]

7. *"Important aspects mentioned were the legitimacy bestowed on using cannabis as medicine, as well as gaining a sense of security, protection, and alleviation of related stress and stigma."*[128(p502)]

8. "*Participants noted a common belief by adolescents and adult clients alike that cannabis is healthy."* [123(p69)]

9. *"Thus, youth who reported seeing any ads for medical marijuana were twice as likely as youth who reported never seeing an ad to use marijuana and to report higher intentions to use marijuana 1 year later."*[129(p615)]

10. *"Adolescents that reported higher than average exposure to MM ads also tended to report greater marijuana use, stronger intentions to use marijuana in the future, stronger positive expectancies about marijuana use, and more negative consequences from use."*[130(p389)]

11. *"Perceived ease of access to marijuana significantly increased from 2013 to 2014 (46.5% to 52.1%, p<0.0001)…. The presence of recreational marijuana store(s) was not associated with perceived easy access to marijuana…."*[131(p453)]

12. *"Public perception of the low risk of marijuana [21] is discordant with available evidence."*[132(p2)]

13. *"Despite risks, many cannabis users do not perceive DUIC as a major risk, especially compared to drunk driving."*[133(p7)]

14. *"Edibles can pose health risks to consumers unfamiliar with their delayed effects, but they provide a smokefree mechanism of ingestion."*[134(p76)]

15. *"Cannabis-infused edibles have become popular in states with legal cannabis markets. In conjunction, reports of unintended accidents surrounding their use have arisen."* [133(p4)]

16. *"Many THC-infused candies purposefully mimic common non-intoxicating candies (MacCoun & Mello 2015)."* [133(p4)]

17. *"Use of e-cannabis has reached high school students, with approximately 5.4% having tried it (18.4% of cannabis users) (Morean et al. 2015)."* [133(p5)]

18. *"Our results show that odds of marijuana concentrate use were greater for those living in the states that have more liberal marijuana policies."*[135(p157)]

19. *"Odds of daily/near daily concentrate use were also significantly greater for users in recreational cannabis use states."* [135(p157)]

20. *"In 2007, the highest THC concentration found in 'dabs' was almost 53%, with the national average around 25% (Brenneisen 2007; RMHIDT 2015). By 2013, average hash oil in US had reached approximately 53% THC. More recent hash oil studies have found concentrations over 75%, with new extraction methods boasting concentrations as high as 90% THC (Raber et al. 2015; Prichard 2015)."* [133(p4)]

21. *"Almost 60% of respondents reported ever using marijuana concentrates for therapeutic purposes, most commonly for pain and sleep disturbances. Therapeutic use was also strongly linked with greater likelihood of daily/near daily use of concentrates. Prior research has also noted increased frequency of cannabis use among therapeutic users compared to non-therapeutic users (Lankenau et al., 2017; Walsh et al., 2013)."* [135(p158)]

22. *"One Web-based study used craiglsist.com to recruit a U.S.-based sample of 357 marijuana concentrate users and found that users viewed concentrates as significantly more dangerous than other forms of cannabis (Loflin and Earleywine, 2014)."* [135(p156)]

23. *"One prominent trend observed by Smart et al. (2017) is the in-creasing market share of extracts for inhalation (hereinafter "extracts"), which differs somewhat from what Daniulaityte et al. (2015) reports for the early years of Colorado's market."* [136(p87)]

7.5.2 Economics

24. *"Medical marijuana registration fees are likely to be offset by lower tax rates paid for medical marijuana, compared to higher taxed recreational marijuana. Medical marijuana is subject to state and local sales taxes, but recreational marijuana is also subject to a 15% excise tax and a special state sales tax rate of 10%."* [137(p13)]

25. *"The final rate a medical marijuana ID holder pays for medical marijuana in Denver is 7.65%, compared to the total tax rate of 36.15% on recreational sales."* [137(p13)]

26. *"Another state policy decision was to invest marijuana tax revenue in social market research, to maximise health messaging impacts…"*[138(p5)]

27. *"Prices in Washington have already fallen significantly (Humphreys, 2016), which can have significant public health consequences."*[134(p78)]

28. *"Prices declined rapidly until the summer of 2015 for all categories of extract products, and afterwards continued declining but at slower rates. Prices in the cartridge and oil categories fell the most even though their average potency increased steadily from 50% to closer to 75%, whereas potency for the other two categories peaked and then decreased slightly, albeit at quite different levels."*[136(p88)]

29. *"Price responsiveness can vary by group. For example, Williams (2004) find that youth are more sensitive to price, and Pacula and Lundberg (2013) report that the evidence, though thin, suggests that falling prices increase not only the prevalence of use but also its intensity, with regular users being more price sensitive than occasional users."*[136(89)]

30. *"The regulatory systems in both states unwittingly provide incentives to increase the THC content of cannabis products. Because cannabis is taxed on weight, anything that increases THC content effectively reduces the rate of tax*."[127(p611)]

31. *"In 2016, 24% of college students reported obtaining their cannabis from black market purchases, up from 18% in 2015 (RMHIDT 2015)."* [133(p5)]

32. *"The same study indicates, however, that by the time the new regulations were implemented, 66% of users were still obtaining cannabis from illegal retailers."*[139(pS430)]

33. *"With the government's supply and licenses to produce being the only legal options for authorized persons, these results indicate that 86% of medical users obtain their cannabis from illegal sources."*[128(p503)]

34. *"The expense of the product at the dispensary and perceived ease of extraction entices people to make their own BHO, often in an unsafe way."*[140(p424)]

35. *"In either case, however, states with legal markets may supply the illegal market outside the state, as California, Washington, and Colorado already do (DEA 2014; Rocky Mountain HIDTA 2015)."*[134(p75)]

36. *"Although the process of marijuana regulation in Uruguay has been gradually implemented, the persistence of illegal trafficking and the problems with pharmacy retail [9,12] have raised concerns about the helpfulness of cannabis legislation."*[139(pS433)]

37. *"The state found that decriminalization had turned a $332,600 governmental expense into a $16,900 profit, and "substantially improved the quality and uniformity of justice administered to marijuana possession defendants in Maine."*[141(p318)]

7.5.3 Gatekeeping

38. *"Comparison of states with these laws shows that states with CBD based laws have a decreased association with eventual passage of recreational marijuana laws compared with states without CBD based laws (p=.037)."*[142(p810)]

39. *"States with medical marijuana laws that are not CBD specific and do not limit the concentration of THC are associated with an increased likelihood of eventual passage of recreational marijuana statutes."* [142(p810)]

40. *"Both Washington and Colorado significantly modified marijuana regulation during the first year of implementation."*[134(p82)]

41. *"Probably the most important lesson they have to take to heart is that legal reform of the cannabis situation should be comprehensive, regulating sales to consumers, wholesale supply, and cultivation so that the results of novel cannabis policies are accountable against clearly stated aims and goals – a desirable state of the art which the cannabis policies analysed in this paper still largely fail to achieve."*[143(p309)]

42. *"The most reported reason for not applying to the programme was that respondents found the process too*

onerous, complicated, or intimidating. There were 18 references to 'red tape' and paperwork, and those who plainly stated it was too much of a hassle."[128(p503)]

43. *"Patient growth has accelerated with the advent of what might be called a new medical specialty, a small cluster of physicians whose practice is largely or exclusively devoted to assessing the eligibility of individuals who sought medical marijuana."Statewide, more than 70% of doctors recommendations were written by fewer than 15 physicians" in Colorado, and severe or chronic pain, a catchall category, accounted for ninety-four percent of all reported conditions."*[145(p130)]

44. *"In an update through the end of January 2011, the CDPHE found that of the approved medical marijuana registrations, 49 percent had been signed by one of fifteen physicians, and 10 percent of all registration forms in the state had been signed by a single physician, as illustrated in Figure 6."*[146(p6)]

45. *"Many applicants were charged by their physician for the service of having their application completed, with charges ranging from $10 to $800."*[100(p696)]

46. *"... with a physician might have a negative impact on their patient/physician relationship: "fear of getting no treatment at all"; "fear of losing my doctor"; "I am afraid they will black list me as a patient and I would not have access to health care!"* [100(p697)]

47. *"Only 2% of respondents were ordering their cannabis supply from the government. Very few others had ever sampled the government supply. Thus perceptions were formed largely based on second-hand assessments that convey little faith in the quality of product or credentials of the relevant authorities."*[128(p504)]

48. *"Although less expensive than the cost on the black market, some still found this too pricy and resented that sick people are being charged to take part in a tax-supported programme."* [128(p505)]

49. *"The upfront ID costs combined with the delay from prerequisite doctor visits are deterrents to medical marijuana customers who find the recreational marijuana market to be the easier alternative."*[137(p12)]

50. *"Among those who said they would definitely or probably register, the preferred method of accessing cannabis*

was through pharmacies (56%), followed by growing their own plants (30%) and cannabis clubs (13%).”[147(p39)]

7.5.4 Community

51. *“Policy related attitudes about medical legalization likely have not had an impact on drug use behaviour because, these variables, together or separately, are not well matched or explicitly linked to youth recreational marijuana use, and therefore did not alter recreational use norms and behavior.”*[149(p762)]

52. *“Virtually all studies based on these four surveys suggest no effect of MMLs on prevalence of adolescent use (Table 2). Collectively, these studies included millions of participants, and data from the years 1991–2014. The only study to find a slight increase in use used incorrect statistical methodology (Stolzenberg et al., 2016; Wall et al., 2016).”*[148(p18)]

53. *“Longitudinal analyses controlling for a statistically significant decreasing trend in marijuana use from 2002-2008 (β=-0.35, t-value= -15.9, p-value <0.0001) found that among the 8 states that passed MML since 2004, the prevalence of use in the years prior to passing the laws was 8.88%, not significantly different (p = 0.25) than states that had already passed laws (8.58%), but significantly higher than the prevalence for states without MML by 2011 (6.94%, p <.0001).*[124(p715)]

54. *“The study showed that since 1991, rates of adolescent cannabis use were higher in MML- than non-MML states prior to law passage. However, importantly, no post-MML increases were observed in MML states, either in the primary analyses or in over fifty sensitivity analyses.”*[148(p18)]

55. *“In contrast, Colorado did not exhibit any change in perceived harmfulness or past-month adolescent marijuana use following RML enactment.”*[122(p146)]

56. *“The public health impact of legalization, based on these findings, is that more young adults are using marijuana but in a pattern of usage similar to that used by those 10 years ago, which nonetheless suggests a higher base rate of daily use within the population.”*[151(p6)]

57. *“…high quality reports examining the impact of cannabis decriminalisation (n=4) show no statistically*

significant change in youths' patterns of use. Similarly, the legalisation of cannabis use for medical purposes, extensively evaluated in the USA, does not appear to have an effect: six studies suggest no change in cannabis use among youths, three observe a decrease and four studies report an increase. However, the legalisation of cannabis for recreational purposes, examined in six studies with a very low or low risk of bias, may be associated with a small increase in levels of use among youths."[150(p9)]

58. *"In Washington, marijuana use among eighth and 10th graders increased by 2.0% and 4.1%, respectively, during this time. In contrast, marijuana use prevalence among eighth and 10th graders in states with no RML decreased by 1.3% and 0.9%, respectively, over the same period."*[124(p1445)]

59. *"In Colorado, authorities have found evidence of diversion of medical marijuana to adolescents."*[152(p684)]

60. *"They reported that adolescents are accessing diverted medical and retail cannabis."*[123(p69)]

61. *"According to participants, greater access to a variety of novel and more potent THC products has increased the potential for dependency among adolescent users."*[123(p69)]

62. *Currently, Black individuals are three times more likely to be arrested for a cannabis-related offense than White individuals in Colorado (Reed 2016). Yet, when examining Colorado use rates, Black individuals report only slightly higher use (19.2%) in the past month compared to Whites (14.1%), and make up significantly less of the population (72.3% White, 3.8% Black; Reed 2016). This troubling inconsistency brings into question the unequal enforcement of cannabis laws, with minority individuals continuing to be disproportionately subjected to repercussions."*[133(p8)]

63. *"Whites and blacks in the United States consume cannabis at similar rates, yet the arrest, sentencing, and imprisonment rates diverge greatly based on race (American Civil Liberties Union, 2013, p. 21)."*[154(p213)]

64. *"Marijuana arrest rates for African Americans 21+ years old dropped after legalization of possession and the absolute disparities decreased, but the relative disparities grew: from a rate 2.5 times higher than Whites to 5 times higher after the retail market opened. For underage adults marijuana arrest rates for African Americans*

dropped after legalization of possession and absolute disparities decreased, but remained nearly twice as high for Whites."[153(p1584)]

65. *"After 40 years of impoverished black men getting prison time for selling weed, white men are planning to get rich doing the same things."*[154(p211)]

66. *"While one may have had experience working with marijuana in the black market, and subsequently received a felony, they are now banned from the industry that prefers workers with experience only as long as legalization has been in place."* [154(p216)]

67. *"Washington, DC bans individuals with felony convictions and drug misdemeanours specifically, but not other misdemeanours (Initiative Measure No. 71, 2014). Therefore, individuals with drug misdemeanours are barred from the industry over those with misdemeanours potentially involving violent crimes or theft."* [154(p216)]

68. *"However, in Colorado, a drug felon is allowed to work in the industry five years post-conviction if their conviction would not be a crime under current law."* [154(p217)]

69. *"Partially in response to this failure to act and because of the racial/ethnic disparity in cannabis convictions, the City of Spokane has begun allowing residents to apply for their past misdemeanour convictions to be vacated (Brunt, 2015)."*[155(p100)]

70. *"Legal scholars argue that by not providing retroactive relief, it increasing the financial costs of continuing to imprison these inmates, the social costs of continued disruption to the family, and lost income (Mitchell, 2009, p. 15)."* [154(p221)]

71. *"Even with legalization, the marijuana consumption and amount limitations will continue to impact the most vulnerable community members. Including retroactive ameliorative relief language in marijuana legalization laws is an important progressive step towards righting these injustices."* [154(p222)]

72. *"Li and colleagues (Li et al. 2012) found that drivers who drove under the influence of cannabis were more than twice as likely as other drivers to be involved in motor vehicle crashes (odds ratio=2.66)."*[133(p7)]

73. *"In 2009–2012, the average yearly percentage of cases positive for THC and carboxy-THC was 19.1% (range: 18.2–20.2%) and 27.9% (range: 26.3–28.6%), respectively. In 2013, the percentages had significantly increased to 24.9 and 40.0%, respectively (P < 0.05)."*[156(p569)]

74. *"State Patrol data for the first 10 months of 2016 show that DUI's where marijuana was noted as an impairing substance were 16% higher than the same period in 2014 (Colorado State Patrol, 2016)."*[138(p5)]

75. *"Data from Washington and Colorado show that increases in positive tests for marijuana are associated with higher rates of traffic accidents and driving infractions. However, it is difficult to determine whether the rise in drugged driving detection is the result of increased access to marijuana, more people using marijuana, or simply stepped-up law enforcement."*[134(p80)]

76. *"Interrupted time series analysis revealed a small but statistically significant annual increase in the proportion of all injured drivers who tested positive for marijuana after medical marijuana was legalized in Arizona compared with what would have been expected without legalization…this association is not equal to causation…might also be partially explained by changes in testing after legalization."*[158(p4)]

77. *"In Colorado, while DUICs decreased by 1% from 2014 to 2015, there was a 12% increase in concurrent cannabis use among all driving under the influence (DUI) arrests (Reed 2016)."*[133(p7)]

78. *"From 2012 to 2013, positive workplace cannabis drug tests increased by 6.2% nationwide and 20% in Colorado (Quest Diagnostics 2014)."*[133(p7)]

79. *"For example, using blood testing instead of urine testing is a more proximal approximation of intoxication and may help differentiate currently intoxicated workers from those who recently used (Phillips et al. 2015). Additionally, understanding dose-dependent effects may help establish better workplace safety guidelines, particularly for those medicating with cannabis."*[133(p7)]

80. *"Results for full-time workers can be seen in columns (5)–(7). Specifically, age groups 30–39, 40–49, and 50–59 are 16, 11 and 13% less likely report absences due to illness/medical issues after MML. These results are*

significant at the 1, 10 and 1% level, respectively."[159(p1325)]

81. *"Availability to other states has also increased since legalization. From 2010 to 2014, the number of seized packages shipped from Colorado to another state containing cannabis ballooned from 15 to 320 per year (RMHIDT 2015)."*[133(p5)]

82. *"In either case, however, states with legal markets may supply the illegal market outside the state, as California, Washington, and Colorado already do (DEA 2014; Rocky Mountain HIDTA 2015)."*[134(p75)]

83. *"In short, we found that border counties, but not necessarily those along the I-80 corridor, experienced a significant growth in marijuana related arrests and jail admissions after the expansion of the medical marijuana program in Colorado."*[160(p847)]

84. *"Respondents noted that legal marijuana from Colorado has put a strain on their resources and have led to an increased in trafficking concerns for many agencies."*[162(p231)]

85. *"It might also be useful to consider whether law enforcement has actively pursued marijuana offenders (e.g., roadside checkpoints) or been more reactive (e.g., typical patrol) subsequent to legalization in neighbouring states, and examine the extent to which these orientations may influence reported rates of marijuana activity."*[160(p862)]

86. *"We find that RML causes a sharp increase in marijuana possession arrests in border counties near both Colorado and Washington relative to non-border counties, suggesting a strong spill over effects of marijuana legalization…findings suggest that an increase in marijuana possession and use is partially responsible for our arrest results. We also provide evidence suggesting that intentional police targeting may also contribute to the increase in arrests…"*[161(p23)]

87. *"As of June 30, 2016, 30% of the state population lived in places that had temporarily or permanently banned retail sales. Communities most frequently enacted zoning policies explicitly regulating where marijuana businesses could be established. Other policies included in ordinances placed limits on business hours and distance requirements (buffers) between marijuana businesses and youth-related land use types or other*

sensitive areas."[164(p102)]

88. *"The findings of this study revealed that most-deprived areas had increased likelihood of cannabis producer and processor density when compared to least-deprived areas."*[165(p796)]

89. *"The national-level estimates averaged across medical marijuana states are close to zero, as are state specific estimates in most medical marijuana states, though California shows about a 20% reduction in both violent and property crimes."*[166(p517)]

90. *"Our results suggest that cannabis laws more broadly, and the legalization of recreational marijuana more specifically, have had minimal effect on major crime in Colorado or Washington State."* [167(p520)]

91. *"There were some immediate increases in crime at the point of legalization, but these did not result in long-term effects."* [167(p20)]

92. *"While our research does not model changes on crime, our results suggest that, just as marijuana legalization proponents argued, the legalization of marijuana influenced police outcomes, which in the context of this article is modelled as improvements in clearance rates."*[168(p47)]

7.5.5 Health

93. *"The odds of marijuana use in the past year were 1.92 times higher (95% confidence interval (95% CI): 1.49,2.47; p<0.0001) among residents of states with rather than without medical marijuana laws…. The odds of marijuana abuse/dependence were 1.81 times higher (95% CI: 1.22,2.67; P=0040) among residents of states that had legalized marijuana."*[170(p24)]

94. *"For adolescents (age 13-18 years), the use was reported 43 of 213 (20.2%) intakes in 2017, 128 of 478(26.8%) intakes in 2018, and 66 of 190(34.7%) intakes in 2019 (X^2=10.8, p<0.01)."*[169(pS168)]

95. *"The three available studies comparing adult prevalence of cannabis use and cannabis use disorders before and*

after passage of medical marijuana laws (Hasin et al., 2017d; Martins et al., 2016; Wen et al., 2015) are consistent in suggesting a causal relationship between the passage of medical marijuana laws and subsequent increases in adult cannabis use and cannabis use disorders."[148(p21)]

96. *"The primary challenge reported was client resistance to treatment. According to observations by study participants, adolescents reference state recreational and medical laws to justify their desire and perceived right or need to consume cannabis products. The adolescents also minimize the underlying problems, risks, and consequences related to their use. Providers reported that the misperceptions adolescents have about cannabis were also shared by adults; such as the belief that cannabis is harmless."*[123(p71)]

97. *"According to participants, greater access to a variety of novel and more potent THC products has increased the potential for dependency among adolescent users."* [123(p71)]

98. *"These include edibles like brownies, gummies, sodas, and concentrated forms including oils, wax, and shatter—some of which can reach nearly 95% THC."* [123(p69)]

99. *"They are also feeling overwhelmed due to an increased treatment need both in quantity and acuity of adolescent patients. As a result, they have fewer resources to devote to policy change."* [123(p71)]

100. *"The majority of providers also described the need to expand substance misuse treatment services in response to the increasing demand resulting from changing cannabis laws."* [123(p71)]

101. *"In the first partially adjusted model (Model 1), similar to the prior report (Anderson et al., 2014), the overall association between medical marijuana policy and suicide risk suggested a statistically significant protective effect (OR= 0.956; 95% CI: 0.923, 0.992; p= 0.02), particularly among men (OR= 0.956; 95% CI: 0.929, 0.984; p= 0.002)."*[171(p70)]

102. *"In the fully adjusted Model 3, the associations between medical marijuana policy and suicide risk among the twelve age-by-sex groups were non-significant with only one exception: men over 60 (OR= 1.04; 95% CI: 1.005, 1.105; p= 0.04)."* [171(p70)]

103. *"We showed that adoption of medical marijuana policy was associated with shifts toward populations that were older and higher in percentages of minorities and women (Table S5, see Supplemental Material), which is problematic because minorities and women have much lower suicide rates than whites and men, respectively (Centres for Disease Control and Prevention (CDC), 2013; Crosby et al., 2011)."* [171(p70)]

104. *"Instead, it appears that medical marijuana legalization is correlated with changes in other factors that contribute to suicide risk, such as the demographic makeup of states and tobacco control policies."* [171(p71)]

105. *"Fatalities where the driver tested positive for cannabinoids increased by 80% between 2013 (55) and 2015 (99) (Colorado Department of Transportation, 2016). Of cannabinoid positive incidents, 42% included alcohol in 2013 and 35% in 2015. Changes in testing practices might contribute to these increases. Additionally, fatality data do not indicate whether the driver was impaired or at fault."* [138(p5)]

106. *"For those over the age of 65, the effect is large and significant. They suggest that there are nearly 30 additional cardiac deaths for men in this age group following MCL implementation."* [172(p4)]

107. *"Our study finds evidence suggesting that MCL was followed by increased cardiac mortality in states passing such laws compared with those that do not. This effect was concentrated among older individuals, particularly males, and states where there are less restrictions on dispensaries and cardholders".* [172(p5)]

108. *"Finally, there have been four high profile deaths related to injuries or violence post-edible use (Ghosh et al., 2015a). These have spurred significant policy changes related to edible packaging. However, monitoring for marijuana-related deaths remains challenging. Death certificates listing marijuana do not necessarily indicate that marijuana was causal, and useful surveillance depends on reporting practices by coroners, medical examiners, and law enforcement."* [138(p5)]

109. *"The results of our study demonstrate that in the two years after recreational marijuana was commercialized in Colorado in 2014, there was an increasing rate of detecting marijuana for patients presenting to Colorado hospitals with traumatic injury, relative to the pre-commercialization period."* [173(p4)]

110. *"The odds ratio of being marijuana positive between post-legalization vs pre-legalization (periods 2 and 3 vs 1) was 1.38 (95% CI 1.11-1.72, p=0.004)…Legalization of medical marijuana is associated with increased use among male trauma patients."*[174(p79)]

111. *"The call rate in non-legal states to poison centres did not change from 2005 to 2011 (1.5% calls per year; 95% CI –3.5% to 6.7%). The call rate in decriminalized states increased by 30.3% calls per year (95% CI 22.5% to 38.5%), with a difference between non-legal and decriminalized state rates of 28.3% (95% CI 19.0% to 38.4%)."*[152(p686)]

112. *"Although there was no long-term morbidity or mortality, a greater proportion of patients in decriminalized states had moderate to major clinical effects and critical care admissions, which may be due to unfamiliarity with the exposure, limited resources, or greater potency of the marijuana. As more states pass legislation to decriminalize medical and recreational marijuana, we expect the rate of marijuana exposures in young children to continue to increase."* [152(p687)]

113. *"In the original law decriminalizing medical marijuana, there were no strict provisions for child-resistant packaging, warning labels, or consumer or health care provider education. After 2009, there was an increase in symptomatic, unintentional paediatric exposures in a children's hospital in Colorado.12 After hearing testimony about the risks to small children, Colorado lawmakers included a requirement for child-resistant packaging for recreational marijuana in 2013."* [152(p688)]

114. *"These edible products are often indistinguishable from non–marijuana containing food products, are highly attractive and palatable to children, and can contain very high amounts of tetrahydrocannabinol (100 to 500 mg)."* [152(p688)]

115. *"The prevalence of prenatal marijuana use trended significantly higher over the time of legalization in Colorado."*[175(pS239)]

116. *"The University of Colorado Burn Centre experienced a dramatic increase in flash burns associated with BHO production following the liberalization of marijuana policy."*[140(p424)]

117. *"Zero cases presented prior to medical liberalization, 19 (61.3 %) during medical liberalization (Oct 2009–Dec 2013), and 12 (38.7 %) in 2014 since legalization."* [140(p422)]

118. *"Only 2 patients were admitted after butane explosion in the 24 months prior to December 2012; however, 9 of the 11 (82%) injuries occurred in only 7 months after legislation passed in December 2012 legalizing marijuana for recreational use."* [176(pS112)]

119. *"There are also several reports of individuals hospitalized or dead due to butane explosions while making hash oil in their homes (e.g. Risling 2013; Damuzi 2004)."* [133(p6)]

120. *"Contamination issues arise for each method of consumption (e.g. smoked, eaten, concentrated). For example, in 2015 three Colorado companies recalled over 30,000 edibles due to pesticide contamination (Baca & Migoya 2015b). The companies blamed dishonest suppliers, which may implicate a larger issue regarding growing regulations and oversight of the cannabis growing industry."* [133(p6)]

121. *"Potencies for edibles, infused mixes, and topicals are not reported because of concerns that not all stores may have been entering potency for those products in a consistent manner."* [136]

122. *"Such products generally have 60–85% THC content (Russo, 2016), which is significantly greater than cannabis plant material, which typically contains 10–12% THC content (ElSohly et al., 2016)."* [135(p155)]

123. *"Approximately one third of self-producers reported that it was difficult or very difficult to learn to cultivate cannabis."* [100(p694)]

124. *"Equipment, supplies, electricity and other costs are not covered; nor are they tax deductible expenses. The hard work that is needed to maintain a garden is particularly difficult in times of poor health."* [128(p504)]

125. *"Novel growers may be uninformed and not know which pesticides to use and how to prevent bacterial or mould growth (Martyny et al. 2013)."* [133(p6)]

126. *"Contamination with various chemicals, such as butane or pesticides, remain a central concern for hash oil production (Raber et al. 2015)."* [133(p6)]

127. *"Colorado cannabis-related emergency room (ER) visits (29%) and hospitalizations (38%) both rose in 2014, the year retail cannabis became available (RMHIDT 2015). Most ER visits were due to anxious reactions to the drug, typically following consumption of a large amount of THC (Hesse 2016)."* [133(p6)]

128. *"The prevalence of cyclic vomiting visits increased from 41 per 113,262 ED visits to 87 per 125,095 ED visits after marijuana liberalization, corresponding to a prevalence ratio of 1.92 (95% confidence interval [CI] = 1.33 to 2.79). Patients with cyclic vomiting in the post liberalization period were more likely to have marijuana use documented than patients in the pre liberalization period (odds ratio = 3.59, 95% CI = 1.44 to 9.00)."* [177(p694)]

129. *"Studies in Los Angeles, for example, showed a relationship between medical marijuana dispensaries and rising marijuana-related hospitalizations (Mair, Freisthler, Ponicki, & Gaidus, 2015)."* [134(p80)]

130. *"Cannabis-related hospitalization incidence rates show an increasing trend in slope before and after legalization. The slope becomes more abrupt following legalization. A reduced segmented (AR1) regression model show a significant increase in trend during the post legalization period (β= 1.8353, SE= 0.2182, p< 0.0001)."* [178(pS361)]

131. *"These results suggest that legalization of recreational cannabis does not impact opioid compliance in the overall population, but may improve compliance in certain groups."* [180(pS352)]

132. *"Using data on all prescriptions filled by Medicare Part D enrolees in the United States from 2010 to 2015, we find that the use of prescription drugs for which cannabis could serve as a clinical alternative fell significantly once a medical cannabis law (MCL) was put in place."* [179(p461)]

133. *"We find that MCLs appear to have the effect of shifting urban patients away from pain medication-and opioid-use and so likely help address the opioid death epidemic there, but these benefits are not shared by rural patients."* [179(p482)]

7.6 Supplement 5: Hawker domain grading for included papers (Legislative review)

First Author	Publication Year	Title	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data Analysis	Ethics and Bias	Results	Transferability or Generalisability	Implications and usefulness	Overall Rating
Maloff[141]	1981	A review of the effects of the decriminalisation of marijuana	Very Poor	Poor	Very Poor	Poor	Fair	Fair	Good	Good	Fair	Fair
Suggs[284]	1981	A qualitative and quantitative analysis of the impact of Nebraska's decriminalisation of marijuana	Very Poor	Fair	Good	Poor	Good	Fair	Good	Good	Good	Good
Abel[186]	1997	Cannabis policy in Australia and New Zealand	Fair	Fair	Not applicable	Not applicable	Poor	Not applicable	Fair	Fair	Poor	Poor
MacCoun[285]	2001	Evaluating alternative cannabis regimes	Fair	Good	Very Poor	Not applicable	Poor	Not applicable	Poor	Good	Fair	Fair
Garmaise[144]	2002	Canadian News. Physicians dislike new medical marijuana regulations	Very Poor	Very Poor	Very Poor	Very Poor	Very Poor	Very Poor	Very Poor	Very Poor	Poor	Poor
Khatapoush[149]	2004	Sending the wrong message: Did medical marijuana legalisation in California change attitudes about use of Marijuana	Fair	Good	Good	Fair	Fair	Fair	Good	Good	Good	Good
Belle-Isle[128]	2007	Barriers to access to medical cannabis for Canadians living with HIV/AIDS	Fair	Fair	Fair	Poor	Fair	Fair	Good	Poor	Fair	Fair
Nussbaum[146]	2011	Mile high macaroons: The medicalization of marijuana in Colorado	Fair	Not applicable	Very Poor	Very Poor	Very Poor	Not applicable	Poor	Fair	Fair	Poor
Wall[124]	2011	Adolescent marijuana use from 2002 to 2008: Higher in states with medical marijuana laws, cause still unclear	Good	Fair	Fair	Fair	Fair	Very Poor	Good	Fair	Fair	Fair

First Author	Publication Year	Title	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data Analysis	Ethics and Bias	Results	Transferability or Generalisability	Implications and usefulness	Overall Rating
Caplan[145]	2012	Medical marijuana: A study of unintended consequences	Not applicable	Fair	Not applicable	Not applicable	Not applicable	Not applicable	Poor	Good	Good	Poor
Cerdá[170]	2012	Medical marijuana laws in 50 states: Investigating the relationship between state legalization of medical marijuana and marijuana use, abuse and dependence	Good	Good	Good	Good	Good	Fair	Good	Fair	Good	Good
Adda[286]	2014	Crime and the depenalization of cannabis possession: Evidence from a policing experiment	Fair	Fair	Good	Good	Good	Fair	Fair	Good	Good	Good
Belle-Isle[100]	2014	Barriers to access for Canadians who use cannabis for therapeutic purposes	Good	Good	Fair	Poor	Good	Good	Good	Fair	Good	Good
Boyle[176]	2014	Butane hash oil manufacturing related burn injury: A disturbing trend	Good	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Very Poor
Couper[156]	2014	The prevalence of marijuana in suspected impaired driving cases in Washington State	Good	Good	Good	Good	Good	Not applicable	Fair	Fair	Good	Good
Wang[152]	2014	Association of unintentional paediatric exposures with decriminalisation of marijuana in the United States	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Williams[287]	2014	Does liberalizing cannabis laws increase cannabis use?	Good	Good	Good	Good	Fair	Not applicable	Good	Fair	Poor	Good
Běláčková[143]	2015	"Should I buy or should I grow?" How drug policy institutions and drug market transaction costs shape the decision to self-supply…	Good	Good	Good	Fair	Fair	Good	Good	Good	Good	Good

First Author	Publication Year	Title	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data Analysis	Ethics and Bias	Results	Transferability or Generalisability	Implications and usefulness	Overall Rating
Bell[140]	2015	Butane hash oil burns associated with marijuana liberalization in Colorado	Fair	Fair	Good	Good	Fair	Good	Good	Good	Good	Good
D'Amico[129]	2015	Gateway to curiosity: Medical marijuana ads and intention and use during middle school	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Grucza[171]	2015	A re-examination of medical marijuana policies in relation to suicide risk	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Hall[127]	2015	Assessing the public health impacts of legalizing recreational cannabis use in the USA	Fair	Fair	Not applicable	Not applicable	Not applicable	Fair	Good	Fair	Good	Fair
Kim[177]	2015	Cyclic vomiting presentations following marijuana liberalization in Colorado	Good	Fair	Good	Good	Good	Good	Good	Fair	Fair	Good
Pacula[288]	2015	Assessing the effects of medical marijuana laws on marijuana use: The devil is in the details	Fair	Good	Good	Good	Good	Fair	Good	Good	Good	Good
Sznitman[289]	2015	Cannabis for Therapeutic Purposes and public health and safety: A systematic and critical review	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Barry[132]	2016	A public health framework for legalized retail marijuana based on the US experience: Avoiding a new tobacco industry	Very Poor	Poor	Not applicable	Not applicable	Not applicable	Very Poor	Fair	Fair	Fair	Poor
Boidi[147]	2016	Cannabis consumption patterns among frequent consumers in Uruguay	Good	Poor	Good	Good	Fair	Poor	Good	Good	Good	Good

First Author	Publication Year	Title	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data Analysis	Ethics and Bias	Results	Transferability or Generalisability	Implications and usefulness	Overall Rating
Caulkins[290]	2016	Considering marijuana legalization carefully: insights for other jurisdictions from analysis for Vermont	Fair	Fair	Not applicable	Not applicable	Fair	Fair	Fair	Fair	Fair	Fair
Davis[291]	2016	Public health effects of medical marijuana legalization in Colorado	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Estoup[292]	2016	The impact of marijuana legalization on adolescent use, consequences, and perceived risk	Good	Good	Good	Fair	Fair	Not applicable	Good	Good	Fair	Good
Freisthler[293]	2016	A micro-temporal geospatial analysis or medical marijuana dispensaries and crime in Long Beach, California	Good	Good	Good	Fair	Good	Good	Good	Fair	Good	Good
Huber[294]	2016	Cannabis control and rime: Medicinal use, depenalization and the war on drugs	Fair	Fair	Good	Good	Good	Fair	Good	Good	Fair	Good
Jensen[155]	2016	Field observations of the developing legal recreational cannabis economy in Washington State	Good	Good	Not applicable	Not applicable	Not applicable	Poor	Fair	Fair	Fair	Fair
Keyes[295]	2016	How does state marijuana policy affect US youth? Medical marijuana laws, marijuana use and perceived harmfulness: 1991-2014	Good	Good	Good	Good	Good	Poor	Good	Good	Good	Good
Kim[296]	2016	Colorado cannabis legalization and its effect on emergency care	Very Poor	Poor	Fair	Fair	Fair	Very Poor	Fair	Poor	Poor	Fair

First Author	Publication Year	Title	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data Analysis	Ethics and Bias	Results	Transferability or Generalisability	Implications and usefulness	Overall Rating
Onders[297]	2016	Marijuana exposure among united States children younger than six years old	Poor	Poor	Fair	Poor	Fair	Very Poor	Good	Good	Fair	Fair
Schmidt[298]	2016	Young people's more permissive views about marijuana: Local impact of State laws or national trend?	Good	Good	Fair	Fair	Good	Good	Good	Good	Good	Good
Sobesky[123]	2016	Cannabis and adolescents: Exploring the substance misuse treatment provider experience in a climate of legalisation	Good	Fair	Fair	Good	Good	Good	Good	Good	Good	Good
Ullman[159]	2016	The effect of medical marijuana on sickness absence	Poor	Fair	Fair	Fair	Fair	Not applicable	Poor	Poor	Poor	Fair
Adam[299]	2017	Cannabis policy and the uptake of treatment for cannabis-related problems	Good	Good	Good	Good	Good	Fair	Fair	Good	Good	Good
Al-Shammari[300]	2017	Effects of the 2009 medical cannabinoid legalisation policy on the hospital use for cannabinoid dependency and persistent vomiting	Poor	Fair	Fair	Fair	Fair		Poor	Fair	Fair	Fair
Al-Shammari[301]	2017	US national trend analysis of cyclic vomiting incidence with liberalisation of cannabis use	Poor	Poor	Poor	Poor	Fair	Very Poor	Fair	Poor	Fair	Fair
Baggio[163]	2017	Is access to marijuana a disamenity?	Fair	Good	Fair	Not applicable	Fair	Not applicable	Good	Fair	Fair	Fair
Banerji[302]	2017	Marijuana and synthetic cannabinoid patterns in a US state with legalized marijuana: a 5-year NPDS review	Fair	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Fair	Fair	Fair	Poor

First Author	Publication Year	Title	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data Analysis	Ethics and Bias	Results	Transferability or Generalisability	Implications and usefulness	Overall Rating
Běláčková[303]	2017	Assessing the concordance between illicit drug laws on the books and drug law enforcement: Comparison of three states on the continuum form "decriminalised" to "punitive"	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Carliner[148]	2017	Cannabis use, attitudes and legal status in the US. A review	Good	Good	Good	Good	Fair	Very Poor	Good	Good	Good	Good
Carnevale[134]	2017	A practical framework for regulating for-profit recreational marijuana in US states: Lessons from Colorado and Washington	Good	Good	Not applicable	Not applicable	Not applicable	Poor	Good	Good	Good	Fair
Cerdá[122]	2017	Association of state recreational marijuana laws with adolescent marijuana use	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Cerveny[304]	2017	Cannabis decriminalisation and the age of onset of cannabis use	Good	Good	Fair	Good	Good	Good	Good	Fair	Fair	Good
Chhabra[142]	2017	Analysis of medical marijuana laws in states transitioning to recreational marijuana- a gateway drug policy?	Good	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Very Poor
Daniulaitye[305]	2017	Retweet to pass the blunt: Analyzing geographic and content features of cannabis-related tweeting across the United States	Good	Good	Good	Fair	Good	Good	Good	Good	Good	Good
Dilley[164]	2017	Community-level policy responses to state marijuana legalization in Washington State	Good	Fair	Good	Good	Good	Fair	Good	Fair	Fair	Good

First Author	Publication Year	Title	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data Analysis	Ethics and Bias	Results	Transferability or Generalisability	Implications and usefulness	Overall Rating
Ellison[160]	2017	Borders up in smoke: Marijuana enforcement in Nebraska after Colorado's legalization of medical marijuana	Fair	Good	Good	Good	Good	Good	Good	Good	Good	Good
Ghosh[138]	2017	Lessons learned after three years of legalized, recreational marijuana: the Colorado experience	Good	Good	Fair	Fair	Fair	Not applicable	Fair	Good	Good	Fair
Thompson[154]	2017	"Good moral characters:" how drug felons are impacted under state marijuana legalization laws	Fair	Good	Fair	Not applicable	Fair	Very Poor	Good	Fair	Good	Fair
Zhang[137]	2017	A review of the impact of marijuana's legalization on Colorado's industrial warehouse lease rates: how high is high?	Fair	Good	Fair	Poor	Poor	Very Poor	Good	Poor	Good	Good
Abouk[172]	2018	Examining the relationship between medical cannabis laws and cardiovascular deaths in the US	Good	Good	Good	Good	Good	Fair	Good	Good	Good	Good
Bradford[179]	2018	The impact of medical cannabis legalization on prescription medication use and costs under Medicare Part D	Good	Fair	Good	Good	Good	Fair	Good	Good	Good	Good
Calcaterra[178]	2018	The impact of legalisation of recreational marijuana on a safety-net health system	Fair	Fair	Good	Not applicable	Not applicable	Not applicable	Good	Fair	Fair	Fair
Caulkins[136]	2018	Big data on a big new market: Insights from a Washington State's legal cannabis market	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good

First Author	Publication Year	Title	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data Analysis	Ethics and Bias	Results	Transferability or Generalisability	Implications and usefulness	Overall Rating
Cruz[139]	2018	The status of support for cannabis regulation in Uruguay 4 years after reform: Evidence from public opinion surveys	Good	Fair	Fair	Good	Good	Good	Good	Fair	Good	Good
D'Amico[130]	2018	Planting the seed for marijuana use: Changes in exposure to medical marijuana advertising and subsequent adolescent marijuana use, cognitions, and consequences over seven years	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Daniulaitye[135]	2018	A Twitter-based survey on marijuana concentrate use	Good	Good	Good	Good	Good	Good	Good	Good	Fair	Good
Grucza[306]	2018	Cannabis decriminalisation- A study of recent policy change in five US states	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Harpin[131]	2018	Adolescent marijuana use and perceived ease of access before and after recreational marijuana implementation in Colorado	Good	Fair	Good	Fair	Good	Good	Good	Good	Good	Good
Jones[307]	2018	The impact of the legalisation of recreational marijuana on college students	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Parnes[133]	2018	A burning problem: cannabis lessons learned from Colorado	Fair	Good	Not applicable	Not applicable	Not applicable	Very Poor	Good	Good	Good	Fair
Amiri[165]	2019	Availability of licensed cannabis businesses in relation to area deprivation in Washington State: A spatiotemporal analysis of cannabis business presence between 2014 and 2017.	Good	Good	Good	Good	Good	Good	Good	Good	Fair	Good

First Author	Publication Year	Title	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data Analysis	Ethics and Bias	Results	Transferability or Generalisability	Implications and usefulness	Overall Rating
Anderson[308]	2019	Association of marijuana laws with teen marijuana use: New estimates from the Youth Risk Behaviour Surveys.	Not applicable	Fair	Fair	Very Poor	Fair	Very Poor	Fair	Fair	Fair	Fair
Aydelotte[309]	2019	Fatal crashes in the 5 years after recreational marijuana legalization in Colorado and Washington	Fair	Good	Fair	Good	Fair	Fair	Fair	Fair	Good	Good
Chu[166]	2019	Joint culpability: The effects of medical marijuana laws on crime	Fair	Fair	Good	Good	Good	Not Applicable	Good	Poor	Fair	Fair
Chung[173]	2019	The impact of recreational marijuana commercialization on traumatic injury	Good	Good	Good	Good	Good	Good	Good	Fair	Good	Good
Eichelberger[157]	2019	Marijuana use and driving in Washington State Risk perceptions and behaviours before and after implementation of retail sale	Good	Fair	Fair	Poor	Fair	Good	Fair	Fair	Fair	Good
Everson[310]	2019	Post-legalization opening of retail cannabis stores and adult cannabis use in Washington State, 2009-2016.	Good	Good	Good	Good	Good	Good	Good	Good	Fair	Good
Firth[153]	2019	Did marijuana legalization in Washington State reduce racial disparities in adult marijuana arrests?	Good	Fair	Good	Fair	Fair	Good	Good	Good	Good	Good
Garcia-Ramirez[311]	2019	Retail availability of marijuana in Oregon counties and co-use of alcohol and marijuana and related beliefs among adolescents	Good	Not applicable	Poor	Very Poor	Fair	Very Poor	Fair	Poor	Poor	Poor

First Author	Publication Year	Title	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data Analysis	Ethics and Bias	Results	Transferability or Generalisability	Implications and usefulness	Overall Rating
Gnofam[175]	2019	Impact of legalization on prevalence of maternal marijuana use and obstetrical outcomes	Good	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Very Poor
Hao[161]	2019	The cross-border spill over effects of recreational marijuana legalization	Fair	Good	Good	Good	Good	Not Applicable	Good	Poor	Poor	Fair
Jones[158]	2019	Marijuana and alcohol use among injured drivers evaluated at level I trauma centres in Arizona, 2008–2014	Fair	Fair	Good	Fair	Fair	Good	Good	Good	Fair	Good
Klassen[312]	2019	The effects of recreational cannabis legalization on forest management and conservation efforts in U.S. national forests in the Pacific Northwest	Poor	Poor	Poor	Fair	Fair	Poor	Poor	Poor	Poor	Fair
Levine[174]	2019	Prevalence of marijuana use among trauma patients before and after medical marijuana became legal	Poor	Very Poor	Fair	Very Poor	Poor	Very Poor	Fair	Poor	Poor	Poor
Lo[180]	2019	Cannabis legalization does not influence patient compliance with opioid therapy	Fair	Fair	Fair	Fair	Fair	Poor	Fair	Poor	Fair	Fair
Lu[167]	2019	The cannabis effect on crime: Time-series analysis of crime in Colorado and Washington State	Fair	Good	Good	Good	Good	Good	Good	Fair	Good	Good
Makin[168]	2019	Marijuana legalization and crime clearance rates: Testing proponent assertions in Colorado and Washington State	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good

First Author	Publication Year	Title	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data Analysis	Ethics and Bias	Results	Transferability or Generalisability	Implications and usefulness	Overall Rating
Melchior[150]	2019	Does liberalisation of cannabis policy influence levels of use in adolescents and young adults? A systematic review and meta-analysis.	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Nelson[169]	2019	Legalized marijuana in California: Prevalence of cannabis use in new patients now that cannabis is legal	Good	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Very Poor
Nemer[313]	2019	Severe acute pancreatitis incidence and outcomes after cannabis legalization in two states	USA	Fair	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Very Poor
Nicksic[314]	2019	Cannabis legalization, tobacco prevention policies, and Cannabis use in E-cigarettes among youth	Good	Good	Good	Good	Good	Good	Good	Fair	Fair	Good
Stormshak[151]	2019	The impact of recreational marijuana legalization on rates of use and behaviour: A 10-year comparison of two cohorts from high school to young adulthood.	Good	Good	Good	Good	Good	Good	Good	Good	Good	Good
Ward[162]	2019	The impact of marijuana legalization on law enforcement in States surrounding Colorado	Fair	Fair	Good	Fair	Fair	Good	Poor	Poor	Poor	Fair
Wen[126]	2019	Addendum to: “The effect of medical marijuana laws on marijuana-related attitude and perception among US adolescents and young adults.”	Very Poor	Fair	Not applicable	Not applicable	Not applicable	Not applicable	Fair	Not applicable	Not applicable	Very Poor

First Author	Publication Year	Title	Abstract and Title	Introduction and Aims	Method and Data	Sampling	Data Analysis	Ethics and Bias	Results	Transferability or Generalisability	Implications and usefulness	Overall Rating
Wen[125]	2019	The effect of medical marijuana laws on marijuana-related attitude and perception among US adolescents and young adults	Fair	Good	Good	Good	Good	Good	Fair	Fair	Fair	Good

7.7 Supplement 6: Search strategy (Labelling review)

Database Searched: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)

Platform or provider used: Ovid SP

Date of coverage: 1946 to February 12 2020

Date Search undertaken: 14 Feb 2020

#	**Searches**
1	*Cannabis/
2	exp *Cannabinoids/
3	*Medical Marijuana/
4	(marijuana or marihuana or cannabi* or "delta-9-tetrahydrocannibinol" or "Δ-9-tetrahydrocannabinol" or "delta-9-tetrahydrocannabinol" or “Δ-9-tetrahydrocannibinol” or 9-tetrahydrocannabinol or 9-thetrahydrocannibinol or “Δ-9-thc” or CBD or THC or tetrahydrocannabinol).ti,kf.
5	or/1-4
6	*Drug Labeling/
7	*Product Labeling/
8	exp *Consumer Product Safety/
9	(label* or mislabel* or mis-label*).ti,kf.
10	exp Pharmaceutical Preparations/st,sd,an.
11	((pack* or wrapping or wrapper) adj6 (content* or ingredient* or constituent* or strength or potency)).ti.kf
12	*Drug Contamination/
13	(contamina* or impurit*).ti,kf.
14	*food handling/ or *food packaging/or *food storage/
15	(storage or shelf-life or degrad*).ti,kf.
16	(((accurate or true) adj3 representation) or misrepresentatison).ti.kf.
17	or/6-16
18	5 and 17
19	open-label.ti.
20	18 not 19

Database Searched: **EMBASE All years 1947-Present with Daily Update**

Platform or provider used: Ovid SP

Date of coverage: 1947 to February 14 2020

Date Search undertaken: 14 Feb 2020

#	**Searches**
1	exp *cannabis sativa/
2	exp *cannabinoid/
3	(marijuana or marihuana or cannabi* or "delta-9-tetrahydrocannibinol" or "Δ-9-tetrahydrocannabinol" or "delta-9-tetrahydrocannabinol" or “Δ-9-tetrahydrocannibinol” or 9-tetrahydrocannabinol or 9-thetrahydrocannibinol or “Δ-9-thc” or CBD or THC or tetrahydrocannabinol).ti,kw.
4	or/1-3
5	*drug labeling/
6	exp *packaging/
7	*product safety
8	(label* or mislabel* or mis-label*).ti,kw.
9	exp *pharmacological parameters/ and exp *quality control procedures/
10	((package* or wrapping or wrapper* or packet*) adj6 (content* or ingredient* or constituen* or strength or potency)).ti.kw.
11	(contamina* or impurit*).ti,kw.
12	*food handling/ or *food packaging/or *food storage/
13	(storage or shelf-life or degrad*).ti,kf.
14	(((accurate or true) adj3 representation) or misrepresentatison).ti.kw.
15	or/5-14
16	4 and 15
17	synthetic cannabi*.ti.
18	16 not 17
19	open-label.ti.
20	18 not 19

Database Searched: **PsycINFO**

Platform or provider used: Ovid SP

Date of coverage: 1806 to February Week 1 2020

Date Search undertaken: 14 Feb 2020

#	**Searches**
1	exp *cannabis/
2	exp *cannabinoids/
3	*tetrahydrocannabinol
4	(marijuana or marihuana or cannabi* or "delta-9-tetrahydrocannibinol" or "Δ-9-tetrahydrocannabinol" or "delta-9-tetrahydrocannabinol" or “Δ-9-tetrahydrocannibinol” or 9-tetrahydrocannabinol or 9-thetrahydrocannibinol or “Δ-9-thc” or CBD or THC or tetrahydrocannabinol).ti,id.
5	or/1-4
6	*warning labels/
7	(label* or mislabel* or mis-label*).ti,id,sh.
8	exp *product design/
9	((package* or wrapping or wrapper* or packet*) adj6 (content* or ingredient* or constituen* or strength or potency)).ti.id.
10	*food safety/
11	(contamina* or impurit*).ti,id.
12	(storage or shelf-life or degrad*).ti,id.
13	(((accurate or true) adj3 representation) or misrepresentatison).ti.id.
14	or/6-13
15	5 and 14
16	synthetic cannabi*.ti.
17	15 not 16
18	open-label.ti.
19	17 not 18

Database Searched: SCOPUS

Platform or provider used: Scopus

Date of coverage: Till 14 Feb 2020

Date Search undertaken: 14 Feb 2020

Search string

((TITLE(marijuana OR marihuana OR cannabi* OR "delta-9-tetrahydrocannibinol" OR "Δ-9-tetrahydrocannabinol" OR "delta-9-tetrahydrocannabinol" OR "Δ-9-tetrahydrocannibinol" OR "9-tetrahydrocannabinol" OR "9-tetrahydrocannibinol" OR "Δ-9-THC" OR "delta-9-thc" OR CBD OR THC OR tetrahydrocannabinol) OR AUTHKEY(marijuana OR marihuana OR cannabi* OR "delta-9-tetrahydrocannibinol" OR "Δ-9-tetrahydrocannabinol" OR "delta-9-tetrahydrocannabinol" OR "Δ-9-tetrahydrocannibinol" OR "9-tetrahydrocannabinol" OR "9-tetrahydrocannibinol" OR "Δ-9-THC" OR "delta-9-thc" OR CBD OR THC OR tetrahydrocannabinol)) AND (TITLE((label* OR mislabel* OR mis-label* OR ((packag* OR wrapping OR wrapper* OR packet*) W/6 (content* OR ingredient* OR constituen* OR strength OR potency))OR contamina* OR impurit* OR storage OR shelf-life OR degradat* OR (((accurate OR true) W/3 representation) OR misrepresentation))) OR AUTHKEY((label* OR mislabel* OR mis-label* OR ((packag* OR wrapping OR wrapper* OR packet*) W/6 (content* OR ingredient* OR constituen* OR strength OR potency)) OR contamina* OR impurit* OR storage OR shelf-life OR degradat* OR (((accurate OR true) W/3 representation) OR misrepresentation)))) AND NOT TITLE(open-label) AND NOT TITLE("synthetic cannabi*"))

Database Searched: **ProQuest**

Platform or provider used: ProQuest

Date of coverage: Till 14 Feb 2020

Date Search undertaken: 14 Feb 2020

#	Searches
S1	ti(marijuana OR marihuana OR cannabi* OR "delta-9-tetrahydrocannibinol" OR "Δ-9-tetrahydrocannabinol" OR "delta-9-tetrahydrocannabinol" OR "Δ-9-tetrahydrocannibinol" OR "9-tetrahydrocannabinol" OR "9-tetrahydrocannibinol" OR "Δ-9-THC" OR "delta-9-thc" OR CBD OR THC OR tetrahydrocannabinol) OR su(marijuana OR marihuana OR cannabi* OR "delta-9-tetrahydrocannibinol" OR "Δ-9-tetrahydrocannabinol" OR "delta-9-tetrahydrocannabinol" OR "Δ-9-tetrahydrocannibinol" OR "9-tetrahydrocannabinol" OR "9-tetrahydrocannibinol" OR "Δ-9-THC" OR "delta-9-thc" OR CBD OR THC OR tetrahydrocannabinol)
S2	ti((label* OR mislabel* OR mis-label* OR ((packag* OR wrapping OR wrapper* OR packet*) NEAR/6 (content* OR ingredient* OR constituen* OR strength OR potency)) OR contamina* OR impurit* OR storage OR shelf-life OR degradat* OR (((accurate OR true) NEAR/3 representation) OR misrepresentation))) OR su((label* OR mislabel* OR mis-label* OR ((packag* OR wrapping OR wrapper* OR packet*) NEAR/6 (content* OR ingredient* OR constituen* OR strength OR potency)) OR contamina* OR impurit* OR storage OR shelf-life OR degradat* OR (((accurate OR true) NEAR/3 representation) OR misrepresentation)))
S3	S1 AND S2
S4	S1 AND S2 (Limit for scholarly journals applied)
S5	S1 AND S2 (Limit for scholarly journals and for Medline records applied)
S6	S4 NOT S5
S7	ti(open-label)
S8	S6 NOT S7
S9	ti("synthetic cannabi*")
S10	S8 NOT S9

Databases Searched: **EBSCO-**

Academic Search Complete, AHFS Consumer Medication Information, Australia/New Zealand Reference Centre, Business Source Complete, CINAHL, Communication & Mass Media Complete, Education Research Complete, EconLit, GreenFILE, Health Business Elite, Health Source - Consumer Edition, Health Source: Nursing/Academic Edition, Hospitality & Tourism Complete, Humanities International Complete, MAS Ultra - School Edition, MasterFILE Premier, Psychology and Behavioral Sciences Collection, SPORTDiscus with Full Text

Date of coverage: Till 14 Feb 2020

Date Search undertaken: 14 Feb 2020

 # Searches

S1 TI (marijuana OR marihuana OR cannabi* OR "delta-9-tetrahydrocannibinol" OR "Δ-9-tetrahydrocannabinol" OR "delta-9-tetrahydrocannabinol" OR "Δ-9-tetrahydrocannibinol" OR "9-tetrahydrocannabinol" OR "9-tetrahydrocannibinol" OR "Δ-9-THC" OR "delta-9-thc" OR CBD OR THC OR tetrahydrocannabinol) OR SU (marijuana OR marihuana OR cannabi* OR "delta-9-tetrahydrocannibinol" OR "Δ-9-tetrahydrocannabinol" OR "delta-9-tetrahydrocannabinol" OR "Δ-9-tetrahydrocannibinol" OR "9-tetrahydrocannabinol" OR "9-tetrahydrocannibinol" OR "Δ-9-THC" OR "delta-9-thc" OR CBD OR THC OR tetrahydrocannabinol) OR AB (marijuana OR marihuana OR cannabi* OR "delta-9-tetrahydrocannibinol" OR "Δ-9-tetrahydrocannabinol" OR "delta-9-tetrahydrocannabinol" OR "Δ-9-tetrahydrocannibinol" OR "9-tetrahydrocannabinol" OR "9-tetrahydrocannibinol" OR "Δ-9-THC" OR "delta-9-thc" OR CBD OR THC OR tetrahydrocannabinol)

S2 TI ((label* OR mislabel* OR mis-label* OR ((packag* OR wrapping OR wrapper* OR packet*) N6 (content* OR ingredient* OR constituen* OR strength OR potency)) OR contamina* OR impurit* OR storage OR shelf-life OR degradat* OR (((accurate OR true) N3 representation) OR misrepresentation))) OR SU ((label* OR mislabel* OR mis-label* OR ((packag* OR wrapping OR wrapper* OR packet*) N6 (content* OR ingredient* OR constituen* OR strength OR potency)) OR contamina* OR impurit* OR storage OR shelf-life OR degradat* OR (((accurate OR true) N3 representation) OR misrepresentation)))

S3 S1 AND S2

S4 S1 AND S2 Limiters - Scholarly (Peer Reviewed) Journals; Exclude MEDLINE records

S5 TI open-label

S6 S4 NOT S5

S7 TI synthetic cannabi*

S8 S6 NOT S7

Database Searched: **Web of Science Core Collection, Web of Science BIOSIS Citation Index**

Platform or provider used: WOS

Date of coverage: Till 14 Feb 2020

Date Search undertaken: 14 Feb 2020

Search String

((TS=(marijuana OR marihuana OR cannabi* OR "delta-9-tetrahydrocannibinol" OR "Δ-9-tetrahydrocannabinol" OR "delta-9-tetrahydrocannabinol" OR "Δ-9-tetrahydrocannibinol" OR "9-tetrahydrocannabinol" OR "9-tetrahydrocannibinol" OR "Δ-9-THC" OR "delta-9-thc" OR CBD OR THC OR tetrahydrocannabinol) AND TI=(label* OR mislabel* OR mis-label* OR ((packag* OR wrapping OR wrapper* OR packet*) NEAR/6 (content* OR ingredient* OR constituen* OR strength OR potency)) OR contamina* OR impurit* OR storage OR shelf-life OR degradat* OR (((accurate OR true) NEAR/3 representation) OR misrepresentation)) NOT PMID=(1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9)) NOT (TI=open-label) NOT (TI="synthetic cannabi*")) OR ((TI=(marijuana OR marihuana OR cannabi* OR "delta-9-tetrahydrocannibinol" OR "Δ-9-tetrahydrocannabinol" OR "delta-9-tetrahydrocannabinol" OR "Δ-9-tetrahydrocannibinol" OR "9-tetrahydrocannabinol" OR "9-tetrahydrocannibinol" OR "Δ-9-THC" OR "delta-9-thc" OR CBD OR THC OR tetrahydrocannabinol) AND TS=(label* OR mislabel* OR mis-label* OR ((packag* OR wrapping OR wrapper* OR packet*) NEAR/6 (content* OR ingredient* OR constituen* OR strength OR potency)) OR contamina* OR impurit* OR storage OR shelf-life OR degradat* OR (((accurate OR true) NEAR/3 representation) OR misrepresentation)) NOT PMID=(1* OR 2* OR 3* OR 4* OR 5* OR 6* OR 7* OR 8* OR 9)) NOT (TI=open-label) NOT (TI="synthetic cannabi*"))

Database Searched: **Food and Science Technology Abstracts**

Platform or provider used: OVID

Date of coverage: 1969 to 2020 January Week 5

Date Search undertaken: 14 Feb 2020

#	**Searches**
1	hemp seeds/
2	(marijuana or marihuana or cannabi* or "delta-9-tetrahydrocannibinol" or "Δ-9-tetrahydrocannabinol" or "delta-9-tetrahydrocannabinol" or "Δ-9-tetrahydrocannibinol" or 9-tetrahydrocannabinol or 9-tetrahydrocannibinol or "Δ-9-THC" or "delta-9-thc" or CBD or THC or tetrahydrocannabinol).mp.
3	or/1-2
4	exp packaging/
5	ingredients/
6	pharmacological properties/
7	(label* or mislabel* or mis-label*).mp.
8	((packag* or wrapping or wrapper* or packet*) adj6 (content* or ingredient* or constituen* or strength or potency)).mp.
9	exp food safety/
10	exp contamination/ or purity/ or spoilage/
11	(contamina* or impurit*).mp.
12	(storage or shelf-life or degradat*).mp.
13	(((accurate or true) adj3 representation) or misrepresentation).mp.
14	or/4-13
15	3 and 14
16	synthetic cannabi*.ti.
17	15 not 16
18	open-label.ti.
19	17 not 18

Database Searched: **International Pharmaceutical Abstracts**

Platform or provider used: OVID

Date of coverage: 1970 to January 2020

Date Search undertaken: 14 Feb 2020

#	Searches
1	(marijuana or marihuana or cannabi* or "delta-9-tetrahydrocannibinol" or "Δ-9-tetrahydrocannabinol" or "delta-9-tetrahydrocannabinol" or "Δ-9-tetrahydrocannibinol" or 9-tetrahydrocannabinol or 9-tetrahydrocannibinol or "Δ-9-THC" or "delta-9-thc" or CBD or THC or tetrahydrocannabinol).mp.
2	(13956-29-1 or 89958-21-4 or 8063-14-7 or 1972-08-3).rn.
3	or/1-2
4	(label* or mislabel* or mis-label*).mp.
5	((packag* or wrapping or wrapper* or packet*) adj6 (content* or ingredient* or constituen* or strength or potency)).mp.
6	(contamina* or impurit*).mp.
7	(storage or shelf-life or degradat*).mp.
8	(((accurate or true) adj3 representation) or misrepresentation).mp.
9	or/4-8
10	3 and 9
11	synthetic cannabi*.ti.
12	10 not 11
13	open-label.ti.
14	12 not 13

7.8 Supplement 7: Process of literature review, data-extraction and quality of evidence review.

Papers were graded using Hawkers Qualitative tool for disparate evidence. Each paper was graded twice in nine domains (Abstract and title, Introduction and aims, Method and data, Sampling, Data analysis, Ethics and bias, Finding/results, Transferability/generalizability, Implications and usefulness). A score out of four (1= Very Poor, 2= Poor, 3= Fair, 4=Good) was given for each domain. Scoring in each domain was compared between authors, and awarded the higher score if disagreement occurred. Papers were then given a score out of 36 and an overall grading of the paper established (0-9= Very Poor quality, 10-18= Poor quality, 19-27= Fair quality and 28-36= Good quality). The quality of evidence is reported in Table 3.3 of the main manuscript.

Data extraction was undertaken using the template below:

Blank Data Extraction Template:

Study details		**Comments**			
Study method					
Title					
Author and date					
Journal					
Study design					
Study population					
Type(s) of cannabis product (e.g vape, edible)					
number of samples					
number of oils					
number of edibles					
number of tinctures					
number of vaporization liquids					
number of other					
Method of obtainment (e.g purchase in store)					
Setting					
Single or multiple site					
Country(s)					
State(s)					
Regulatory guidelines (if known)					
Method of obtainment (e.g purchase in store)					
Method of sampling					
Intervention; Exposure					
Method of product analysis (e.g HPLC, GCMS)					
Regulatory guidelines (if known)					
Outcomes assessed					
Other data for narrrative					
Adjustment for potential confounding					
Reviewer name and comments					

	Data Reported	**Overall**			
		Label	Actual/measured	Deviation from label	Percentage difference
Primary outcomes					
Oils					
THC					
CBD					
Cannabinol (CBN)					
Cannabidiolic acid (CBDA)					
Cannabigerol (CBG)					
THCA					
Edibles					
THC					
CBD					
Cannabinol (CBN)					
Cannabidiolic acid (CBDA)					
Cannabigerol (CBG)					
THCA					
Tinctures					
THC					
CBD					
Cannabinol (CBN)					
Cannabidiolic acid (CBDA)					
Cannabigerol (CBG)					
THCA					
Vaporization liquid					
THC					
CBD					
Cannabinol (CBN)					
Cannabidiolic acid (CBDA)					
Cannabigerol (CBG)					
THCA					

	Data Reported	**Overall**			
		Label	Actual/measured	Deviation from label	Percentage difference
Other					
THC					
CBD					
Cannabinol (CBN)					
Cannabidiolic acid (CBDA)					
Cannabigerol (CBG)					
THCA					
Secondary outcomes					
Contaminants					
proportion of samples with contaminants					
quantity of contaminant (ppm, x per g, etc)					

7.9 Participant Information Sheet for all questionnaires

"Medical Cannabis: Knowledge, Attitudes and Expectations amongst NZ Health Care Professionals and their Patients"

Thank you for considering taking part in my study.

Who am I?

My name is Karen Oldfield and I am a Doctoral student in Clinical Research at Victoria University of Wellington and Medical Research Fellow at the Medical Research Institute of New Zealand. The Medical Research Institute of New Zealand is an independent medical research organization that is dedicated to improving knowledge about important public health problems in New Zealand.

Why are we doing this study?

The aim of the study is to find out what doctors and patients in New Zealand currently know about medical cannabis and its uses, their feelings around discussions about medical cannabis and how they would like information about medical cannabis to be delivered to them. For the purposes of this study medical cannabis is defined as "any use of cannabis plants and/or medications derived from cannabis that have been used by a patient to treat a medical condition".

This is a currently a topical issue, especially with recent moves to make law changes in New Zealand. I hope that this study will give us information to create an educational tool pertinent to medical cannabis in NZ for use by both health care professionals and their patients, allowing for informed discussions to take place for the benefit of all involved. Understanding current knowledge will also help in the future planning of clinical trials to determine evidence for how we use medical cannabis in the future.

This research has been approved by the Victoria University of Wellington Human Ethics Committee #25835.

Who is being asked to participate?

I am surveying a selection of New Zealand doctors (General Practitioners and Hospital Specialists/Trainees) and a group of adult patients associated with each of their specialties. You must be over 18 years of age to participate in this study. The study aims to interview approximately 40 General Practitioners, 80 Hospital Specialists and 400 patients.

How are we doing the study?

The study will be a questionnaire administered via iPad or a paper copy, you may choose which you prefer. On the iPad you will be asked to click on the survey link below which will connect you to a questionnaire. The questionnaire contains between 10-12 questions and is expected to take 5-10 minutes to complete.

In relation to the questionnaire we will not ask you for personally identifying information such as name, birth date or address, however you will be asked general characterising information such as medical condition, age-range, gender and ethnicity. If you are a health care professional we will also ask your specialty, training level and number of years in practice.

At the end of the patient questionnaire there is an optional question/link about becoming a patient advocate for future development of clinical trials. A patient advocate is consulted during the process of development of a clinical trial to encourage input from the trials target population, allowing for concerns and ideas about the trial to be shared with the trial developers. If you are interested, you may choose to write your contact details here and place this form in the box provided or you can contact us directly via the email address or phone number provided.

All information collected will be treated in a confidential manner and will not be disclosed to any other agencies.

What will happen to the information collected?

Once all the surveys have been completed the information will be securely stored, analysed and reported. The study findings will be reported and published in peer reviewed journals and used in my PhD dissertation. The findings may also be presented at academic conferences.

Can I choose to withdraw my answers?

Due to the fact this questionnaire contains no personal identifiers I will not be able to remove your answers after the survey is complete as I will be unable to identify which answers you gave. At any time you may choose not to complete the questionnaire, however once you have clicked the submit button it is implied that you are happy for your answers to be used in this study.

Thank you again for taking the time to consider participating in our study! If you are happy to proceed, please click the link below or complete the paper questionnaire.

If you have any questions or problems, who can you contact?

If you have any concerns arising from the process of taking this questionnaire please contact:

Student:

Name: Dr Karen Oldfield

Ph: (04) 805-0147

Email: karen.oldfield@vuw.ac.nz

Supervisor:

Name: Dr Irene Braithwaite

Role: Deputy Director

Medical Research Institute of New Zealand

Phone: Content Unavailable

Email: irene.braithwaite@vuw.ac.nz

Human Ethics Committee information

If you have any concerns about the ethical conduct of the research you may contact the Victoria University HEC Convenor: Dr Judith Loveridge. Email hec@vuw.ac.nz or telephone +64-4-463 6028.

7.10Medicinal cannabis questionnaire for health practitioners: General Practice, neurology and oncology

GENERAL KNOWLEDGE

1) ***Are you aware of any pharmaceutical grade cannabis medications available worldwide?***

Yes ◯ No ◯

a) If yes, please indicate which medications you are aware of, the primary constituents, whether they are licensed in NZ, the delivery route and rough cost to the patient. If no, please continue to page 2.

	Aware of product? (Y/N)	**Primary Constituents (tick all that apply)**		**Licensed in NZ? (Y/N)**	**Capsule/tablet (tick all that apply)**	**Buccal/Sublingual (tick all that apply)**	**Estimated cost per year (NZ $ amt)**
		THC*	**CBD***				
Dronabinol (Marinol)							
Nabiximols (Sativex)							
Nabilone (Cesamet)							
Epidiolex							

***THC= delta-9-tetrahydrocannabinol, CBD= Cannabidiol**

b) What medical conditions, if any, would you prescribe each medication for?

	Condition 1	**Condition 2**	**Condition 3**	**Don't know**
Dronabinol (Marinol)				
Nabiximols (Sativex))				
Nabilone (Cesamet)				
Epidiolex				

MEDICAL CONDITIONS

Cannabis has been suggested as a treatment for numerous medical conditions:

1) ***What conditions are you aware of that DO have Grade A/Level I RCT evidence for use of medicinal cannabis products? Please list up to 5.***

   i) _____

   ii) _____

   iii) _____

   iv) _____

   v) _____

2) ***What conditions are you aware of in which there is substantive evidence of NO benefit to support the use of medicinal cannabis products, but for which such products may have been recommended? Please list up to 5.***

   i) _____

   ii) _____

   iii) _____

   iv) _____

   v) _____

3) ***Please list up to 5 side effects that are associated with use of medicinal cannabis products***

   i) _____

   ii) _____

   iii) _____

   iv) _____

   v) _____

REGULATORY REQUIREMENTS

There are three Ministry of Health categories of cannabis-based products in New Zealand presently. Please mark where the responsibilities of approval, funding and import lie with each (you may tick more than one option):

	Approval					Funding					Import				
	PHO	**DHB**	**Specialist**	**MOH**	**PHARMAC**	**PHO**	**DHB**	**Patient**	**MOH**	**PHARMAC**	**Prescribing Doctor**	**Pharmacy**	**Patient**	**MOH**	**PHARMAC**
CBD															
Sativex															
Other															

PHO = Primary Health Organisation; DHB == District Health Board; MOH = Ministry of Health; PHARMAC = Pharmaceutical Management Agency

PROFESSIONAL EXPERIENCE

1) ***Have you been approached by patients seeking a prescription for medical cannabis products over the past 12 months?***

Yes ◯ No ◯

a) ***If yes, how many patients have approached you?***

1-4 ◯ 5-10 ◯ 10+ ◯

i) ***For what condition/s?***

_____

_____

b) ***Did you facilitate any of the requests?***

Yes ◯ No ◯

i) ***If Yes:***

i. ***What impediments (if any) occurred when facilitating the request?***

_____

_____

ii. ***Did the patient receive their product?***

Yes ◯ No ◯

ii) ***If No, why not:***

◯ Cost

◯ Insufficient evidence base

◯ Side effects

◯ Insufficient understanding of process

◯ Aware of process but considered potential clinical benefit vs logistics/cost inappropriate

2) ***Have any patients for whom you are the named GP/Specialist been prescribed a medical cannabis product?***

Yes ◯ No ◯

a) ***If yes, who prescribed this?***

Me ◯ Another GP ◯ Specialist ◯

3) Have any of your patients informed you that they are using cannabis for medical conditions in the last 12 months?

Yes ◯ No ◯

a) If yes, how many patients?

1-4 ◯ 5-10 ◯ 10+ ◯

i) For what condition/s?

_____

_____

b) What are they using (tick more than one if required)?

◯ Cannabis (smoked)

◯ Cannabis (edible)

◯ Other (please specify) _____

4) Have you accessed information about medical cannabis from any of the following sources?

◯ CME session

◯ Journals

◯ MOH website

◯ Other (please detail)

5) Do you have reservations or concerns in relation to prescribing medical cannabis products, either currently or in the future?

Yes ◯ No ◯

a) If yes, please give a reason:

◯ Cost

◯ Insufficient evidence base

◯ Side effects

◯ Insufficient understanding of process

◯ Aware of process but considered potential clinical benefit vs logistics/cost inappropriate

6) How would you prefer to receive educational content about medical cannabis?

◯ CME session

◯ CME online module

◯ Information sheet

◯ Podcast

◯ Other (please detail) _____

7) If there was a PHARMAC funded, licensed product with good RCT evidence for specific conditions how likely would you be to prescribe this in your day to day practice?

◯ Very Likely

◯ Somewhat Likely

◯ Neutral

◯ Somewhat Unlikely

◯ Very Unlikely

8) Demographic Information:

Age (Years):

◯ Under 20

◯ 20-29

◯ 30-39

◯ 40-49

◯ 50-59

◯ 60-69

◯ 70-79

◯ 80 +

Gender:

◯ Male

◯ Female

◯ Other (please specify) _____

◯ Prefer not to disclose

Ethnicity: Which ethnic group do you belong to? (Tick all that apply)

◯ NZ European

◯ Māori

◯ Samoan

◯ Cook Island Maori

◯ Tongan

◯ Niuean

◯ Chinese

◯ Indian

◯ Other (such as Dutch, Japanese, Tokelauan). Please state:

_____

Source: SNZ, 2001 Census

Specialty: _____

◯ Consultant/GP

◯ Senior Registrar

◯ Junior Registrar

◯ Senior House Officer

◯ House Officer

◯ Other (please specify) _____

Years in Practice: _____

7.11Images used for Facebook advertising for patient recruitment

Images created by Dr Ciléin Kearns, MRINZ, for purposes of this study

7.12Medicinal cannabis patient experience questionnaire (GP patient)

1) Are you aware of any prescribed medical cannabis products?

Yes ◯ No ◯ - go to question 3

2) If yes, have you heard of any of the following medications?

	Aware of product? (Y/N)	**Primary Constituents (tick all that apply)**		**Available in NZ? (Y/N)**	**Estimated cost per year to patient (NZ $ amt)**
		THC*	**CBD***		
Dronabinol (Marinol)					
Nabiximols (Sativex)					
Nabilone (Cesamet)					
Epidiolex					

*THC= delta-9-tetrahydrocannabinol, CBD= Cannabidiol

3) Would you take a prescribed medication made from medical cannabis?

Yes ◯ No ◯

4) Please can you state what medical conditions you see your doctor for:

_____

_____

_____

_____

_____

5) Please list the prescribed medications you take for your medical conditions:

_____

_____

_____

6) Do you believe that medical cannabis products may be helpful for your medical conditions?

Yes ◯ - go to part a) No ◯ - go to part b)

a) If Yes, what benefits do you think medical cannabis products will give you (tick all that apply)?

◯ Symptom Control (e.g Spasticity, Nausea/Vomiting) (please list specific symptoms)

_____

_____

◯ Pain relief

◯ Decrease Anxiety

◯ Cure my condition

◯ Any other benefits (please list)

_____

_____

b) If No, why not?

_____

_____

_____

_____

7) Have you ever used recreational cannabis to treat a medical condition or symptom?

Yes ◯ No ◯ - go to question 8

a) If Yes, what medical condition or symptom did you treat?

_____

_____

_____

_____

_____

b) ***How did you take*** **it?**

◯ Smoked (pure)

◯ Smoked (with tobacco)

◯ Vaped

◯ Oil

◯ Edibles

◯ Other (please specify) _____

c) Did you find it effective for your symptoms or condition?

Yes ◯ No ◯ - go to question 8

d) If effective, have you decreased the amount of your prescribed medications for your medical condition?

Yes ◯ No ◯

8) Would you feel comfortable discussing using cannabis (whole plant and/or medical product) as a medication with your GP?

Yes ◯ - go to part a) No ◯ - go to part b)

a) If Yes, have you discussed medicinal cannabis (whole plant and/or medical product) with your GP?

Yes ◯ No ◯ - go to question 9

i) If Yes, did you feel you were informed about the evidence for/against use as well as any possible side effects associated with use of medicinal cannabis (whole plant and/or medical product)?

Yes ◯ No ◯

ii) Did your GP prescribe a medical cannabis product for you?

Yes ◯ No ◯

iii) Did you fill your prescription? How much did it cost you per month?

Yes ◯ No ◯

Cost (NZ$)_____

iv) Have you found it effective?

Yes ◯ No ◯ - go to question 9

v) If effective, have you decreased the amount of your other prescribed medications for you medical condition?

Yes ◯ No ◯

b) If No, why not (tick all that apply)?

◯ Stigma

◯ Worried about legal implications

◯ Cost of Product

◯ Other (please specify)

_____

_____

9) Would you feel comfortable discussing medicinal cannabis (whole plant and/or medical product) with your Specialist(s)?

Yes ◯ - go to part a) No ◯ - go to part b) I don't see a Specialist ◯ - go to question 10

a) If Yes, have you discussed medicinal cannabis (whole plant and/or medical product) with your Specialist (s)?

Yes ◯ No ◯ -go to question 10

i) If Yes, did you feel you were informed about the evidence for/against use as well as any possible side effects associated with use of medicinal cannabis (whole plant and/or medical product)?

Yes ◯ No ◯

ii) Did your Specialist prescribe a medical cannabis product for you?

Yes ◯ No ◯

iii) Did you fill your prescription? How much did it cost you per month?

Yes ◯ No ◯

Cost (NZ$)_____

iv) Have you found it effective?

Yes ◯ No ◯ - go to question 10

v) If effective, have you decreased the amount of your other prescribed medications for you medical condition?

Yes ◯ No ◯

b) If No, why not (tick all that apply)?

◯ Stigma

◯ Worried about legal implications

◯ Cost of Product

◯ Other (please specify)

_____

_____

10) What information from your doctor would you like about cannabis as a medicine and medical cannabis products?

_____

_____

_____

_____

_____

11) What would be the best way we could communicate this information?

◯ Website

◯ Pamphlet

◯ Poster

◯ Podcast

◯ Social Media (Facebook/twitter/Instagram)

◯ Other (please specify)

12) Demographic information

Age (Years):

◯ Under 20

◯ 20-29

◯ 30-39

◯ 40-49

◯ 50-59

◯ 60-69

◯ 70-79

◯ 80 +

Gender:

◯ Male

◯ Female

◯ Other (please specify) _____

◯ Prefer not to disclose

Ethnicity: Which ethnic group do you belong to? (Tick all that apply)

◯ NZ European

◯ Māori

◯ Samoan

◯ Cook Island Maori

◯ Tongan

◯ Niuean

◯ Chinese

◯ Indian

◯ Other (such as Dutch, Japanese, Tokelauan). Please state:

_____

Source: SNZ, 2001 Census

7.13Medicinal cannabis patient experience questionnaire (Oncology/neurology)

1) Are you aware of any prescribed medical cannabis products?

Yes ◯ No ◯ - go to question 4

2) If yes, have you heard of any of the following medications?

	Aware of product? (Y/N)	**Primary Constituents (tick all that apply)**		**Available in NZ? (Y/N)**	**Estimated cost per year to patient (NZ $ amt)**
		THC*	**CBD***		
Dronabinol (Marinol)					
Nabiximols (Sativex)					
Nabilone (Cesamet)					
Epidiolex					

*THC= delta-9-tetrahydrocannabinol, CBD= Cannabidiol

3) Have you heard of any other named cannabis products that are being used as a medicine in NZ?

a) Yes ◯ No ◯

i) If Yes, please list their names below:

_____

_____

_____

4) Would you take a prescribed medication made from medical cannabis?

Yes ◯ No ◯ Don't know ◯

5) Please can you state what medical conditions you see your doctor for:

_____

_____

_____

_____

_____

6) ***Please list the prescribed medications you take for your medical conditions:***

_____

_____

_____

7) ***Do you believe that medical cannabis products may be helpful for your medical conditions?***

Yes ◯ - go to part a) No ◯ - go to part b) Don't Know ◯ - go to part b)

a) ***If Yes, what benefits do you think medical cannabis products will give you (tick all that apply)?***

◯ Symptom Control (e.g Spasticity, Nausea/Vomiting) (please list specific symptoms)

_____

_____

◯ Pain relief

◯ Decrease Anxiety

◯ Cure my condition

◯ Any other benefits (please list)

_____

_____

b) ***If No or Don't Know please give a reason why you have given that answer:***

_____

_____

_____

_____

8) Have you ever used recreational cannabis to treat a medical condition or symptom?

Yes ◯ No ◯ - go to question 8

a) If Yes, what medical condition or symptom did you treat?

_____

_____

_____

_____

b) *How did you take* it?

◯ Smoked (pure)

◯ Smoked (with tobacco)

◯ Vaped

◯ Oil

◯ Edibles

◯ Other (please specify) _____

c) Did you find it effective for your symptoms or condition?

Yes ◯ No ◯ - go to question 8

i) If Yes, please indicate which type and method of administration you found effective and which symptoms you found it effective for?

_____

_____

_____

_____

d) If effective, have you decreased the amount of your prescribed medications for your medical condition?

Yes ◯ No ◯

9) Would you feel comfortable discussing using cannabis (whole plant and/or medical product) as a medication with your GP?

Yes ◯ - go to part a) No ◯ - go to part b)

a) If Yes, have you discussed medicinal cannabis (whole plant and/or medical product) with your GP?

Yes ◯ No ◯ - go to question 9

i) If Yes, did you feel you were informed about the evidence for/against use as well as any possible side effects associated with use of medicinal cannabis (whole plant and/or medical product)?

Yes ◯ No ◯

ii) Did your GP prescribe a medical cannabis product for you?

Yes ◯ No ◯

iii) Did you fill your prescription? If yes, how much did it cost you per month?

Yes ◯ No ◯ I haven't filled it yet ◯ - go to question 9

Cost (NZ$)_____

iv) Have you found it effective?

Yes ◯ No ◯ - go to question 9 I haven't used it yet go ◯ -go to question 9

***a) If Yes, please indicate which type and method of administration you found effective and which symptoms you found it effective for*?**

_____

_____

_____

_____

v) If effective, have you decreased the amount of your other prescribed medications for you medical condition?

Yes ◯ No ◯

b) If No, why not (tick all that apply)?

◯ Stigma

◯ Worried about legal implications

◯ Cost of Product

◯ Other (please specify)

_____

_____

10) Would you feel comfortable discussing medicinal cannabis (whole plant and/or medical product) with your Specialist(s)?

Yes ◯ - go to part a) No ◯ - go to part b) I don't see a Specialist ◯ - go to question 10

a) If Yes, have you discussed medicinal cannabis (whole plant and/or medical product) with your Specialist (s)?

Yes ◯ No ◯ -go to question 10

i) If Yes, did you feel you were informed about the evidence for/against use as well as any possible side effects associated with use of medicinal cannabis (whole plant and/or medical product)?

Yes ◯ No ◯

ii) Did your Specialist prescribe a medical cannabis product for you?

Yes ◯ No ◯

iii) Did you fill your prescription? If yes, how much did it cost you per month?

Yes ◯ No ◯ I haven't filled it yet ◯ - go to question 10

Cost (NZ$)_____

iv) Have you found it effective?

Yes ◯ No ◯ - go to question 10 I haven't used it yet go ◯ -go to question 10

***a) If Yes, please indicate which type and method of administration you found effective and which symptoms you found it effective for*?**

_____

_____

_____

_____

v) If effective, have you decreased the amount of your other prescribed medications for you medical condition?

Yes ◯ No ◯

b) If No, why not (tick all that apply)?

◯ Stigma

◯ Worried about legal implications

◯ Cost of Product

◯ Other (please specify)

_____

_____

11) ***What information, if any, from your doctor would you as a patient like about the use of cannabis as a medicine and medical cannabis products?***

_____

_____

_____

_____

_____

12) ***What would be the best way doctors and researchers could communicate this information?***

◯ Website

◯ Pamphlet

◯ Poster

◯ Podcast

◯ Social Media (Facebook/twitter/Instagram)

◯ Face to face consultation

◯ I don't want information

◯ Other (please specify) _____

13) ***Do you have any further comments about the use of cannabis as a medicine that you would like to make that have not been covered in the questions above? Please comment below:***

_____

_____

_____

14) ***Demographic information***

Age (Years):

◯ Under 20

◯ 20-29

◯ 30-39

◯ 40-49

◯ 50-59

◯ 60-69

◯ 70-79

◯ 80 +

Gender:

◯ Male

◯ Female

◯ Other (please specify) _____

◯ Prefer not to disclose

Ethnicity: Which ethnic group do you belong to? (Tick all that apply)

◯ NZ European

◯ Māori

◯ Samoan

◯ Cook Island Maori

◯ Tongan

◯ Niuean

◯ Chinese

◯ Indian

◯ Other (such as Dutch, Japanese, Tokelauan). Please state:

_____

Source: SNZ, 2001 Census

7.14 Pharmacokinetic study of single ascending and multiple ascending doses of a whole plant Cannabis sativa (material/extract) containing THC in (a capsule/oil): a single-blind, Phase I trial

7.14.1 Synopsis

Trial Title	***Pharmacokinetic study of single ascending and multiple ascending doses of a whole plant Cannabis sativa (material/extract) containing THC in (a capsule/oil)***	
MRINZ reference		
Clinical Phase	Phase 1	
Trial Design	Prospective trial, single centre	
Name of Product		
Trial Participants	Healthy adult males	
Planned Sample Size	Up to 28 (7 participants for Part A and 14 to21 participants for Part B)	
Treatment duration	**Part A (SAD):** 4 x 32-hour admissions to Clinical Trial Unit with a minimum of 21 days between the start of the admissions **Part B (MAD):** 1 x admission period to the Clinical Trial Unit. The length of the visit and amount of dosing will be dependent on results from Part A. (2 to 3 cohorts)	
Follow up duration	**Part A:** up to 30 days after final dose **Part B:** 30 days	
Planned Trial Period	9-12 months	
Part A	**Objectives**	**Outcome Measures**
Co-Primary	To determine the pharmacokinetics of THC following ascending single doses of whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil) containing concentrations of 5mg, 10mg, 20mg and 30/40mg THC. Through the measurement of: • Peak concentration and time after administration of THC when the maximum plasma concentration is reached. • Change from baseline of serum concentration of THC over time. • Time taken for the drug concentration to fall to one half of its original value.	• Peak concentration ($C_{(max)}$) and time to maximum concentration ($T_{(max)}$) • Area under the curve from 0-24h (AUC_{0-24h}) • Serum half-life ($t_{1/2}$)
	To ascertain feasibility of further clinical studies	Safety and tolerability data

Part A	Objectives	Outcome Measures
Secondary	To determine the pharmacokinetics of Δ8-THC, THCA, 11-OH-THC, THC-COOH, CBD, 7-COOH-CBD, CBDA, and urinary excretion of free THC and THC-COOH following a single dose of whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil) of 5mg, 10mg, 20mg and 30/40mg THC. Through the measurement of: • Peak concentration and time after administration of Δ8-THC, THCA, 11-OH-THC, THC-COOH, CBD, 7-COOH-CBD, CBDA when the maximum plasma concentration is reached. • Change from baseline of serum concentration over time of Δ8-THC, THCA, and 11-OH-THC, THC-COOH, CBD, 7-COOH-CBD and CBDA. • Time taken for the drug concentration to fall to one half of its baseline value.	• Peak concentration ($C_{(max)}$) and time to maximum concentration ($T_{(max)}$) • Area under the curve from 0-24h (AUC_{0-24h}) • Serum half-life ($t_{1/2}$)
	To determine the tolerability and acceptability of fixed ascending dose concentrations of 5mg, 10mg, 20mg and 30/40mg THC in a whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil).	The change from the baseline DEQ score/STAI Y/CANTAB/MUSE tests at each time point over 24 hours following administration of single dose.
	To determine the cardiovascular response to a single dose of a whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of 5mg, 10mg, 20mg and 30/40mg THC.	Measurement of: • blood pressure • heart rate • electrocardiography (ECG)
	To determine renal and hepatic response to a single dose of a whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC 5mg, 10mg, 20mg and 30/40mg THC.	Measurement at set points over the study period of: • serum liver function tests • creatinine • urea and electrolytes • full blood count

For Part B, the following specific parameters are dependent on the outcomes of Part A:

1. **Dose for serial administration will be confirmed by response and tolerability outcomes of Part A**
2. **Interval between serial doses will be the CBD $T_{1/2}$ established in Part A**

Part B	**Objectives**	**Outcome Measures**
Co-Primary	To determine the pharmacokinetics of THC following multiple ascending doses of whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil) (signaled by Part A). Through the measurement of: • Peak concentration and time after administration of CBD when the maximum plasma concentration is reached (t_{max}). • Change from baseline of serum concentration of THC over time following serial doses. • Time taken for the drug concentration to fall to one half of its original value following serial doses • The measurement of C_{max} multiple dose/ C_{max} single dose • Minimum plasma concentration of parent and metabolites prior to administration of next dose.	• Peak concentration ($C_{(max)}$) and time to maximum concentration ($T_{(max)}$) • Area under the curve from 0-24h (AUC $_{0\text{-}24h}$) • Serum half-life ($t_{1/2}$) • Accumulation Ratio • Trough concentrations
Secondary	To determine the pharmacokinetics following multiple ascending doses of whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil) (dose to be determined by Part A) for each of the cannabinoid metabolites, Δ8-THC, THCA, 11-OH-THC, THC-COOH, 7-COOH-CBD, CBD, CBDA, and urinary excretion of free THC and THC-COOH. Through the measurement of: • Peak concentration and time after administration of Δ8-THC, THCA, 11-OH-THC, THC-COOH, 7-COOH-CBD, CBD, CBDA when the maximum plasma concentration is reached. • Change from baseline of serum concentration overtime following serial doses. • Time taken for the drug concentration to fall to one half of its original value following the serial doses. • The measurement of AR= C_{max} multiple dose/ C_{max} single dose	• Peak concentration ($C_{(max)}$) and time to maximum concentration ($T_{(max)}$) • Area under the curve from 0-24h (AUC $_{0\text{-}24h}$) • Serum half-life ($t_{1/2}$) • Accumulation Ratio • Trough concentration

	• Minimum plasma concentration of metabolites prior to administration of next dose. • Change from baseline of urinary concentration over time of free THC and THC-COOH.	
	To determine the tolerability and acceptability of multiple ascending doses of a whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil) (dose to be determined by Part A) in a population of healthy males.	The change from the baseline DEQ/STAI-Y/CANTAB/MUSE test score at each time point over 24 hours following administration of multiple ascending doses.
	To determine the cardiovascular response to multiple ascending doses of a whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil) (dose to be determined by Part A).	Measurement of: • blood pressure, • heart rate • electrocardiography (ECG)
	To determine renal and hepatic response to multiple ascending doses of a whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil) (dose to be determined by Part A).	Measurement at set points over the study period of: • serum liver function tests • creatinine • urea and electrolytes • full blood count
Investigational Medicinal Product(s)	**Part A:** 4 x Single ascending doses of whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil) **Part B:** Multiple ascending doses of whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil)). The number of doses and dose level in Part B are dependent on Part A.	
Formulation, Dose, Route of Administration	To be determined. Plant (material/extract) in (a capsule/oils); Oral route of administration.	

7.14.2 Abbreviations

11-OH-THC	11-hydroxy-delta-9-tetrahydrocannabinol
AE	Adverse event
AR	Adverse reaction
CBD	Cannabidiol
CBDA	Cannabidiolic Acid
CCDHB	Capital and Coast District Health Board
CRA	Clinical Research Associate (Monitor)
CRF	Case Report Form
CRP	C-Reactive Protein
CTU	Clinical Trials Unit
DEQ	Drug Effect Questionnaire
DLAE	Dose Limiting Adverse Event
DMC/DMSC	Data Monitoring Committee / Data Monitoring and Safety Committee
ESR	Institute of Environmental Science and Research
ECG	Electrocardiography
GCP	Good Clinical Practice
GP	General Practitioner
HDEC	Health and Disability Ethics Committees
IB	Investigators Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IL-6	Interleukin 6
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MAD	Multiple Ascending Dose
MRINZ	Medical Research Institute of New Zealand
MSU	Mid-Stream Urine
PI	Principal Investigator

PIS	Participant/ Patient Information Sheet
SAD	Single Ascending Dose
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCOTT	Standing Committee on Therapeutic Trials
SDV	Source Data Verification
sICAM-1	Soluble intercellular adhesion molecule-1
SMPC	Summary of Medicinal Product Characteristics
sP-selectin	Soluble platelet selectin
SOP	Standard Operating Procedure
STAI-Y	State –Trait Anxiety Inventory (Form Y)
sVCAM-1	Soluble vascular cell adhesion molecule-1
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBD	To Be Determined
Δ9-THC	Delta – 9 Tetrahydrocannabinol
Δ8-THC	Delta – 8 Tetrahydrocannabinol
THCA	Delta - 9 Tetrahydrocannabinolic acid
THC-COOH	11-Nor-9-carboxy-delta-9-tetrahydrocannabinol

7.14.3 Background and Rationale

There is increasing demand for licensing and prescription of medical cannabis in New Zealand, however, robust evidence of efficacy in standardised, pharmaceutical grade product, via adequately sized and generalisable confirmatory randomised controlled trials (RCTs) is limited.

Tetrahydrocannabinol (Δ9-THC) is well known for its psychoactive properties due to its partial agonism of CB_1 receptors in the brain. THC acts at the CB_1 and CB_2 receptors, with the CB_1 receptors concentrated in areas that regulate appetite, memory, fear extinction, motor responses and posture, as well as non-neural tissues.[4] CB_2 receptors are primarily expressed on the cells and organs of the immune system,[315] but they can also be found in neural tissues as well. Cannabidiol (CBD) acts in a number of distinct receptor pathways,[316] suggesting a wide range of potential therapeutic applications[317] with clinical trials reported in epilepsy, glaucoma, anxiety and

dementia.[4] CBD has been shown to have a synergistic effect with THC, antagonising CB_1 when THC is present despite having a low binding affinity for the receptor, and potentially mitigating some of the negative THC mediated effects.[5] This 'entourage' effect has been postulated to involve the many phytocannabinoids and terpenoids present in the whole cannabis plant, described by Mechoulam as a 'neglected pharmacological treasure trove'[5] and to date, there have been few studies looking at the potential therapeutic effect of whole plant cannabis extracts with known fixed ratios of constituents.

Cannabis plants can usually be categorised by 'chemotype' according to the relative concentrations of Δ^9-THC and CBD (Table 1).[4] In addition to Δ9-THC and CBD, there are more than 104 phytocannabinoids and terpenoids present in the cannabis plant.[4]

Chemotype	**Δ^9-THC**	**CBD**	**CBD: Δ^9-THC ratio**
THC-type	0.5 – 15%	0.01 – 0.16%	<0.02
Hybrid	0.5 – 5%	0.9 – 7.3%	0.6 - 4
CBD-type	0.05 – 0.7%	1.0 – 13.6%	>5

Table 1. Cannabis Phenotypes

There is currently only one cannabis-based pharmaceutical grade product available in NZ called Sativex (nabiximols).[13] This is an oro-mucosal spray that contains 2.7mg Δ9-tetrahydrocannabiol (Δ9-THC) and 2.5mg cannabidiol (CBD) per spray. Pharmacokinetic studies were done with 4 sprays of nabiximols (equivalent to 10.8mg Δ9-THC) and this was generally well tolerated with little evidence of psychoactivity after a single dose. In clinical practice the number of sprays that a patient uses is titrated gradually over two dosing periods in a day until optimal symptom relief is reached, to a maximum of 12 sprays in a day (32.4mg Δ9-THC).[13] Nabiximols is approved for use as an add on treatment for spasticity in Multiple Sclerosis, with the current evidence behind its use based on patient-reported symptoms of reduction of spasticity as there is limited evidence for an effect on clinician-measured spasticity.[4,13]

There is also a growing interest into the use of Δ9-THC derived medications for use in chronic pain. A meta-analysis of 5 randomised controlled trials of inhaled cannabis in regards to neuropathic pain indicated there may be evidence of short term pain relief from Δ9-THC, however this needs to be further researched with larger clinical trials with the long term risks vs benefits of inhaled cannabis to be established.[318] When considering overall administration of THC medications, primarily oral, a systematic review and meta-analysis of cannabis in chronic non-cancer pain indicated that there was low to moderate quality evidence of a reduction of pain by 30% on a NRS in neuropathic pain.[52]

This study also reported the number needed to treat for effect was 24 compared with the number needed to treat to harm of six for all adverse events.[52] There remains the need for further larger RCT trials to establish the effects of cannabinoids in pain relief.

The majority of pharmaceutical grade cannabis derived medications, such as nabiximols, contain the psychoactive ingredient Δ9-THC. A significant number of studies have been done examining the clinical effect of Δ9-THC containing medications on spasticity[32,319–321] and chemotherapy induced nausea and vomiting[40], with limited evidence showing that these may be effective, however further large clinical trials are required. During some of these studies patients have withdrawn due to intolerable side effects such as hallucinations and paranoia.[322] Other known side effects from even single doses of Δ9-THC are reduction in performance in memory, attention, impulse control and motor function.[323]

There has been increasing research into CBD as an active medication on its own- with small clinical trials done in glaucoma, anxiety and dementia.[4] Epidiolex (a purified 98% oil-based CBD extract) has undergone larger clinical trials for use in drug resistant seizures in severe childhood epilepsy syndromes which showed a greater reduction in convulsive-seizure frequency than placebo.[60] Epidiolex has recently been approved for use by the United States Food and Drug Administration (FDA).

The Investigational Medical Product (IMP) for this study will be an oral administration of whole plant cannabis (material/extract) containing a fixed amount of Δ9-THC with proportions of other cannabinoids, including CBD, to be determined by laboratory testing at the Institute of Environmental Science and Research (ESR). There will be varying strengths of IMP available for study use, depending on the study design.

The determination of the pharmacokinetics, pharmacodynamics and tolerability of the IMP in a healthy male adult population will inform an appropriate dosing regimen of a whole plant cannabis (material/extract) containing Δ9-THC for future clinical pilot studies.

The study will be divided into Part A (Single Ascending Dose- (SAD)) and Part B (Multiple Ascending Doses-(MAD)). The doses for Part B will be informed by Part A.

Seven healthy adult males able to provide informed consent will be recruited to undertake Part A of the Study. This will be a single ascending dose study (SAD) of up to four dose levels. Two to three cohorts of seven healthy adults will be recruited to undertake Part B of the study, which is a multiple ascending dose study (MAD). Exclusion criteria include but are not limited to; previous use of cannabis in the six months prior to the study, positive cannabinoid urine toxicology, current

smoker, any medical condition requiring regular treatment, any prescription or regular over the counter medications, any history of psychosis, depression or other psychological/psychiatric disorder.

Participants will be recruited from the MRINZ database with use of General Practice mail-out/social media advertising if required.

7.14.3.1 Part A (SAD):

Seven participants will be admitted to a Clinical Trials Unit for four separate dosing visits. At each visit they will receive a single dose of IMP. Each dose of IMP will contain a fixed dose of THC. At the first visit, participants will receive 5mg Δ9-THC increasing to 10mg, 20 mg and 30/40 mg Δ9-THC at each of the subsequent dosing visits. These doses have been determined following review of other clinical trials and medications currently available worldwide - dronabinol, a synthetic THC oral formulation, has a maximum dose reported of 40mg per 24 hours and nabiximols, an oro-mucosal spray has a maximum dose of 32.4mg Δ9-THC per 24 hours when prescribed in NZ.[13,324] Oral bioavailability of Δ9-THC is estimated to be about 6-10%, with studies in chronic cannabis users giving oral doses of up to 120mg per 24 hours.[325] Participants in this study will not be required to be chronic cannabis users to participate, hence much lower doses due to potential naiveté.

During this study participants will be blinded to the specific amount in milligrams of active ingredient they will be receiving. Participants will be aware that the doses are ascending but they will not know increments that are being applied between the four dosing visits. The participant will provide urine and blood tests, undergo cardiovascular monitoring including an electrocardiogram (ECG) and complete Drug Effect Questionnaires (DEQ), State-Trait Anxiety Inventory-Y (STAI-Y), visual analogue scales and a neuro-psychological test battery (CANTAB/MUSE) at pre-determined times over a 32-hour period. Fourteen days after their first dosing visit the participants will attend a follow up visit with provision of further blood and urine samples at the Medical Research Institute of New Zealand (MRINZ). This interval has been determined as cannabinoids have been shown to have varying elimination half-lives, ranging from 20-30- hours to 5-6 days for THC-COOH and CBD when taken orally.[326,327] For urinary clearance of metabolites, one study showed last negative urine results obtained at an average of 12.9 days (range 3-29) for infrequent cannabis users.[327] If necessary, further samples will be collected at seven days intervals until clearance of Δ9-THC and Δ9-THC metabolites is achieved. When all seven participants have demonstrated clearance of the metabolites the next study visit for the next dose level will be scheduled.

7.14.3.2 Part B (MAD):

Two to three cohorts of seven new participants will be admitted to the Clinical Trials Unit for up to 6 days. All participants will then receive up to four doses of IMP per day for up to five days, X hrs apart, containing a fixed amount of Δ9-THC that will be determined by Part A. The participant will provide urine and blood tests, undergo cardiovascular monitoring including an ECG and complete DEQ, STAI-Y, visual analogue scales, and neuro-psychological cognitive tests (CANTAB or MUSE) at pre-determined times over each 24-hour period. At days 14 and 21 the participants will attend a follow up visit with provision of further blood and urine samples at MRINZ. If necessary, further samples will be collected at seven-day intervals until clearance has been achieved, following which study participation is complete.

If there is a requirement for IMP dosing beyond five days as determined by Part A, a new protocol will be developed and submitted for ethics review.

7.14.4 Objectives and Outcome Measures

7.14.4.1 Part A (SAD)

Objectives (safety, feasibility)	**Outcome Measures**	**Time point(s) of evaluation**
Co-Primary Objectives		
To determine the pharmacokinetics of THC following ascending single doses of whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil) containing concentrations of 5mg, 10mg, 20mg and 30/40mg THC. Through the measurement of: • Peak concentration and time after administration of THC when the maximum plasma concentration is reached. • Change from baseline of serum concentration of THC over time. • Time taken for the drug concentration to fall to one half of its original value.	• Peak concentration ($C_{(max)}$) and time to maximum concentration ($T_{(max)}$) • Area under the curve from 0-24h (AUC_{0-24h}) • Serum half-life ($t_{1/2}$)	Outcome measure time points: • See Schedule of procedures

Secondary Objectives		
To determine the pharmacokinetics of Δ8-THC, THCA, 11-OH-THC, THC-COOH, CBD, 7-COOH-CBD, CBDA, and urinary excretion of free THC and THC-COOH following a single dose of whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil) of 5mg, 10mg, 20mg and 30/40mg THC. Through the measurement of: • Peak concentration and time after administration of Δ8-THC, THCA, 11-OH-THC, THC-COOH, 7-COOH-CBD, CBD, CBDA when the maximum plasma concentration is reached. • Change from baseline of serum concentration overtime following serial doses. • Time taken for the drug concentration to fall to one half of its original value following the serial doses. • The measurement of AR= C_{max} multiple dose/ C_{max} single dose • Minimum plasma concentration of metabolites prior to administration of next dose. • Change from baseline of urinary concentration over time of free THC and THC-COOH.	• Peak concentration ($C_{(max)}$) and time to maximum concentration ($T_{(max)}$) • Area under the curve from 0-24h (AUC $_{0\text{-}24h}$) • Serum half-life ($t_{1/2}$)	Outcome measure time points: • See Schedule of procedures
To determine the tolerability and acceptability of fixed ascending dose concentrations of 5mg, 10mg, 20mg and 30/40mg THC in a whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil).	The change from the baseline DEQ, STAI-Y, visual analogue test and Neuropsychological test (CANTAB/MUSE tests) score at each time point over 24 hours following administration of single dose.	Outcome measure time points: • See Schedule of procedures
To determine the cardiovascular response to a single dose of a whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of 5mg, 10mg, 20mg and 30/40mg THC.	Measurement of: • blood pressure, • heart rate • electrocardiography (ECG)	Outcome measure time points: • See Schedule of procedures

To determine renal and hepatic response to a single dose of a whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC 5mg, 10mg, 20mg and 30/40mg THC.	Measurement of: • serum liver function tests • creatinine • urea and electrolytes • full blood count	Outcome measure time points: • See Schedule of procedures

7.14.4.2 Part B (MAD)

Each cohort will have the same outcome measures.

Objectives	**Outcome Measures**	**Time point(s) of evaluation**
Co-Primary Objectives		
To determine the pharmacokinetics of THC following multiple ascending doses of whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil) (signaled by Part A). Through the measurement of: • Peak concentration and time after administration of THC when the maximum plasma concentration is reached (t_{max}). • Change from baseline of serum concentration of THC over time following serial doses. • Time taken for the drug concentration to fall to one half of its original value following serial doses • The measurement of C_{max} multiple dose/ C_{max} single dose • Minimum plasma concentration of parent and metabolites prior to administration of next dose.	• Peak concentration ($C_{(max)}$) and time to maximum concentration ($T_{(max)}$) • Area under the curve from 0-24h (AUC $_{0\text{-}24h}$) • Serum half-life ($t_{1/2}$) • Accumulation Ratio • Trough concentrations	Outcome measure time points: • See Schedule of procedures

Secondary Objectives		
To determine the pharmacokinetics following multiple ascending doses of whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil) (dose to be determined by Part A) for each of the cannabinoid metabolites, Δ8-THC, THCA, 11-OH-THC, THC-COOH, 7-COOH-CBD, CBD, CBDA, and urinary excretion of free THC and THC-COOH. Through the measurement of: • Peak concentration and time after administration of Δ8-THC, THCA, 11-OH-THC, THC-COOH, 7-COOH-CBD, CBD, CBDA when the maximum plasma concentration is reached. • Change from baseline of serum concentration overtime following serial doses. • Time taken for the drug concentration to fall to one half of its original value following the serial doses. • The measurement of AR= C_{max} multiple dose/ C_{max} single dose • Minimum plasma concentration of metabolites prior to administration of next dose. • Change from baseline of urinary concentration over time of free THC and THC-COOH.	• Peak concentration ($C_{(max)}$) and time to maximum concentration ($T_{(max)}$) • Area under the curve from 0-24h (AUC $_{0\text{-}24h}$) • Serum half-life ($t_{1/2}$) • Accumulation Ratio • Trough concentration	Outcome measure time points: • See Schedule of procedures
To determine the tolerability and acceptability of multiple ascending doses of a whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil) (dose to be determined by Part A) in a population of healthy males.	The change from the baseline DEQ score, STAI-Y, Visual analogue tests and Neuropsychological test (CANTAB/MUSE tests) at each time point over 24 hours following administration of serial doses.	Outcome measure time points: • See Schedule of procedures
To determine the cardiovascular response to multiple ascending doses of a whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil) (dose to be determined by Part A).	Measurement of: • blood pressure, • heart rate • electrocardiography (ECG)	Outcome measure time points: • See Schedule of procedures

To determine renal and hepatic response to multiple ascending doses of a whole plant, *Cannabis sativa* (material/extract) with a fixed concentration of THC in a (a capsule/oil) (dose to be determined by Part A)	Measurement of: • serum liver function tests • creatinine • urea and electrolytes • full blood count	Outcome measure time points: • See Schedule of procedures

7.14.5 Trial Design

This is a Phase I prospective, single blind study examining the pharmacokinetics, safety and tolerability of the single dose of whole plant cannabis (material/extract) containing Δ9-THC in a (a capsule/oil) with fixed ascending doses of 5mg Δ9-THC, 10mg Δ9-THC, 20mg Δ9-THC and 30/40mg Δ9-THC in Part A. Part B involves serial doses of IMP determined by Part A, based on safety and pharmacokinetic outcomes.

A total of seven participants in Part A and 14 to 21 participants for Part B. The participants for Part B will be different to Part A.

Participants will be enrolled in the study for a minimum period of 120 days for Part A and a minimum period of 20 days for Part B.

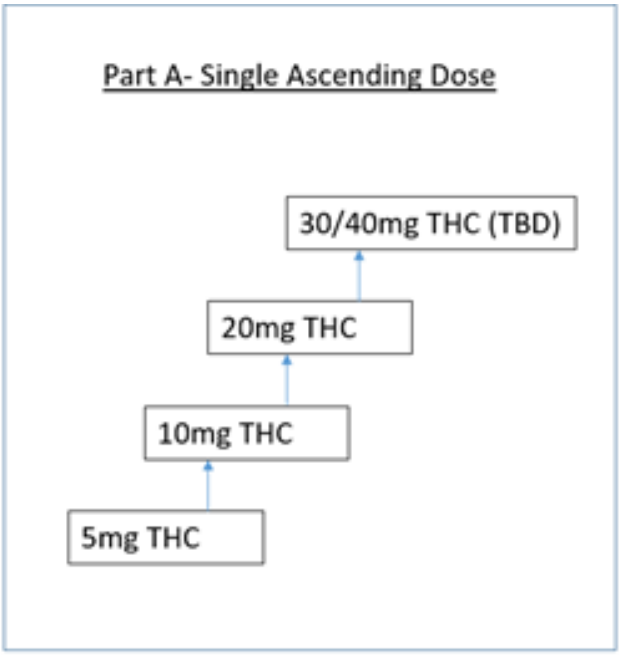

Figure 1. Proposed dosage escalation for Part A.

7.14.5.1 Part A (SAD):

Includes a minimum nine visits with potential additional visits required to establish full metabolite clearance. Seven participants will be recruited.

Visit One: Consisting of eligibility, informed consent, and the following procedures: weight, height, vital sign measurements, screening bloods (including fasting glucose) and urinary drug screen test. All seven participants will be assigned to treatment of IMP.

Visit Two, Visit Four, Visit Six and Visit Eight: A 32-hour admission for single dosing and pharmacokinetic measurements. Participants will receive single dose of complete cannabis extract IMP at a fixed dose of of whole plant cannabis (material/extract) containing Δ9-THC in a (a capsule/oil) with fixed ascending doses of 5mgΔ9-THC (V2), 10mgΔ9-THC (V4), 20mg Δ9-THC (V6) and 30/40mg Δ9-THC (V8) (Figure 1). Repeated blood samples will be collected at pre-specified time points, preferably via an insertion of an intravenous (IV) catheter (as per MRINZ SOP) or individual collection if required. Serial urine collections for pharmacokinetic (PK) measurements will be collected. Cardiovascular monitoring (intermittent 12 lead ECG and blood pressures), DEQ, STAI-Y, visual analogue scales and a neuro-psychological test battery (CANTAB/MUSE) Tests will also be completed and according to the schedule of procedures (PK Study Appendix 1).

Participants will be fasted for a minimum of 6 hours prior to presentation and present to the Clinical Trials Unit (CTU) at 7 AM for confirmation of consent, inclusion and exclusion criteria. Baseline vital signs will be measured and baseline blood and urinary samples taken. They will then be fed a standardised breakfast meal 60 minutes prior to first IMP dose. Following the dose, participants will have serum samples taken at 30 minutes, 1, 1.5, 2, 3, 4, 6, 8, 12 and 24 hours post dose. A standardised meal will be provided four and eight hours post dose followed food served at standardised times until discharge. Oral fluids will be restricted from breakfast completion until after two hours post dose. Concentration data between the baseline, maximum concentration; dose-concentration and -response curves, clearance, exposure (AUC) and half-life will be measured to assess inter-individual variation in saturable clearance pathways. Participants will be monitored for any adverse events, especially adverse events of interest (PK Study Appendix 2) and if a pre-defined proportion (TBD) are report these then the dose at which this occurs will be determined to be the maximum tolerated dose (MTD) and the SAD study will be halted.

Participants will have a final blood test at 24 hours post dose and provide a blood sample for pharmacokinetics.

Participants will be discharged no less than 24 hours following their last dose, unless any medical concerns are raised by the attending study physician or carer.

The interval between dosing visits will be a minimum of 21 days to allow for the clearance visits to be undertaken. This process for each visit is the same as the one above except a doubling of the Δ9-THC dose will occur.

Visit Three, Visit Five, Visit Seven and Visit Nine: Follow up clinic visit for urine and serum samples at 14 days (PK Study Appendix 1) with subsequent unscheduled sampling visits as required.

7.14.5.2 Part B (MAD):

Includes two to three cohorts of seven participants with a minimum of four visits per cohort with potential additional visits required to establish full metabolite clearance. Up to 21 new participants, different from Part A will be recruited.

The IMP dose will be determined by the findings in Part A, namely the maximum tolerated dose.

Visit One: Consisting of eligibility, informed consent, screening bloods (including fasting glucose), urine samples, 12 Lead ECG, vital signs, height and weight. All new participants will be assigned to treatment of IMP. Dose of IMP is determined from Part A.

Visit Two: A maximum six night/seven day admission for serial dosing and pharmacokinetic measurements. If the dosing time is required to be longer a new protocol will be submitted to ethics for approval. HDEC will be advised on the exact dose concentration and regime that will be given to participants for Part B prior to commencement. Participants will receive up to four IMP doses (determined from Part A), administered each day in intervals to be determined from the Δ9-THC half-life established in Part A. Repeated blood samples will be collected at pre-specified time points, preferably via an insertion of an IV catheter (as per MRINZ SOP) or individual collection if required. Serial urine collections for PK will be collected. Cardiovascular monitoring (intermittent 12 lead ECG and blood pressures), DEQ, STAI-Y and Visual Analogue Scales and Neuro-psychological test (CANTAB/ MUSE tests) will also be completed and according to the schedule of procedures (PK Study Appendix 1).

Participants will be fasted for a minimum of six hours prior to presentation and present to the Clinical Trials Unit at 7 AM for confirmation of consent, inclusion and exclusion criteria. Baseline vital signs will be measured and baseline blood and urinary samples taken. They will then be fed a standardised breakfast meal 60 minutes prior to first IMP dose. Following the first dose,

participants will have multiple serum samples taken at 30 minutes, 1, 1.5, 2, 3 and 4 hours post dose and immediately prior to subsequent doses (PK Study Appendix 1). A final serum sample will be taken 24 hours after the last dose. A standardised meal will be provided four and eight hours post dose followed by food served at standardised times until discharge. Oral fluids will be restricted from completion of breakfast through to two hours post dose.

Concentration data between the baseline, maximum concentration; dose-concentration and response curves, clearance, exposure (AUC) and half-life will be measured to assess inter-individual variation in saturable clearance pathways.

Participants will be monitored for any adverse events, especially adverse events of interest (PK Study Appendix 2) and if a pre-defined proportion (TBD) are reported these then the dose at which this occurs will be determine a change in dosage schedule/termination of the MAD dosing schedule.

Participants will be discharged no less than 24 hours post their last unless any medical concerns are raised by the attending study physician or carer.

Visit Three: Follow up clinic visit for urine and serum samples 14 days (PK Study Appendix 1) post last dose (determined by Part A).

Visit Four: Follow up clinic visit for urine and serum samples at 21 days (PK Study Appendix 1) post last dose (determined by Part A).

7.14.6 Participant Identification

7.14.6.1 Trial Participants

- Anticipated 28 healthy adult males.

7.14.6.2 Inclusion Criteria

All the following must be met:

- Willing and able to give informed consent for participation in the trial
- Willing and able to comply with all trial requirements
- Male
- 18 years or over
- Body Mass Index ≤30 and ≥ 18.5

- Normal Variant ECG
- No medical disorders requiring regular pharmacological or medical management, including psychological/psychiatric disorders.
- No prescribed regular medications.
- No regular over the counter medications.
- Willing to allow their General Practitioner to be notified of participation in the trial and to give access to relevant medical history for the purposes of eligibility.
- Willing to remain abstinent or use a condom for the period of the study and 28 days post last dose.

7.14.6.3 Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Participants who are not deemed ‘healthy’ by the attending study physician- either through review of medical history or significant concerns following undertaking of physical exam and screening bloods.
- Use of cannabis, medical or otherwise, in the previous six months.
- Participants who have participated in the past six months, or are planning to enrol in another research trial involving an investigational product.
- Positive urine toxicology screen for cannabinoids or other drugs of abuse.
- Current smoker.
- History of substance abuse.
- Use of herbal remedies or medications.
- History of psychosis or other psychological/psychiatric disorder.
- History of cardiovascular disease or liver disease.
- History of allergy to cannabinoids or cannabis products.

7.14.7 Trial Procedures

7.14.7.1 Recruitment

Participants will be identified from the Medical Research Institute of New Zealand (MRINZ) Database. They will be contacted by phone or email and offered pre-screening to assess potential eligibility. If required, recruitment via social media and GP mail-out will be undertaken.

Respondents interested in enrolling in the study will be sent a participant information sheet via post or email and invited to discuss further any aspect of the trial. Part A will enrol and complete the study prior to ongoing recruitment for Part B.

7.14.7.2 Informed consent (Part A-Visit One and Part B-Visit One)

Informed consent for the study will be undertaken by a study investigator prior to any physical examination or study-related procedures.

The participant must personally sign and date the latest approved version of the Informed Consent form before any trial specific procedures are performed.

Participants will be considered 'enrolled' at the time the inclusion and exclusion criteria have been met and the study specific consent form has been completed by both the Participant and Study Investigator.

7.14.7.3 Eligibility Assessments (Part A-Visit One and Part B-Visit One)

After consent, a screening urine toxicology test will be undertaken. If positive for cannabinoids or other drugs of abuse, the participant will be deemed to be ineligible and included on the screening log. If eligible, participants will be asked for demographics, a full medical history including concomitant medications, and undergo a physical examination including height and weight to determine BMI. They will also undergo vital signs, urine tests for ECG and screening bloods.

7.14.7.3.1 Medical History, Concomitant Medications, Demographics

Participants will be asked their sex, age and ethnicity as demographic data.

Full medical history will include current and previous medical and surgical problems, psychiatric disorders, any food and drug allergies, smoking, drug and alcohol history.

Concomitant medications will be recorded. If participants are on any regular medications they will be deemed ineligible. During the course of the study, participants may require irregular use of

analgesics, antipyretics, anti-histamines, inhalers which will be discussed with study physician and recorded on the concomitant medication form.

7.14.7.3.2 Physical Examination, Body Mass Index

A full physical examination will be undertaken examining the following systems: Cardiovascular, Respiratory, Ear Nose and Throat (ENT), Lymph Nodes, Gastro-instestinal, Gross Neurology and Cranial Nerves, Musculoskeletal, Dermatology. A Genitourinary examination is not required as part of the physical exam and any indications for this on medical history should be referred back to the participants GP for review.

Limited physical examination may be undertaken during enrolment during the study as required according to patient reports of adverse events.

Participants' height and weight will be measured at Visit 1 in light clothing and no shoes to calculate their Body Mass Index (BMI).

7.14.7.3.3 Vital Signs

The following vital signs will be measured at visit one and at pre-determined points throughout the study visit (PK Study Appendix 1):

- Heart Rate
- Respiratory Rate
- Blood Pressure
- Temperature

If a study clinician has concerns about the participants' health they may choose to measure and record vital signs outside the pre-determined time points.

7.14.7.3.4 Urine Tests

Participants will be asked to provide a mid-stream urine (MSU) for urine cannabinoid and drug of abuse screening as well as urine dipstick analysis for health screening purposes. At screening a dipstick will be determined to see if there are any cannabinoids or drugs of abuse present. If so, the participant is deemed ineligible for the study.

The MSU will be assessed for colour and cloudiness and urine dipstick analysis will be undertaken to assess for leucocytes, red blood cells, glucose, protein, pH, specific gravity and ketones. If symptoms of a UTI with the presences of 3+ leucocytes or nitrites then the sample will be sent to

the lab for culture and sensitivities. If presence of 2+ blood then the sample will be sent for microscopy and examination for casts. All participants with blood in their urine will be advised that their GP will be notified for ongoing follow up as required post study completion. Presence of glucose will be referred to participants GP for further investigation.

7.14.7.3.5 Electrocardiogram (ECG)

Participants will undergo a single ECG at baseline to ensure that they have a normal variant ECG as determined by the study clinician. Isolated sinus bradycardia between 50-60bpm will be considered a normal variant for the purposes of this study. If the study clinician is unable to determine if the ECG is a normal variant or not this may be reviewed by a cardiologist for their opinion.

Participants will undergo single ECGs at pre-determined time points throughout the study to examine cardiovascular effects of the medication. ECGs must be reviewed by an investigator at the time of obtaining them. Any acute change must be managed according to the accompanying symptoms and if thought to be attributable to the IMP be recorded as a dose limiting adverse event (DLAE).

7.14.7.3.6 Serum Blood tests

Participants will undergo a series of screening blood tests (PK Study Appendix 3 for full list) prior to enrolment in the study. Eligibility will only be affected if the results of the screening bloods are considered relevant to a medical diagnosis that is significant in the investigators opinion.

Safety bloods (PK Study Appendix 3) will be taken at pre-determined times throughout the dosing admissions (PK Study Appendix 1) and sent to a local laboratory for processing. Results will be reviewed by investigators. Significant changes in blood results will be recorded as adverse events if they are either; accompanied by clinical signs, related to a change in study medications, result in a medical intervention or are considered significant in the eyes of the investigator. Results will be graded for severity using the WHO toxicity grading system (PK Study Appendix 4).

7.14.7.4 Blinding and code-breaking

7.14.7.4.1 Blinding

This is a single blind study. Participants only are blinded.

7.14.7.5 Visits

7.14.7.5.1 Part A

7.14.7.5.1.1 Visit Two, Visit Four, Visit Six and Visit Eight

7.14.7.5.1.1.1 Baseline Assessments

At the time of the 32 hour admission to the CTU subjects will undergo the following baseline assessments:

- Urine toxicology screening for cannabinoids with a positive urine toxicology resulting in participant withdrawal from the study.
- Preferably an IV cannula for blood sampling will be placed and blood samples obtained for analysis of baseline serum pharmacokinetics, liver function tests, coagulation screen, full blood count, urea and electrolytes, creatinine, glucose, and lipids, however separate blood tests may be obtained if required.
- ECG
- Heart Rate, Respiratory Rate, Blood pressure, Temperature
- DEQ
- STAI-Y
- Visual analogue scales
- Neuro-psychological tests (CANTAB/MUSE)

7.14.7.5.1.1.2 Dosing of IMP

One hour following a standard breakfast meal, the participant will receive a single ascending dose of IMP containing whole plant, *Cannabis sativa* (material/extract)with a fixed concentration of THC) with 5mg Δ9-THC during Visit Two, 10mg Δ9-THC during Visit Three, 20mg Δ9-THC during Visit Four, or 30/40mg Δ9-THC during Visit Five. There will be a minimum 14-day wash out period from initial dosing (Day 1) between each of the dosing visits.

7.14.7.5.1.1.3 Post Dose Assessments

- Blood samples will be taken as per the schedule of procedures (PK Study Appendix 1).
- ECG will be completed according to the schedule of procedures (PK Study Appendix 1).
- The DEQ will be administered according to the schedule of procedures (PK Study Appendix 1).

- Heart Rate, Respiratory Rate, Blood pressure according to the schedule of procedures (PK Study Appendix 1).
- On-going monitoring for adverse effects of the IMP. Adverse events of interest include intoxication, sedation, change in cognition, anxiety, paranoia, nausea and heart palpitations, which will be measured by a structured checklist of AEs related to cannabinoids (PK Study Appendix 2). The checklist includes AEs reported in trials of nabiximols and in experimental THC administration studies. Participants will rate daily, the extent to which they experienced intoxication, sedation and other subjective effects of cannabinoids using (0-100).
- The STAI-Y scale will be administered at the same time as the DEQ for analysis of acute anxiety levels (PK Study Appendix 1).
- The Neuropsychological test battery (CANTAB/MUSE) will be used to measure changes in cognitive functioning (PK Study Appendix 1).

7.14.7.5.1.2 Visit Three, Visit Five, Visit Seven and Visit Nine

14 days after IMP dosing on Visit Two, Visit Four, Visit Six and Visit Nine, participants will return to clinic for follow up visits. This will include ECG, vital signs, AE and concomitant medications check, serum and urine samples. If metabolite clearance is not demonstrated further sampling will take place on a weekly basis until a negative result for Δ9-THC metabolites is obtained.

7.14.7.5.2 Part B

7.14.7.5.2.1 Visit Two

7.14.7.5.2.1.1 Baseline Assessments

At the time of admission to the CTU subjects will undergo the following baseline assessments:

- Urine toxicology screening for cannabinoids with a positive urine toxicology resulting in participant withdrawal from the study.
- Preferably, an IV cannula for blood sampling will be placed and blood samples obtained for analysis of baseline serum cannabinoids, liver function tests, full blood count, urea and electrolytes, and creatinine, however separate blood tests may be obtained if required.
- ECG
- Heart Rate, Respiratory Rate, Blood pressure.

- DEQ
- STAI-Y
- Visual analogue test baseline
- CANTAB/MUSE

7.14.7.5.2.1.2 Dosing of IMP

The participant will receive serial doses IMP for x days via orally administered capsule, with maximum of four doses in a 24-hr period. The dose and the dosing interval for Part B will be dependent on Part A.

7.14.7.5.2.1.3 Remaining assessments

- Blood samples will be taken as per the schedule of procedures (PK Study Appendix 1).
- ECG will be completed according to the schedule of procedures (PK Study Appendix 1).
- The DEQ will be administered according to the schedule of procedures (PK Study Appendix 1).
- Heart Rate, Respiratory Rate, Blood pressure (PK Study Appendix 1).
- There will be on going monitoring for adverse effects of the IMP. Adverse events of interest include intoxication, sedation, change in cognition, anxiety, paranoia, nausea and heart palpitations, which will be measured by a structured checklist of AEs related to cannabinoids (PK Study Appendix 2). The checklist includes AEs reported in trials of nabiximols and in experimental THC administration studies. Participants will rate daily, using Visual Analogue Scales (0-100) the extent to which they experienced intoxication, sedation and other subjective effects of cannabinoids.
- The STAI-Y scale will be administered at the same time as the DEQ for analysis of acute anxiety levels (PK Study Appendix 1).
- The Neuro-psychological tests (CANTAB/MUSE) will be administered at a minimum daily over the period of the seven day admission PK Study (Appendix 1).

7.14.7.5.2.2 Visit Three – outpatient visit

Fourteen days after the final IMP dose participants will return to clinic for a further visit to provide serum and urine samples.

7.14.7.5.2.3 Visit Four – Final follow up visit

Twenty-one days after the final IMP dose participants will return to clinic for a final follow up visit. This will include ECG, vital signs, AE and concomitant medications check, serum and urine samples. If Δ9-THC metabolite clearance is not demonstrated further sampling will take place on a weekly basis until a negative result is obtained.

7.14.7.6 Dietary Requirements

To insert standardised food plan here (as per schedule of event).

7.14.7.7 Sample Handling

Blood samples and Urine.

To be performed in conjunction with the following MRINZ standard operating procedures:

- CP.005 Blood sampling
- CP.006 Urine sampling
- HS.002 Infection Prevention and Control
- LA.002 Biohazard Waste

7.14.7.8 Discontinuation/Withdrawal of Participants from Trial Treatment

Each participant has the right to withdraw from the trial at any time. In addition, the Investigator may discontinue a participant from the trial at any time. Reasons may include:

- Previously undisclosed or new information resulting in ineligibility
- Significant protocol deviation or violation
- Non-compliance with treatment regimen or trial requirements
- Any adverse event requiring discontinuation of IMP or resulting in inability to comply with trial procedures
- Withdrawal of consent

Withdrawn participants will not be replaced.

The reason for withdrawal will be recorded in the source data/eCRF.

If the participant is withdrawn due to an adverse event, the Investigator will arrange appropriate medical consultation, follow-up visits or telephone calls until the adverse event has resolved or stabilised.

If a participant choses to withdraw or discontinue during the admission period to the clinical trials unit they will be advised to remain until a study physician is confident that they are no longer under the influence. If they choose to leave against medical advice they will be asked to sign a waiver. This waiver will be discussed as part of the enrolment process and will be revisited as required at the time of withdrawal.

7.14.7.9 Definition of End of Trial

End of trial will be last participant discharge from the final clinical visit of Part B.

7.14.8 Investigational Medical Product (IMP)

To be inserted when IMP is known, from supplied investigators brochure.

7.14.8.1 IMP Description

7.14.8.2 Storage of IMP

7.14.8.3 Known Risks associated and Safety Information

7.14.8.4 Accountability of the Trial Treatment

All study IMP will be stored in locked cabinets within a secure facility onsite at Wellington Hospital and accessed only by authorised study investigators. Numerical logs of IMP delivery will be maintained from receipt through to administration on the MRINZ monitoring database and will be regularly reconciled by the MRINZ independent monitoring team. IMP will be handled exclusively by an MRINZ study investigator including administration, which will be under direct supervision of a qualified medical study physician.

7.14.8.5 Concomitant Medication

All prescription cannabinoid medications are contraindicated, and specific history will be obtained as to their use at each visit. Reported use will lead to withdrawal of the participant from the study.

During the course of the study, participants may require irregular use of antibiotics, analgesics, antipyretics, anti-histamines, inhalers which will be discussed with study physician and recorded on the concomitant medication form.

7.14.8.6 Post-trial Treatment

IMP will not be available to participants post study completion.

7.14.9 Safety Reporting

7.14.9.1 Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to an investigational medicinal product which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening • requires inpatient hospitalisation or prolongation of existing hospitalisation • results in persistent or significant disability/incapacity

	• consists of a congenital anomaly or birth defect. Other 'important medical events' may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences. NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product • in the case of any other investigational medicinal product, in the investigator's brochure (IB) relating to the trial in question.
Dose Limiting Adverse Event	Any adverse event (including those adverse events of interest) of a moderate or higher severity (WHO Grade 2 or above) that meets the following criteria: • The adverse event is clinically significant as determined by the investigator and the Dose Safety Monitoring Committee • The adverse event is related to the administration of the study drug as determined by the investigator and Dose Safety Monitoring Committee.

NB: to avoid confusion or misunderstanding of the difference between the terms “serious” and “severe”, the following note of clarification is provided: “Severe” is often used to describe intensity of a specific event, which may be of relatively minor medical significance. “Seriousness” is the regulatory definition supplied above.

Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of “serious”.

7.14.9.2 Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Related: The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.

Not Related: The adverse event is probably produced by the participant’s clinical state or by other modes of therapy administered to the participant.

7.14.9.3 Procedures for Recording Adverse Events

All AEs occurring during the trial period until final follow up visit that are observed by the Investigator or reported by the participant, will be recorded on the CRF, whether or not attributed to trial medication.

The following information will be recorded: description, date of onset and end date, severity, assessment of relatedness to trial medication, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The severity of events will be assessed on the following scale (as per the WHO toxicity guidelines, PK Study Appendix 4): 1 = mild, 2 = moderate, 3 = severe.

AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor will be followed either until resolution, or the event is considered stable.

All DLAE’s must be reported to the Sponsor within 24 hours. All DLAEs will be reviewed promptly and confirmed by the Dose Safety Monitoring Committee and the decision to escalate the dose to the next level will be decided according to pre-determined schedule (to be inserted).

Participants who experience a DLAE will not be given and subsequent doses of the IMP and will be withdrawn from the study.

For Adverse events not DLAEs the investigator will determine whether or not the next dose of IMP should be administered. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable.

7.14.9.4 Reporting Procedures for Serious Adverse Events

All SAEs (other than those defined in the protocol as not requiring reporting) must be reported on the SAE reporting form to the PI, or next most senior representative within 24 hours of the Site Study Team becoming aware of the event. The PI will perform an initial check of the report, request any additional information, and ensure it is reviewed by the Medical Monitor on a weekly basis. All SAE information must be recorded on an SAE form prior to reporting to the HDEC committee.

7.14.9.5 Expectedness

Expectedness will be determined according to the Investigators' Brochure/Summary of Product Characteristics.

7.14.9.6 SUSAR Reporting

All SUSARs will be reported by the PI to the relevant Competent Authority and to the REC and other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than seven calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within eight calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Treatment codes will be un-blinded for specific participants.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current trial.

7.14.10 Safety Monitoring Committee

A Data and Safety Monitoring Committee (DSMC) will be established, which is independent from the study team. The DSMC will review all serious adverse events after visit two, visit four, visit six and visit eight in Part A and visit two in cohort in Part B.

7.14.11 Development of Safety Updates

To be inserted, include protocol deviation information here.

7.14.12 Data Analysis

7.14.12.1 Analysis and software platform

Plan provided by Dr Zheng Liu, University of Newcastle.

All data will be extracted from the electronic reporting format in Excel using R (Version i386 3.3.1)[328] and manipulated into a format that is compatible with the analysis software.

Non-compartment analysis (NCA) will be used to calculate the AUC, Cmax, Tmax etc, and investigate e.g. dose proportionality. NCA is performed with pkr-package (Pharmacokinetics in R).[329]

The pharmacokinetic model will be developed. The software for this used include NONMEM Version 7.2.0 in combination with gfortran compiler, PsN (Perl-speaks-NONMEM) version 4.7.0 , PLT tool , and R.[330–333]

7.14.12.2 Observational outliers

Preliminary analysis with NONMEM will be performed first to identify observational outliers in the observed data. The criterion for identifying an observational outlier is a conditional weighted residual (CWRES) of the observed from the expected data of more than 6 standard deviations.

The formula used to calculate the CWRES is presented in equation (1).[334]

$$CWRES = \frac{y_i - E_{FOCE}(y_i)}{\sqrt{COV_{FOCE}(y_i)}} \quad (1)$$

Where,

$FOCE$: first-order with conditional estimation;

y_i: the measurements for the ith individual in a population

$E_{FOCE}(y_i)$: the expectation of y_i given the model, approximated with FOCE

$COV_{FOCE}(y_i)$: the covariance of y_i given the model, approximated with FOCE

Observations that have CWRES > 6 will be omitted from the model building. The sensitivity of the final model will then be considered in the presence and absence of outliers.

7.14.12.3 Handling of missing data

We consider that there are three overall types of missing data that might plausibly occur in longitudinal study designs:

1) Missing dependent variables (i.e. samples)
2) Missing independent variables (i.e. covariates)
3) Missing participants

Missing data for types 1 and 2 may occur from three processes

1) Missing Completely At Random (truly random missingness) - MCAR
2) Missing At Random (missingness that is conditioned on some observed variable) - MAR
3) Not Missing At Random (missingness that is conditioned on some non-observed variable) - NMAR

Despite this classification in a fully parametric approach we need only consider ignorable missingness (MCAR) and non-ignorable (MAR and NMAR). For non-ignorable missingness a dropout model will be constructed and jointly implemented that contributes the probability of missingness to the overall likelihood. Data that are below the limit of detection are an example of this type of missingness.

Missing type 1 data (observations) will be considered as MCAR if they occur flanked by observed variables on either side (on the time domain) or NMAR if they occur at the end of a profile. MCAR data will be ignored. NMAR data will be modelled with a dropout model.

Missing type 2 data (e.g. covariates such as weight) will be treated as MCAR and a single imputation performed at the median value of the appropriate study population.

Missing type 3 data will be treated as MCAR. No imputation will be performed.

7.14.13 Data Management

7.14.13.1 Source Data

Source documents are where data are first recorded, and from which participants' case report form (CRF) data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

It is the intention of the MRINZ to capture as much (material/extract) as possible immediately into the electronic case report form (eCRF), particularly with respect to patient reported outcomes and investigator/patient interactions. All eCRF entries will be considered source data if the eCRF is the site of the original recording (e.g. there is no other written or electronic record of data, or CRF). CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code and initials, not by name.

7.14.13.2 Access to Data

Direct access will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections.

7.14.13.3 Data Recording and Record Keeping

All trial data will be entered directly into REDCap (Research Electronic Data Capture)[222] using electronic data capture tools hosted and supported by the MRINZ. REDCap is a secure, HIPAA (United States Health Insurance Portability and Accountability Act 1996) compliant web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages, including de-identified data sets; and 4) procedures for importing data from external sources.[222]

Study documents including electronic CRFs (if applicable) will be stored on site at MRINZ, or offsite under MRINZ control for 15 years after the completion of the trial to comply with GCP standards.

7.14.13.4 Quality Assurance Procedures

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

Regular monitoring will be performed according to GCP. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted, and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

7.14.13.5 Serious Breaches

The Medicines for Human Use (Clinical Trials) Regulations contain a requirement for the notification of "serious breaches" to the HDEC within seven days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to affect to a significant degree –

(a) The safety or physical or mental integrity of the subjects of the trial; or

(b) The scientific value of the trial”.

In the event that a serious breach is suspected the Sponsor must be contacted within one working day. In collaboration with the PI, the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the relevant regulatory authority within seven calendar days.

7.14.14 Ethical and Regulatory Considerations

7.14.14.1 Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

7.14.14.2 Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in accordance with relevant regulations and with Good Clinical Practice.

7.14.14.3 Approvals

Ethics submission will be made to one of the Health and Disability Ethics Committees of New Zealand. The opinion of the Ethics Committee will be given in writing. Locality approval must be granted at each site before any participants are recruited, as per Ethics Committee guidelines. The Ethics Committee should approve all advertising used to recruit participants for the study.

A SCOTT submission will be made seeking approval for use of the IMP as a new medicine.

Approval for the study will also be sought from the Regional Advisory Group – Māori (RAG-M), and such approval will be given prior to locality being activated.

7.14.14.4 Reporting

The PI shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the HDEC and Sponsor and six-monthly report to SCOTT. In addition, an End of Trial notification and final report will be submitted to the HDEC, SCOTT and RAG-M and Sponsor as required.

7.14.14.5 Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. It is the intention of the study site to capture as much participant-related information directly into an eCRF, and to use this eCRF as source documentation. This will include identifying details of participants and relevant demographic information. The eCRF is an encrypted secure system that is protected by unique username and password requirements for log-in, which are only provided to trained study staff.

7.14.14.6 Expenses and Benefits

Participants will be reimbursed for all reasonable study related expenses and inconvenience as per below:

- X per 24 hours of admission.
- X per outpatient clinic attendance, inclusive of any additional required follow up for prolonged metabolite clearance.

Maximum total reimbursement per participant part A: $

Maximum total reimbursement per participant part B: $

Reimbursement will be paid according to the MRINZ internal SOP RP.001 Reimbursement of Study Participants and all participants will be required to complete an IRD Tax Code Declaration Form IRD330.

7.14.15 Finance and Insurance

7.14.15.1 Funding

The study is fully funded by XXX.

7.14.15.2 Insurance

All participants will be informed as to the potential for ACC non-payment whilst participating in a clinical trial, should a harmful event occur. Full sponsor insurance will be in place prior to study commencement. As a contractual requirement with the MRINZ, the sponsor's policy must provide a minimum compensation up to the equivalent ACC payment in the event of any harm suffered by a participant.

7.14.16 Publication Policy

The study findings will be published by MRINZ, in a scientific peer reviewed journal, according to the International Committee of Medical Journal Editors recommendations. The Investigators listed on page one will be listed as authors, in recognition of their contribution to the design, implementation and oversight of the study.

Results of the study will be sent to participants on request (once available) and will be made available on a publicly available trial registry website, recognised by the World Health Organisation International Clinical Trials Registry Platform (WHO ICTRP) as a Primary Registry.

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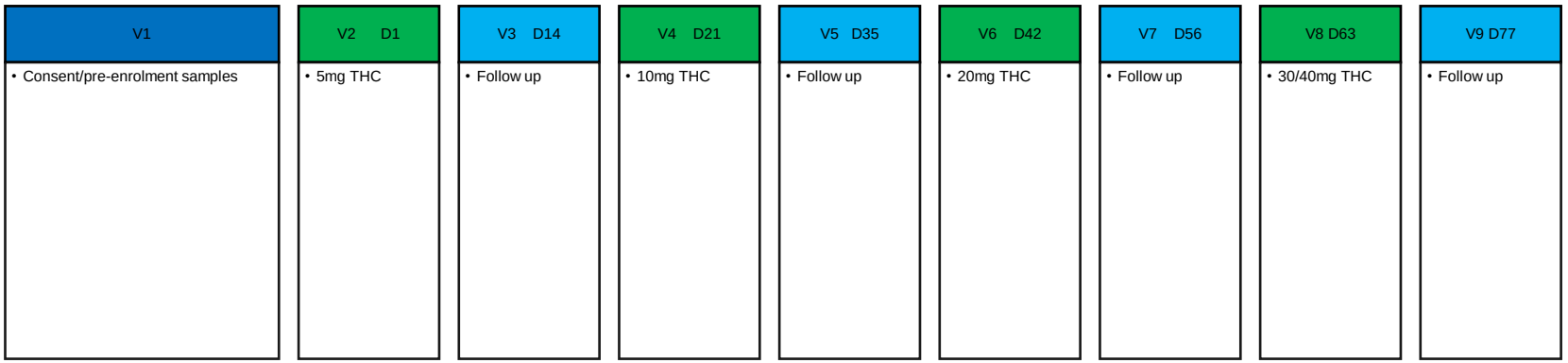
7.14.17 PK study Appendices

7.14.17.1 Appendix One: Trial flow chart and schedule of assessments

7.14.17.1.1 Part A (SAD)



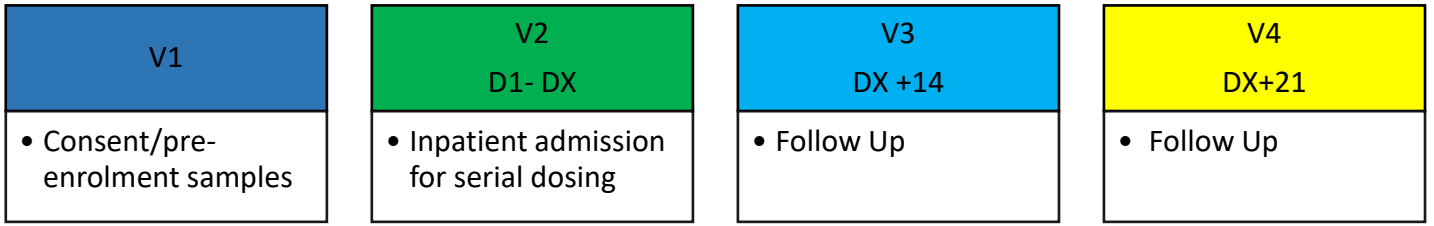
7.14.17.1.2 SAD Schedule of Assessments

Assessment	**Screening**	**Visit Day**											**Study Completion/Early withdrawal**	**Unscheduled (clearance visit)**
Day	**-28-1**	**1**	**2**	**14**	**21**	**22**	**35**	**42**	**43**	**56**	**63**	**64**	**77**	**N/A**
Informed Consent	x													
Review Eligibility Criteria	x	x			x			x			x			
Enrolment[a]	x													
Medical History	x													
Concomitant Medications	x	→	→	→	→	→	→	→	→	→	→	→	x	x
Height (cm)	x													
Weight (kg)	x													
Vital Signs[b]	x	x[c]	x[c]	x	x[c]	x[c]	x	x[c]	x[c]	x	x[c]	x[c]	x	x
Complete Physical Exam	x												x	
Limited Physical Exam[d]		x			x			x			x			x
Urine Drug Screen	x													
Urinary cannabinoid screen.		x		x	x		x	x		x	x		x	x
Admission to research facility [e]		x			x			x			x			
Discharge [f]			x			x			x			x		
Haematology[g]	x	x	x		x	x		x	x		x	x	x	x
Chemistry[g]	x	x	x		x	x		x	x		x	x	x	x
Coagulation[g]	x	x	x		x	x		x	x		x	x	x	x
Fasting Glucose and Lipids[h]	x												x	
HIV	x													
Hep B and Hep C	x													
Urinalysis[i]	x	x	x		x	x		x	x		x	x	x	x
Urine Microscopy	x												x	
12 Lead ECG[j]	x	x	x		x	x		x	x		x	x	x	
PK Serum Cannabinoids Samples[k]		x	x	x	x	x	x	x	x	x	x	x	x	x

Assessment	Screening	Visit Day											Study Completion/ Early withdrawal	Unscheduled (clearance visit)
Day	**-28-1**	**1**	**2**	**14**	**21**	**22**	**35**	**42**	**43**	**56**	**63**	**64**	**77**	**N/A**
Pooled urine sample for Urine Cannabinoids[l]		x			x			x			x			
PK Urine Sample (not pooled)[m]		x		x	x		x	x		x	x		x	x
Psychological tests[n]		x	x		x	x		x	x		x	x	x	x
Cognitive tests[o]		x	x		x	x		x	x		x	x	x	
Adverse Events[p]		x	→	→	→	→	→	→	→	→	→	→	x	x
Study drug admin[q]		x			x			x			x			

a: After informed consent, screening assessments are complete and eligibility criteria has been met.
b: Supine vitals. Heart Rate, BP, Respiratory Rate and Temperature.
c: Supine Vitals- To be performed pre-dose (within 1 hour) and then at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24hrs (+/- 15mins).
d: As indicated following review of adverse events.
e: Overnight visit. Participants will stay within the supervised clinical unit until the scheduled discharge time.
f: Approx. 3pm after all safety test results have been reviewed
g: See Appendix 4 for full list of blood tests.
h: Fasting period 10 hrs prior to test. Participant may drink water.
i: Send for unscheduled microscopy and culture if clinical symptoms of UTI OR 3+ Leucocytes, 2+ Blood, Nitrite positive on urinalysis.
j: Participant to be lying for 5 minutes prior to ECG. On admission visits single 12-lead ECG to be performed pre-dose (within 1 hour) and then at 2, 3, 4, 6, 8, 12, 24 hours (+/- 15mins).
k: Serum cannabinoids: THC, THCA, 11-OH-THC, THC-COOH, CBD and CBDA. On dosing admissions PK bloods to be performed pre-dose baseline (within 5mins) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 and 24 hrs (+/- 5mins). Single samples to be taken at Day 14, may be repeated at 7 day intervals until clearance is achieved.
l: Pooled urine collections, collected over the following 4 time periods: 0-4 hrs, 4-8 hrs, 8-16hrs, 16-24hrs. . Initial pre-dose void (urinalysis and urinary spot test can also be taken from this) within 15 mins prior to start of collection period. Final void of each collection within 15 mins of the end of the collection period.
m: PK sample to be taken from single MSU sample pre-dose and Day 14.
n: Drug Effects Questionnaire (DEQ), STAI-Y, VAS. To be administered pre-dose (within 1 hour) and then at 2, 3, 4, 8, 12 and 24 hours post dose (+/- 15 mins).
o: Neuro-Psychological Test Automated Battery (CANTAB/MUSE). To be administered pre-dose (within 2 hours) and then at 2, 8 and 24 hours post dose (+/- 30 mins).
p: During screening period (after informed consent and enrolment) until baseline visit (0hrs on Day 1) only SAE caused by a protocol- mandated intervention should be reported. Starting from the baseline period (0hrs on Day 1) all AEs should be classified and reported as per the protocol for the duration of the study until the close out date (14 days past the last dose of study drug). All AEs should be followed up until the AE has resolved or returned to baseline grade or the participant withdraws consent or is lost to follow up
q: To be administered following the completion of pre-dose assessments. Dosing window 730-1030am.

7.14.17.1.3 Part B (MAD- Two to three cohorts)



7.14.17.1.4 MAD Schedule of Assessments

Assessment	**Screening**	**Inpatient Visit[q]**							**Follow up**	**Study Completion/ Early withdrawal**
Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**21**
Informed Consent	x									
Review Eligibility Criteria	x	x								
Enrolment[a]	x									
Medical History	x									
Concomitant Medications	x	→	→	→	→	→	→	→	→	x
Height (cm)	x									
Weight (kg)	x									
Vital Signs[b]	x	x	x	x	x	x	x	x	x	x
Complete Physical Exam	x									x
Limited Physical Exam[c]		x								
Urine Drug Screen	x									
Urinary Cannabinoid screen		x								
Haematology[d]	x	x			x			x		x
Chemistry[d]	x	x			x			x		x
Coagulation[d]	x	x			x			x		x
Fasting Glucose and Lipids[e]	x									
HIV	x									
Hep B and Hep C	x									
Urinalysis[f]	x	x			x			x		x
12 Lead ECG[g]	x	x	x	x	x	x	x	x		x
PK Serum Cannabinoids (Full Day)[h]	x	x					x			
PK Serum Sample (pre morning dose)[i]			x	x	x	x		x	x	x
Pooled urine sample for urine cannabinoids[j]		x					x			
PK Urine Sample (not pooled)[k]		x					x		x	x
Psychological tests[l]		x	x	x	x	x	x	x		

Assessment	**Screening**	**Inpatient Visit[q]**							**Follow up**	**Study Completion/ Early withdrawal**
Day	**-28 to -1**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**14**	**21**
Cognitive tests[m]		x	x	x	x	x	x	x		
Adverse Events[n]		x	→	→	→	→	→	→	→	x
Study drug administration[h]		x	x	x	x	x	X[p]			

a: After informed consent, screening assessments are complete and eligibility criteria has been met.
b: Supine vitals. Heart Rate, BP, Respiratory Rate and Temperature. To be performed pre-dose (within 1 hour) on Day 1 and at 0.5, 1, 1.5, 2, 3, 4, 6 and 8 hrs (+/- 15 mins) and then 2 hrs following each dose (+/- 15 mins). Final vitals will be taken 24 hours after the final dose, prior to discharge.
c: As indicated following review of adverse events.
d: See Appendix 4 for full list of blood tests.
e: Fasting period 10 hrs prior to test. Participant may drink water.
f: Send for unscheduled microscopy and culture if clinical symptoms of UTI OR 3+ Leucocytes, 2+ Blood, Nitrite positive on urinalysis.
g: Participant to be lying for 5 minutes prior to ECG. Single 12-lead ECG to be performed on Days 1 and 6 pre morning dose (within 1 hour) and then at 2, 4, 6 and 8hrs post morning dose (+/- 15mins). Days 2,3,4,5 will have an ECG performed once daily 2hrs after the first dose (+/- 15 mins) and a final ECG will be performed 24 hours following the last dose, prior to discharge.
h: Serum cannabinoids: THC, THCA, 11-OH-THC, THC-COOH, CBD and CBDA. On PK days (Day 1 and Day 6) bloods to be performed pre-dose baseline (within 5mins) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12 hrs (+/- 5mins).
I: Serum Cannabinoids: Single samples to be taken pre morning dose on Days 2,3,4,5,7 and Day 14, may be repeated at 7 day intervals until clearance is achieved.
j: Pooled urine collections, collected over the following 4 time periods: 0-4 hrs, 4-8 hrs, 8-16hrs, 16-24hrs. Initial pre-dose void (urinalysis and urinary spot test can also be taken from this) within 15 mins prior to start of collection period. Final void of each collection is to be done within 15 mins of the end of the collection period.
k: Pre-dose urine PK sample and MSU PK sample to be taken on Day 14 and Day 21.
l: Drug Effects Questionnaire (DEQ), STAI-Y, VAS. To be administered pre-dose (within one hour) then 2, 3, 4, 8, 12 hrs (+/-15mins) on Days 1 and 6 and 2 hours post dose (+/-15mins) for Days 2,3,4,5 and with a final assessment 24 hours following the final dose (Day 7).
m: Neuro-Psychological Test Automated Battery (CANTAB/MUSE). To be administered pre-dose (within one hour) then at 2hr, 8hr (+/- 30mins) on Days 1 and 6 then 2 hours (+/- 30mins) post dose for Days 2,3,4,5 and with a final assessment 24 hours following the final dose (Day 7) (+/- 30mins).
n: During screening period (after informed consent and enrolment) until baseline visit (0hrs on Day 1) only SAE caused by a protocol- mandated intervention should be reported. Starting from the baseline period (0hrs on Day 1) all AEs should be classified and reported as per the protocol for the duration of the study until the close out date (14 days past the last dose of study drug). All AEs should be followed up until the AE has resolved or returned to baseline grade or the participant withdraws consent or is lost to follow up.
o: To be administered following the completion of pre-dose assessments.
p: Final single dose to be administered on morning of day 6.
q: 6 night visit. Participants will stay within the supervised clinical unit until the scheduled discharge time.

7.14.17.2 Appendix Two: Adverse events of interest

Preliminary List

Liver Function tests: ALT, AST (3x Upper limit normal), Bilirubin (2x Upper limit normal)

Nausea

Vomiting

Right Upper Quadrant Pain

Fatigue

Anorexia

Somnolence and sedation

Decreased appetite

Diarrhoea

Rash

Psychological disturbance- anxiety, paranoia, cognitive disturbance

Tachycardia

7.14.17.3 Appendix Three: Laboratory Tests (subject to change)

Chemistry	**Haematology**	**Coagulation**
Albumin	Haemaglobin	INR
Alkaline Phosphatase	Haematocrit	aPTT
Gamma Glutamyl Transferase	MCV	PT
Alanine aminotransferase	MCH	
Aspartate aminotransferase	Red Cell Count	**Fasting Lipid and Glucose**
Total Bilirubin	Platelets	Total Cholesterol
Direct Bilirubin	White Cell Count	Triglycerides
Total Protein	White Cell Count Differential	LDL
Bicarbonate	Neutrophils	HDL
Adjusted Calcium	Lymphocytes	Fasting Glucose
Sodium	Basophils	
Potassium	Monocytes	**Urinalysis**
Creatinine	Eosinophils	Colour and appearance
Chloride		pH and Specific Gravity
Blood urea nitrogen	**Urine Drug Screen**	Glucose
	Including but not limited to:	Protein
Serum Pharmacokinetics	Amphetamine	Leucocytes
Δ9-THC	Barbiturates	Nitrites
Δ8-THC	Benzodiazepines	Blood
THCA	Cocaine	Ketones
11-OH-THC	Cannabinoids	Microscopy and Culture if clinically indicated (as per section 8.3.4)
THC-COOH	Methadone	
CBD	Methamphetamine	**Urine Pharmacokinetics**
7-COOH-CBD	Opiates	Free THC
CBDA	Phencyclidine	THC-COOH

7.14.17.4 Appendix Four: WHO Toxicity Grading

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All tables above taken from https://www.fda.gov/media/73679/download.[335]

7.14.17.5 Appendix Five: Amendment History

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made

Protocol amendments must be submitted to the Sponsor for approval prior to submission to the HDEC and SCOTT

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