ACRE
Australian Centre for Cannabinoid Clinical and Research Excellence

Jeanette Radcliffe
Secretary
The Senate Standing Committee on Community Affairs
References Committee
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Dear Jeanette

RESPONSE

The Senate Standing Community Affairs References Committee:
Inquiry into current barriers to patient access to medicinal cannabis in Australia

I write to you in response to the Senate Standing Community Affairs References Committee's call for submissions to the inquiry into current barriers to patient access to medicinal cannabis in Australia.

The Australian Centre for Cannabinoid Clinical and Research Excellence (ACRE) was established through the National Health and Medical Research Council's (NHMRC) Centre of Research Excellence scheme. It draws together over twenty Australian research leaders and clinicians from major national universities and research institutions to establish a research evidence base to inform safe clinical use of medicinal cannabinoids and to guide policy as cannabinoids are introduced into therapeutic practice in Australia.

As the first federally-funded research centre in medicinal cannabis, ACRE is pleased to provide a submission to the Senate Standing Community Affairs References Committee inquiry.

ACRE's responses to the inquiry's Terms of Reference are detailed below. Please note that our responses are in reference to cannabis medicines that have met TGO93 requirements and not the broader medicinal cannabis nor recreational cannabis context.

a. **the appropriateness of the current regulatory regime through the Therapeutic Goods Administration (TGA) Special Access Scheme (SAS), Authorised Prescriber Scheme and clinical trials;**
ACRE supports the current regulatory regime for cannabis medicines as implemented through the Therapeutic Goods Administration (TGA). All unregistered medicines are subject to this regulatory process, which was introduced in 1963, post thalidomide tragedy, to protect consumers[1].

We believe that as cannabis medicines are molecularly complex chemicals with inconsistent and variable constituents, combination and potency, cannabis should not be an exception to the regulatory process for patients. However, we can see the potential patient benefit from aligning important regulatory process to the current scientific and clinical evidence as it continues to emerge. Thus, as a necessary safeguard for patients, we would still encourage rigorous and independent assessment of the clinical justification for access to cannabis medicines prior to TGA registration. We also recommend that there is an imperative for specific outcome data to be regularly provided and clinically assessed in the event of reapplication for access to cannabis medicines through the TGA schemes.

[1] https://www.tga.gov.au/book/fifty-years-independent-expert-advice-prescription-medicines-02

To continue to address the paucity of clinical evidence for cannabis medicines across indication, there needs to be a broader and accelerated capacity to undertake the necessary pre-clinical to clinical trials research, and to advance our understanding of the therapeutic use of cannabis medicines in the clinical setting.

Monitoring of medications (pharmacovigilance), including new medical products released on the market is a key area of health safety. To this effect we also believe that better data linkage of adverse reporting to the Sponsor States and TGA should be mandated, including data captured around morbidity and mortality directly or indirectly attributed to medical cannabis usage. This aspect will require significant investment into health data linkage, ethics approval to collect human unregistered (and registered, in the case of Sativex®) data across different states and territories, and funding of medicines and data information experts at the TGA. Whilst ACRE has made significant inroads into understanding and discussing feasibility of such a system, including the preparation and submission of a proposal to develop a national Pharmacovigilance System for Australia submitted to Government in 2017, Federal Government leadership and funding is required in this space.

b. the suitability of the Pharmaceutical Benefits Scheme for subsidising patient access to medicinal cannabis products;

We recommend that the current PBS system is suitable for assessment, however cannabis medicines should be subject to the same considerations as other medicines being considered for taxpayer subsidisation under the scheme. Cost effectiveness studies and overall financial impact on the PBS therefore must be considered[2].

c. the interaction between state and territory authorities and the Commonwealth, including overlap and variation between state and territory schemes;

Currently, there is significant variance between state-specific requirements. Difficulties arise in the context of health practitioners navigating state-specific requirements with interstate prescribing. A standardised national system, accreditation of S8 prescribers, and streamlining of other poisons legislation would streamline regulatory requirements.

d. Australia's regulatory regime in comparison to international best practice models for medicinal cannabis regulation and patient access;

A number of other countries, including Denmark, Germany and Israel maintain patient registries to gather 'real-world evidence' for cannabis medicines. However, it remains unclear how useful this data is, as important information on patient outcomes is often lacking, as well as accurate data about actual cannabis medicine taken, concomitant therapies and comorbidity, and incomplete toxicity data. For example, patients may stop cannabis because they found a better option, it doesn't work, or it causes toxicity, which is not acceptable to the patient (e.g. sedation, cognitive impairment). This may all be coded in the Registry as 'stopped medicine', although the reasons are very different. Overall, Registries are very reliant on what data the prescriber wishes to enter (including unconscious omissions), and can be influenced, for example, if the prescriber has links with Industry (particularly if they are prescribing specific products based on commercial interests). To this effect, the information that may be collected via Registries has a high potential to be biased.

Having said that, we would recommend that Australia considers a registry-style model, which could be improved by being underpinned by terms of reference to reduce the incomplete reporting and the known biases that can occur in Registries. We acknowledge there are privacy data controls in Australia that would need to be examined before this could occur. However, it would be a system worth investing in for Australia as adverse events from other new medicines could also benefit from such an approach. We also acknowledge that registries are very expensive, and that maintaining them has been a significant problem in Australia in the past.

For an international comparison, Australia's medicines regulatory system is world class. It has been involved in identifying signals causing morbidity and mortality with new drugs, sometimes first in the world. However over the last 10 years, Governments have reduced funding to the TGA and also encouraged an industry-facing approach. It would be timely for Government to consider if the funding pendulum should focus more on individual patients and population groups, around safety of medicines.

[2] As per The Pharmaceutical Benefits Scheme: a quick guide - 'Before a medicine can be listed on the PBS, it must first be approved for use in Australia by the Therapeutic Goods Administration (TGA). The sponsor of the medicine, usually a pharmaceutical company, applies to the TGA to have the medicine entered in the Australian Register of Therapeutic Goods (ARTG) so that it can be sold in Australia. The sponsor must provide evidence (such as from clinical trials) that the medicine meets the required standards of quality, safety and effectiveness for the intended use.'

Employment of academic pharmacists, pharmacologists, IT and other experts in this space would enable our regulatory system to be the actual best in the world. It is also noted that ACRE does have an international advisory board of senior policy makers and clinical/researchers from the countries across the world often seen inside Australia (but interestingly often not to them nor to outsiders) as being world leaders in this space. It is not uncommon for international cannabis experts to remark in the public domain how appropriate for patients our regulatory system is in managing this issue.

e. the availability of training for doctors in the current TGA regulatory regime for prescribing medicinal cannabis to their patients;

The current TGA regulatory regime does not provide training for any doctors on medicines, and based on the Therapeutic Goods Act 1990 it is not expected to.

An interest in the prescribing of cannabis in the therapeutic setting would have to be seen in the overall knowledge required to prescribe. In Australia and New Zealand, teaching about therapeutic groups, such as cannabinoids, is also not done in siloes. Students learn principles of physiology, pathophysiology (including the endocannabinoid system along with many other G Protein-coupled receptor (GPCR) negative feedback endocrine systems, such as endorphins). Many of the cannabinoids bind to a variety of GPCR, including hormones that work on the stress, energy and other systems, and switching off such systems in response to exogenous medicines is a long taught principle (and clinical concern) of physiology and pharmacology. Students then learn about pharmacokinetics and pharmacodynamics. Therapeutic groups only come in towards the end of clinical training, unless they are used as examples during the study of disease and pharmacology. We know this teaching is consistent with the UK at least, as we use their exit exam for pharmacology across almost all of the medical schools in Australia and New Zealand. Knowledge of the actual prescribing process is also taught by universities.

For already graduated doctors needing refreshers, currently there is lack of specialist training from pharmacologically-qualified professional providers who can place the role of cannabis medicines within an unbiased therapeutic framework overall for a patient population, or disease. 'Siloed' education on cannabis alone without the broader context only attracts a specific audience, has been said to be aligned with specific agendas, and doesn't help clinicians understand how to utilise this within their therapeutic armamentarium, and in the context of comorbidity and complicated other medicines regimens.

ACRE recommends that the development of training programs (and other resource) should follow the evolving evidence base, be situated within the clinical and regulatory context, and must address scientific evidence not administrative procedures. For undergraduate education and training, new knowledge about clinical evidence will come into clinical practice via the usual channels as the research develops and products meet the ARTG listing criteria.

Due to the rapid-paced publication of cannabinoid related research, the TGA Guidances for the use of medicinal cannabis need to be more regularly updated. There are numerous educational resources available, including ACRE NSW Cannabis Medicines Prescribing Guidance documents and Royal Australian College of General Practitioners (RACGP) webinars. However, there is also international literature that suggests that health professionals perceive that they have inadequate education about cannabis medicines and desire further information and training. Therefore, it will be important for each State health department and the TGA to continue to highlight evidence-based educational resources that exist, ensure their currency, and build upon these.

f. the education of doctors in the Endogenous Cannabinoid System (ECS), and the appropriateness of medicinal cannabis treatments for various indications;

Education about research regarding the ECS and the use of cannabis medicines for certain indications should be integrated into health professional education curricula. This should be based on the inclusion of appropriate quality resources in the curricula, to remedy health professionals' need to seek other, less reliable educational resources, particularly when they may not have adequate insight into the limitations of these resources.

g. sources of information for doctors about uses of medicinal cannabis and how these might be improved and widened;

Greater resources designed to provide support specifically for doctors and specialists must be provided. The NSW Cannabis Medicines Advisory Service, a State government funded service that provides evidence-based information to NSW-registered health professionals, is a valuable exemplar, however to date there is a lack of equivalent for health practitioners external to NSW.

The service has been funded for a three-year period (2018-2020). The free-to-practitioner service is staffed by two specialist medicines information pharmacists and a clinical pharmacologist, the service operates 9 a.m. – 5 p.m. weekdays (contactable by phone and email) and primarily receives enquiries from medical practitioners in NSW considering prescribing a cannabis medicine for a patient in their care.

The service assists doctors with:

- Understanding the latest evidence around cannabis medicines
- Understanding the regulatory requirements for cannabis prescription
- Considering tools to monitor a patient's progress whilst using cannabis medicines
- Provision of protocols to facilitate cannabis medicine prescribing
- Information about dosing and titration in individual patients

All enquiries are followed up one-week post enquiry response and to date feedback from clinicians has been positive. Service methodology is focused on supporting clinicians in understanding the latest evidence related to cannabis medicines and patient safety considerations. It is important that health professionals have access to an independent and evidence-based service to compile and translate rapidly emerging cannabinoid research.

The service has also provided a number of additional services, including:

- Collaborations with key stakeholders to develop and review educational resources for health practitioners. NSW CMAS collaborations to date include but are not limited to: the Royal Australian College of General Practitioners; NPS MedicineWise; HealthPathways; NSW Therapeutic Advisory Group; NSW Poisons Information Centre; and the Agency for Clinical Innovation.
- In collaboration with ACRE, NSW CMAS was involved in the preparation and development of a suite of NSW Cannabis Medicine Prescribing Guidance documents.

h. delays in access, and the practice of product substitution, due to importation of medicinal cannabis and the shortage of Australian manufactured medicinal cannabis products;

As with other medicines in the last few years (including heparins, antibiotics, epilepsy medicines and others) measures should also be taken to mitigate imported cannabis medicines shortages and improve continuity of patient care. This may mean contracts with cannabis providers on agreed supply and stability data before being licensed to provide to patients. There is a lack of research related to the substitution of one cannabis medicine for another, with different batches, excipients and decay (oxidation), and the resultant effects may not be equivalent. Whilst this may not be a problem in relatively well people, for sick patients, particularly in vulnerable groups, this presents a concern. In the event of stock shortages for NSW patients, the NSW Cannabis Medicines Advisory Service has assisted health practitioners with sourcing alternative, similar products, however as per our response above, there are no equivalent services in other states and territories.

i. the current status of the domestic regulated medicinal cannabis industry;

NA

j. the impacts on the mental and physical wellbeing of those patients struggling to access medicinal cannabis through Australia's regulatory regime;

NA

k. the particular barriers for those in rural and remote areas in accessing medicinal cannabis legally;

Access to a quality pharmaceutical product and medical follow-up care depends on the willingness and capacity of the rural and remote clinicians to support and facilitate access to cannabis medicines. This affects access, particularly in areas with few clinicians, and may increase the likelihood of patients in this context not having a "regular practitioner" or established therapeutic relationship, potentially resulting in issues with continuity of care, specialist access etc.

Further, lack of clinical infrastructure and resourcing is a barrier, especially for trials-based access. While health providers strive for equity in rural and remote areas this is not always the reality – for example, NSW is a large state with low clinical infrastructure outside of the main east coast Wollongong to Newcastle region. Further, in regional and remote NSW there are often no staff specialists and routine care falls to Clinical Nurse Consultants and Nurse Practitioners, with patients transferred interstate or to a major metropolitan facility for acute or complex care. e.g. NSW's Far West is supported by South Australia, Northern NSW by QLD, Southern NSW by ACT and South-Western

by Victoria (note: this is consistent for access to every health area for standard of care and not is specific to medicinal cannabis).

Whilst consideration of the tele-trials model to give access to clinical trials involving cannabis medicines (e.g. COSA tele-trials model) would provide greater access for rural and remote patients, it also presents risks in terms of ongoing monitoring. This also applies to telehealth prescribing models.

l. the significant financial barriers to accessing medicinal cannabis treatment;

Certainly, there is significant variance in the cost of cannabis medicine, particularly between different formulations (for example, CBD is typically more expensive). However, the overall trend in recent years is a gradual reduction in the costs of cannabis medicines. Whilst cost is a barrier to access for some patients, given the current paucity of scientific and clinical evidence for cannabis medicines, it is appropriate that patients pay for cannabis products without government subsidy. We understand businesses (even the non-cannabis ones) would desire taxpayer funding for their products, however this is not realistic without the establishment of clinical evidence that cannabis medicines will improve health outcomes for Australians. We also hope that pressure can be put on the cannabis businesses to provide the information and invest in the research and development necessary to enable consideration of their product for taxpayer funding.

It is worth noting that in some situations there is a broader issue of access to other services – e.g. chronic pain services, palliative care services that also impacts patients in terms of therapeutic treatment.

m. the number of Australian patients continuing to rely on unregulated supply of medicinal cannabis due to access barriers and the impacts associated with that;

Our experience is that patients who have a history of taking unregulated cannabis product discuss this point with seemingly little or incorrect knowledge about the current regulatory and prescribing process within Australia. Most have not ever asked their doctor about access to safe products, and many have indicated anecdotally that they do not want to go down this pathway. Many patients have reported to clinicians that they prefer the 'natural' smoked experience rather than a Pharma product. Further, in some aspects of therapeutics (e.g. cancer care), the intent of access may be to try to cure their cancer, which wouldn't be an indication for which prescribing through the TGA SAS schemes is intended. Therefore this point (m) is complex and the evidence and issues need to be carefully teased apart.

Overall though, we wish to acknowledge that continued use of unregulated supply of cannabis has inherent safety risks for patients, including potential contamination with pesticides, heavy metals and microbes. The composition of unregulated supply is also unknown and may be significantly different from what it is purported to contain. Ongoing supply and cost issues therefore need to be addressed as the scientific evidence base for the efficacy of cannabis medicines is developed. Many of these access barriers for patients and negative impacts could be improved through the more comprehensive support of research, health professional education and access to independent, evidence-based information services (similar to the NSW Cannabis Medicines Advisory Service model).

n. any related matters.

Pharmacovigilance

Monitoring of medications (pharmacovigilance), including new medical products released on the market, such as cannabis medicines, is a key area of health safety. It relies on the voluntary reporting of side-effects, adverse events and other risks by prescribers, community and product Sponsors. This reliance on voluntary reporting, and many patients and prescribers may either not think of reporting, may not report because it is a known adverse event of cannabinoids (e.g. anxiety), or may not have access to reporting systems. This together with the rapid recent expansion of therapeutics on the market, earlier and more rapid time to market and an antiquated pharmacovigilance reporting system has been recognised as contributing to sub-optimal areas of national medication safety.

To this relatively complex pharmacovigilance system, monitoring of the effects of unregistered medicinal cannabinoids presents an unprecedented challenge for Australia. Unlike other new therapeutics, cannabis medicines include an unparalleled diversity of products comprising a wide range of formulations for use in the treatment of a broad range of conditions. Yet, despite its increasing public profile and community demand for access, scant data for the efficacy of medicinal cannabinoids exist for these indications. Furthermore, there is an inadequacy of information regarding the side-effects or other adverse events for the many different formulations of medicinal cannabis which are becoming available, relative to the requirements for registration of therapeutic goods. In addition,

quality control measures for medicinal cannabinoid products is lacking, with many locally grown products potentially containing substantial levels of heavy metals and other contaminants that can impact on a person's health. Although in Australia prescribed cannabis medicines must adhere to the TGO93 standard, many patients continue to grow, import and use non-TGO93 certified products, which have unknown constituents and contaminants.

With the rapid introduction of cannabis medicines into the national health care setting, a unique opportunity exists for Australia to establish a pharmacovigilance system that is recognised as an international exemplar in terms of monitoring the quality and safety of medicinal cannabinoids. ACRE has tendered a formal proposal to the Department of Health previously, without response. ACRE's proposed system would enable early, systematic identification and quantification of the indications medicinal cannabinoids are being prescribed for and by whom, and capture the effectiveness and efficacy, side effects and risks to health from cannabis medicines use. The proposed system is significantly more sophisticated and extensive in terms of reporting and data linkage compared to what is currently available in Australia, and is designed to provide real time, robust evidence to inform and guide prescribers around safe and optimal use of specific medicinal cannabis products.

Australia, unlike many other countries in the world, has introduced cannabis medicines to the community and practicing doctors as carefully as possible within the socio-political context. Due to this cautious approach, there is a rare opportunity for Australia to methodically capture critical pharmacovigilance data on cannabis medicines. This pivotal moment has elapsed for other countries who have introduced medicinal cannabis more rapidly, therefore the introduction of a contemporary and efficient national system of medicinal cannabis pharmacovigilance will place Australia as a world leader in informed and safe evidence-based implementation and monitoring of medicinal cannabinoids in both specialist and primary health care contexts. Furthermore, ACRE's proposed system would enable analysis of concurrent health and concomitant medication trends (e.g. opioids), which is a timely and much needed concurrent health monitoring opportunity, albeit that opioids are already registered products.

A copy of ACRE's proposal to develop a 'National Pharmacovigilance System for Cannabis Medicines' was submitted in 2017 and again in 2018 to the Federal Minister for Health's Australian Advisory Council on the Medicinal Use of Cannabis (AACMC) where it received a positive recommendation. The proposal, which would be a world-first, sits neatly within the MRFF Data and Infrastructure/Digital Health Intelligence priorities and received broad support from AACMC members. The proposed project was also discussed with the Greens Health Policy Advisor, the Shadow Minister for Health, and the Minister for Health's Chief of Staff and Health Policy Advisor, together with the former TGA Principal Medical Adviser, however it did not have the opportunity to gain traction prior to his departure from the TGA. It was subsequently provided to the Federal Minister for Health in October 2019. To date no response has been received. A copy of the proposal can be provided on request.

Other key points to consider:

- Whilst ACRE recommends that usual treating practitioners are best placed to considered if a prescribing a cannabis medicine is suitable for a patient in their care, a register of doctors who are willing and/or authorised to prescribe is not available to patients. This may result in increased access to costly cannabis 'clinics' or illicit sources of cannabis.
- If a patient locates a doctor willing to prescribe, it may not be their primary health provider and therefore the practitioner may not be aware of all of patient's medical details, leading to potential issues in quality of care.
- Where a willing doctor or specialist can prescribe, supply of consistent product, and reliable access to a prescribed product is also an issue. As an unregistered product with tight expiry dates, often requiring refrigeration, and with known supply issues, local community pharmacies are unwilling to stock, or obtain the necessary authorisations to stock, and price of product can vary as there is no fixed agreed price.
- Limitations on driving whilst using cannabis medicines is regularly raised as a barrier for patients and research linking detectable THC levels with impairment will be critical if we are to address this issue.
- Whilst local hospitals are generally supportive of the theory of prescribing, they often do not have the experience, knowledge or staffing resources to support and allow access and monitoring of patients, within a clinical trial or through TGA schemes.

Should you require any further information please do not hesitate to contact my office on 02 4042 0908.

Yours sincerely,

Professor Jennifer Martin
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ACRE