The 21st of August, 2017.

An open letter to the TGA.

I have written this letter to clarify my position in response to the Therapeutic Goods Administration's (TGA) statement: *Responding to Lateline – accessing medicinal cannabis products*', published online on the 17th of August, 2017. [1]

There is currently a great deal of confusion and false hope amongst medical practitioners, patients, advocacy groups, industry and the general public regarding access to legal medicinal cannabis products in Australia through authorised government pathways.

It is clear that more needs to be done to rectify this problem in the interest of public health and safety, whilst also maintaining appropriate levels of regulation balanced with compassion for the suffering.

I am encouraged to hear that the federal government is working to streamline and optimise the current regulatory pathways to encourage patient access to safe, quality-assured products whilst under the supervision of a licensed medical practitioner. Furthermore, I am also hopeful that this will include working with state and territory governments to harmonise the process and reduce unnecessary or duplicative regulatory requirements.

It is expected that any new legislation such as this will encounter teething problems and if lessons from the past are something to draw upon, the government might consider open and collaborative consultation with all of the aforementioned key stakeholders to address this unfolding issue in the hope of optimising outcomes for all concerned.

I am not opposed, nor will I ever be, to appropriately weighted regulation around medicinal cannabis. I congratulate the government for the speed with which it has listened to the Australian people and implemented initial legislative change. This being said, I and many academics and medical practitioners are led to believe that it is due to the rigid evidentiary requirements currently employed within both TGA and State and Territory government frameworks that is forcing many patients to go back to managing their conditions with illicit cannabis when they would much rather be law-abiding citizens under appropriate medical care.

Let me explain and offer a potential solution for consideration. In the TGA response it was stated that:

"Australia operates an evidence based system of medicine, which provides for the best possible care and, importantly, protection of patients. Mr Sinclair is correct and the very fact that there is a great paucity of evidence, including that of safety, means that it would be inappropriate to allow access without appropriate clinical oversight and would risk the health and safety of patients."

As has been highlighted by the TGA's statement above, Australia operates an evidence-based system of medicine, but what is confusing is that denying patients legal access due to lack of the highest levels of scientific evidence means many are left with the only option of tackling complex health problems alone and without appropriate clinical oversight by a licensed medical practitioner. Such policy seems to contradict itself and is risking the health and safety of patients by subjecting them to illicit, unregulated products. Is it not conceivably safer and within the scope of duty of care to medically monitor patient use of a regulated medicinal cannabis product for a condition with sub-optimal scientific evidence than to subject that patient by default to unregulated product and unsupervised care via illicit use?

According to the National Health and Medical Research Council (NHMRC), [2] evidence comes in the form of systematic reviews (Level I), randomised controlled trials (Level II), pseudo-randomised controlled trials (Level III-1), comparative studies with concurrent controls (Level III-2), comparative studies without concurrent controls (Level III-3) and case series with either post-test or pre-test/post-test outcome measures (Level IV). This 'hierarchy of evidence' underpins the clinical decision-making process of government departments, research institutes and universities as well as individual medical practitioners making informed clinical judgements for the health and wellbeing of their patients on a day-to-day basis.

Of particular relevance to this discussion is the N of 1 clinical trial, which fits within the hierarchy of evidence framework. This level of evidence considers an individual patient as the sole unit of observation in a study investigating efficacy or side-effect profiles of different interventions, with the goal being to determine the optimal intervention for an individual patient using objective data driven criteria and outcome measures. [3]

Results of such studies can be collected and collated to ascertain proof of concept and establish a scientific rationale for treatment of a particular condition, which can then lead to more rigorous forms of evidence such as randomised, double blind, placebo controlled clinical trials being implemented.

I have previously spoken publically of the benefit of pursuing the use of open label N of 1 clinical trials for medicinal cannabis over the last 2 years, and am ever hopeful that the Government not only considers this a valid form of evidence in assessing the clinical justification of medicinal cannabis for SAS Category B applications, but may also openly finance and support such clinical research in Australia. Medically supervised case study evidence, based on a patient's previous use of illicit cannabis to manage a medical condition, may also be considered as a potential clinical justification, particularly in intractable cases where no current medical intervention is assisting the patient. After 70 years of cannabis prohibition, which has stifled scientific and medical research in this area, [4] such concessions may provide a rational and balanced approach to the problem at hand.

Clarification around my statement regarding the "great paucity of evidence" should also be put into context. My statement, however correct, should not be construed as representing my personal support for the current evidentiary requirements, but rather highlight that it is these stringent evidentiary requirements that are driving many patients back to sourcing illicit supply due to little Level I or II evidence being available for their named disease, disorder of condition.

Throughout my research and lectures over the years, I have come into contact with many hundreds of people utilising cannabis medicinally both in Australia and in overseas jurisdictions such as the USA and Canada. The overwhelming majority of these patients are utilising cannabis across a broad and complex range of conditions due to the sole reason that current pharmaceutically derived therapies do not assist them, or actually produce undesirable adverse effects. Below is a short list of the diseases, disorders and conditions that patient's (or their carers) report they are taking cannabis for in obtaining symptomatic relief or assisting with disease management:

Ulcerative Colitis	Crohn's Disease	Rheumatoid Arthritis
Glaucoma	Migraine / Cluster headache	Tourette's syndrome
Parkinson's Disease	Dravet syndrome	Lennox-Gastaut syndrome
Breast cancer #	Colorectal cancer #	Brain cancers #
Lung cancers #	Skin cancers	Chemotherapy induced nausea and vomiting *
Stiff Person syndrome	Huntington's disease	Sleep apnoea **
Benzodiazepine withdrawal	Endometriosis / Pelvic pain	Opiate withdrawal (recovery)
Post Herpetic Neuralgia	HIV / AIDS	Anorexia
Cerebral Palsy	Terminal illness (end of life care)	Trigeminal neuralgia
Epilepsy	Irritable Bowel Syndrome	Amyotrophic Lateral Sclerosis (ALS)
Systemic Lupus Erythematosus (SLE)	Chronic pain in adults *	Alcoholism (recovery)
Osteoarthritis (OA)	Autism	Attention Deficit Hyperactivity Disorder (ADHD)
Muscular dystrophy	Cachexia/Wasting syndrome	Generalised Anxiety Disorder (GAD)
Alzheimer's Disease	Sjogren's syndrome	Dystonia
Complex Regional Pain syndrome	Traumatic Brain injury	Post-Concussion syndrome
Depression	Schizophrenia (Mild)	Fibromyalgia **

Multiple Sclerosis (MS) *	Nausea / Emesis	Neuropathic pain
Post traumatic Stress Disorder (PTSD)	Bipolar disorder	Spinal cord injury
* Denotes conclusive human clinical evidence available in the scientific literature [5]		
** Denotes moderate human clinical evidence available in the scientific literature [5]		
# Denotes supportive therapy		

As can be seen, my original claim of a great paucity of significant Level I or II evidence for medicinal cannabis use is incontrovertible, but this is not to say that evidence does not exist that is clinically relevant.

After careful consideration and open consultation, it could be reasonable to initiate various N of 1 studies enmeshed within the SAS category B framework for certain conditions that have less evidence (e.g. Crohn's disease, Ulcerative colitis, etc.). Pre-determined biomedical tests, patient-reported outcome measures and other clinical metric tools, (i.e. as used in day-to-day medical practise) could be utilised for such patients that medical practitioners could monitor and report back to a central data collection body that can then collate and synthesise it for analysis.

Such a model could have numerous benefits:

1) It ensures patients can get access to medicinal cannabis products grown and manufactured to high quality standards, protecting them from potential harm from illicit supply, which is in line with good Public Health policy;

2) It increases the likelihood of therapeutic efficacy through the use of products utilising defined standardised ratios and concentrations of phytochemicals (e.g. cannabinoids) which can produce statistically meaningful and reproducible clinical results in trials and ongoing patient care;

3) Dosage can be titrated by the medical practitioner for the individual patient, reducing the potential for adverse effects or side effects;

4) It keeps patients firmly enmeshed within the medical system. Instead of going back to the illicit market, they are under the supervision and guidance of a medical practitioner who can use various clinical metrics and outcome measures to assess efficacy and adverse effects...this later aspect being important for pharmacovigilance data collection.

5) Such a program would start collecting large amounts of useable clinical data that would assist government in guiding further clinical trial design and prescribing guidelines for medical practitioners;

6) It allows doctors to educate themselves on medicinal cannabis in a meaningful way by being directly involved in research whilst collaborating with and supporting their patients ongoing health needs. Dr Bastian Seidel, President of the RACGP, has already indicated strong support for this type of model which, when integrated into general practice, does not disadvantage rural and remote patients who are otherwise isolated from specialist access; and

7) In patients who are non-responsive to standard pharmaceutical treatments, or have terminal illnesses, it provides another medicine for the physician to employ, which for many patients and carers can provide hope in desperate times.

As a scientist and lecturer, I acknowledge that nothing is more important than having appropriate evidence to make educated and informed decisions for improved patient outcomes. With over 16,000 entries already in PubMed, and a growing amount of evidence accumulating worldwide on this plant, I feel an evidence-based compassionate program such as an N of 1 model enmeshed within the current SAS Category B pathways may be the balanced approach that satisfies both the Regulator and the Australian patients it serves. It addresses key issues of patient safety, clinical oversight, reduction in illicit activity and increasing the evolving scientific evidence base for medicinal cannabis whilst doing so in a responsible and compassionate manner.

Earlier this year, Dr Michael Gannon, President of the Australian Medical Association, stated that we are seeing more damage from prescription opioids like codeine than we are from illegal opioids like

heroin and that more needs to be done to help people struggling with prescription drug addictions. [6] Whilst the TGA has stated that medicinal cannabis products are not products of first choice, I am sure that health ministers and their advisors alike are heartened by the impact medicinal cannabis is having on reducing prescription opioid-related overdose mortality rates in countries such as the USA, [7] and are seeking to investigate this further. Furthermore, politicians and taxpayers alike are likely rejoicing to see significant health care savings to Medicare (USA) spending when medicinal cannabis programs have been implemented. [8]

Currently in Australia, millions of taxpayers' dollars are being spent conducting clinical trials on medicinal cannabis products from overseas companies across clinical conditions such as intractable epilepsy, palliative care and chronic pain. I look forward to the federal, state and territory governments providing similar financial support to our own appropriately licensed Australian medicinal cannabis industry members to continue to build the clinical evidence from Australian-grown and produced products. The flow-on benefits include supporting a start-up industry that could be an incredibly important source of jobs and revenue for the people of Australia well into the future, and potentially put Australia on the map as an exemplar of compassionate and evidence-based best practice.

Trust me when I say that I look forward to the day when I can wake up to an empty email inbox and no missed calls from doctors or patients trying to navigate the pathways for access to medicinal cannabis. I sincerely hope that such a time is not too far away for the thousands of Australian citizens facing health challenges each and every day. I shall end this letter with a quote that continues to inspire me each day, and one I hope our nation's leaders and government representatives can aspire to implement:

Salus populi suprema lex esto

Let the welfare of the people be the supreme law.

Yours sincerely,

Justin Sinclair

MHerbMed (USyd) BHSc (UNE) (FNHAA MICRS MSCC)

N.B. Throughout the entirety of my contact with patients and medical practitioners over the last 5 years, I have not received any remuneration and continue to work *pro bono* for the benefit of my fellow Australians. The views expressed above are my own and are not associated with any groups, institutes or associations that I am affiliated with.

1. *Responding to Lateline - accessing medicinal cannabis products*. 2017; Available from: https://www.tga.gov.au/behind-news/responding-lateline-accessing-medicinal-cannabis-products.
2. *NHMRC additional levels of evidence and grades for recommendations for developers of guidelines.* National Health and Medical Research Council. Australian Government: Canberra.
3. Lillie, E.O., et al., *The n-of-1 clinical trial: the ultimate strategy for individualizing medicine?* Per Med, 2011. **8**(2): p. 161-173.
4. Mechoulam, R. and L.A. Parker, *The endocannabinoid system and the brain.* Annu Rev Psychol, 2013. **64**: p. 21-47.
5. in *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. 2017: Washington (DC).
6. *Interview: Dr Michael Gannon, Australian Medical Association*. 2017: Lateline ABC News. http://www.abc.net.au/lateline/content/2016/s4709756.htm
7. Bachhuber, M.A., et al., *Medical cannabis laws and opioid analgesic overdose mortality in the United States, 1999-2010.* JAMA Intern Med, 2014. **174**(10): p. 1668-73.
8. Bradford, A.C. and W.D. Bradford, *Medical Marijuana Laws Reduce Prescription Medication Use In Medicare Part D.* Health Aff (Millwood), 2016. **35**(7): p. 1230-6.