PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Implementation of Medicinal Cannabis in Australia: Innovation or Upheaval? Perspectives from Physicians as Key Informants, a Qualitative Analysis.
AUTHORS	Hallinan, Christine; Gunn, Jane; Bonomo, Yvonne

VERSION 1 – REVIEW

REVIEWER	Wagstaff, Duncan University College London Research Department of Epidemiology and Public Health
REVIEW RETURNED	11-Jul-2021

GENERAL COMMENTS	This study addresses an important and topical issue. The manuscript is clearly laid out and describes an appropriate study design. I recommend the manuscript is accepted for publication if the following concerns can be addressed: Major concerns Have the authors followed a qualitative research checklist (e.g. COREQ)? Items from this checklist I believe to be missing in the manuscript include: researcher's credentials; participant knowledge of interviewers; interviewer characteristics; whether transcripts and/or findings were checked with participants; an example of the coding tree. The authors describe a 'qualitative narrative analysis approach' but little attention is paid to how participants constructed or reported these narratives. Furthermore, it is unclear how the data were coded apart from through 'inductive coding'.. was there no deductive coding given the use of DoI conceptual model? Some of the conclusions though seemingly very sensible are not clearly drawn from the study findings. Please could the authors make the link clearer between these claims and their data. For instance, the first mention of 'monitoring consumer experience' is in the discussion, citing other research, rather than the empirical data from this study. Secondly, although the case for pharmacovigilance is well made, why does it need to use 'innovative methods'? Finally the call for 'substantial collaboration' is well intentioned but does this reflect the power tensions described by interviewees? Please add a section on the study' limitations. Minor concerns

	p11. Please define and distinguish between any intended differences in interpretation of 'implicit knowledge' vs 'tacit knowledge'. I'm not sure if these terms are being used interchangeably or to denote different concepts. Spelling / typographical / grammar / syntax Throughout: delete commas at end of sentences before reference Abstract Line 17: 'Informant' not 'Informants' Line 26: 'in interviews' not 'in a interviews' Line 48: doesn't make sense tensions that arise during? Because of? Strengths and Limitations Line 12: insert 'that' after 'strategy' Results: page 12 the use of mixed metaphors ('bolting horse' and 'trojan horse') is not very helpful and I'm not sure really sure all the quotes in box 6 are needed Discussion P16 – paragraph beginning 'levers…' has multiple syntax errors Conclusions Line 43 – repetition of 'substantial collaboration'

REVIEWER	Kisa , Adnan Kristiania University College
REVIEW RETURNED	25-Aug-2021

GENERAL COMMENTS	-It is an interesting topic but the manuscript needs revisions -The manuscript requires a grammar check and the manuscript needs editing. Fluency of the manuscript is weak -Keywords are not reflecting the manuscript -Abstract: Dublications in the design and participants sections -Abstract: "The findings are not only currently relevant to MC, but to other potential novel therapeutics in the future, where there is already consumer and political pressure for their introduction into practice." Results should only be expressed based on this research. Whether the model used on other pharmaceutical products would work or not was not tested in this study. -page 3, repetitions in the "Strengths and limitations of this study". It should be re-written -Methods: repetition in sentences lines 33 and 54 -Methods:Dublications in sample selection. Please rewrite the method section and prevent dublications -Method: No detailed information about the data collection tools. How were the questions created? Any validity and reliability checks? -Demographic characteristics of the respondents are missing (age, practice in medicine-years, foreign graduate? etc) -Page 8, line 18, use exact number of respondents, do not use Several key informants -Line 30, use exact numbers not several individuals. Please use exact number of respondents throughout the manuscript. For

	example, page 9, A few informants, Many reported, Several informants, Some described, etc -integrating the information in the boxes (1-8) into the manuscript and only the relevant results given is recommended. It is recommended to remove boxes (1-8) - abbreviations are not used enough, checking the whole manuscript is necessary

REVIEWER	Oldfield, Karen Medical Research Institute of New Zealand
REVIEW RETURNED	01-Sep-2021

GENERAL COMMENTS	Review Implementation of Medicinal Cannabis: Innovation or Upheaval? Perspectives from Physicians as Key Informants ID: bmjopen-2021-054044 Thank you for the opportunity to review this paper. The authors have used a qualitative framework to explore the implementation of medicinal cannabis within Australia, using physicians as their key informants. This research provides insight into the challenges associated with the implementation of prescription of medicinal cannabis into clinical practice within the Australian context, and identifies areas where this may be improved through application of an adapted Diffusion of Innovation model to their results. I feel that it is an informative addition to the emerging area of research associated with medicinal cannabis. There are some areas that need to be addressed, which in general are minor, with some more major clarifications in the Method section. Comments and suggestions about each section of article are outlined below: Abstract Well written and clear. Reflects the research that is presented in the main article. Page 3, Line 7: Suggest the term ‘narrative’ be added to describe the type of qualitive analysis undertaken. Strengths and Limitations of the study The limitations of the study have not been fully addressed in this statement. Although there is acknowledgement that the research may not be generalisable to countries outside Australia, I think it would be appropriate to mention the potential sampling bias from using the snowball method of recruitment. Background This provides a summary of the background as to the use of cannabis as a medical product, the legislative frameworks surrounding it, and recent research into physician perspectives regarding the use of cannabis as a medicine. There is also a description of the Diffusion of Innovation framework and how this

	applies to medicinal cannabis. The authors provide a clear explanation of the current situation of legislation and prescribing processes in Australia at the current time. Page 4, Line 27: Please can you clarify what legislation was enacted in 1961 in the UK, US and Europe? Is this in reference to the International Drug treaty- "1961 United Nations Single Convention on Narcotic Drugs", in which case these countries were signatories? Page 4, Line 39: Suggest that the 'in the brain' is removed, as the endocannabinoid system is not solely located there. Page 4, Line 58: Please can you review the sentence starting "The Canada and United Kingdom legalised MC…." as Canada had legislation in place from 2001 allowing the use of medicinal cannabis under specific conditions (Marijuana for Medical Purposes Regulations), and legalised for recreational use in 2018. Page 5, Line 42: The section of the paragraph "Specifically, this research aimed to provide evidence around key informant perspectives…" would be better moved to the end of the introduction, as it summarises and outlines the aims of the research being undertaken for the reader. Page 5, Line 47: Please use the full term for Therapeutic Goods Authority here, as this is the first time it is referred to in the manuscript. Page 5, Line 64: Just a suggestion- the paragraph describing the DoI Framework may be more suited to go prior to the aims and objectives at the end of the introduction as it is relevant to the method of research undertaken- currently the flow of the background feels interrupted when reading. Page 6, Line 62: Please can you provide appropriate Figure titles to both figures attached? It may just be a result of the article upload process that they are missing though! Methods The method section requires some clarification and reworking to inform the reader of the methods undertaken. My primary concerns are around the explanation of the recruitment strategy and inclusion criteria, key question development and explanation of thematic saturation. Page 7, Line 33: How were the key questions developed? In Table 1, they are presented next to themes- were these themes based on the DoI framework? The selection of key informants covers two quite separate areas- those who are involved in clinical practice and those in the development of policy for MC prescribing- what is the rationale for including those groups in the same analysis? Page 7, Line 45: If non-prescribed artisanal products and their effects were included in the analysis, then why was recreational cannabis for health reasons considered out of scope, as they are both under the umbrella of illegal access for medicinal purposes?

	Or have I misinterpreted this- if so please could you clarify in the text? Page 7, Line 56: Please can you elaborate on how an environmental scan and rapid review of the literature led you to select key informants? Were the professional networks used involved in medicinal cannabis research? What were the full criteria required for an informant to be selected? Was there anything that would lead to you excluding a potential informant? Page 8, Line 8: Please can you expand on how thematic saturation would be determined to be interviews from at least 20 key informants- whilst I assume that is to meet the pre-determined themes from the DoI model that I think you have used to develop the key questions, it is not clear why twenty informants exactly was selected? Page 8, Line 14: I think this is meant to read (PILS), not (PLIS). Also, was informed consent done in person or did the participant just sign the consent form? Results This section provided a lot of analysis and I commend the authors on extracting and synthesising a large amount of information. I found it a very interesting read. It appears that there was an imbalance of prescribers vs non-prescribers and policy makers. Was any attempt made to balance this? As stated above, I think this needs to be addressed in the strengths and limitations of the study. Also, a general statement regarding the supporting quotes- is it possible to attribute the quotes to either prescriber, non-prescriber or policy-maker? Page 8, Line 54: Were informants in SA, WA and NT sought? How was it determined that there was minimal MC prescribing in these jurisdictions- is it lack of availability or lack of willingness to prescribe? I think this needs to be expanded on slightly. I found myself going back and forth from Figure 2, the results section and the discussion section. The authors have identified that a number of components were described by informants in relation to the model, however there are subheadings within the provided model that are not clearly explored in the results section, or absorbed into other themes. For example, under the Relative advantage against other medicines heading in Innovation, there is a section about the risks and harms that does not really fit in the section about advantages, and may more suitable in a Risks heading, as per the model. Please can you review the results subheadings against the model provided and amend for clarity? Is there a way of identifying within Figure 2 the themes that informants have identified as taking place separately from those subsequently identified as gaps in the implementation of medicinal cannabis? Or provide another Figure?

	I was surprised by the informants reporting involvement in trials of medicinal cannabis products- is this usual practice in Australia? Or does this just reflect the sampled population? This could be expanded on in the Discussion section. Page 12, Line 57: I think CBD technically is psychoactive, but non-euphoriant. Page 14, Line 8: Implementation of the 'roll-out' of medicinal cannabis-preparedness for regulation- should this read System fit-preparedness for regulation? Discussion This section uses the DoI model to discuss the effective measures of the cannabis roll out in Australia and what further steps should be taken for a continued roll-out. Page 16, Line 48: Please review this sentence. I think there is a bracket in the wrong place. What are 'distributer resources' and how are they catergorised into System antecedents? Page 17, Line 36: Can you please explain the Medicare item number? I admit that I have some discomfort about the idea of a financial incentive related to prescribing a specific medication, even as an innovation- who would benefit from such an incentive? How does this balance against evidence-based prescribing? Page 18, Line 2: What is meant by the term "relevance is threatened' in regards to medical colleges and regulatory bodies? Is the pressure to change how they operate substantiated? Page 18, Line 26: Whilst the informants were "comfortable with the increasing trend for consumer-led advocacy", I am not sure if this is generalisable to the physicians as a whole, and reinforces the need for a clearly defined informant population. Page 18, Line 41: The sentence 'Substantial collaboration is therefore needed moving forwards with MC,' is redundant, as the following sentence repeats this expands on the what is needed. There is no mention of any study limitations within the discussion, and a short paragraph addressing these would add to the validity of the study (if it cannot be expanded fully in the earlier sections of the paper).

VERSION 1 – AUTHOR RESPONSE

Review	Manuscript	Comments	Responses
1	Abstract Page 3, Line 7	Suggest the term 'narrative' be added to describe the type of qualitive analysis undertaken.	A thematic qualitative analysis of 21 in-depth Key Informant interviews was undertaken to explore the 'narrative' on the policy and practice of MC prescribing

2	Strengths and Limitations of the study	The limitations of the study have not been fully addressed in this statement. Although there is acknowledgement that the research may not be generalisable to countries outside Australia, I think it would be appropriate to mention the potential sampling bias from using the snowball method of recruitment.	We have added below to the manuscript: The purposive and snowball sampling techniques provides qualitative data around informant experience in policy, prescribing, advocacy for and against MC. This is a non-random technique, and may not be generalisable across population groups which do not have experience of and or interest in, MC prescribing.
3	Background Page 4, Line 27	Please can you clarify what legislation was enacted in 1961 in the UK, US, and Europe? Is this in reference to the International Drug treaty- "1961 United Nations Single Convention on Narcotic Drugs", in which case these countries were signatories?	We included evidence from the Single Convention on Narcotic Drugs into this section: Legislation enacted by the Single Convention on Narcotic Drugs in 1961, however re-classified cannabis from a therapeutic medicine to a prohibited drug, (Social Council of the United Nations 1961, Grinspoon and Bakalar 1993, Kalant 2001, Taylor 2008, Bridgeman and Abazia 2017). This legislation not only criminalised the use of cannabis, including for medical purposes but also contributed to a lack of pursuit of evidence for its medicinal effects, as procurement of cannabis for scientific studies became restricted, (Taylor 2008, Bridgeman and Abazia 2017).
4	Background Page 4, Line 39	Suggest that the 'in the brain' is removed, as the endocannabinoid system is not solely located there.	We have removed 'the brain' from this sentence.
5	Background Page 4, Line 58	Please can you review the sentence starting "The Canada and United Kingdom legalised MC…." as Canada had legislation in place from 2001 allowing the use of medicinal cannabis under specific conditions (Marijuana for Medical Purposes Regulations), and legalised for recreational use in 2018.	We have addressed reviewers comments as follows: This recommendation has followed legislative changes across the globe where in the early 2000s, Israel (2001), Canada (2001), the Netherlands (2003), and later other countries, including Switzerland (2011), Italy and Czechia (2013), Australia (2016) and Germany (2017) legislated the use of MC under specified conditions,(EMCDDA 2019). An increasing number of states in the United States are also legalising both medicinal and non-medicinal cannabis use, and this is in despite of opposing Federal Laws,(EMCDDA 2019, Shover and Humphreys 2019). The United Kingdom legalised MC in late 2018, and other countries such as Luxembourg are

			following suit with the introduction of pilot programs for MC,(CPFG 2018, EMCDDA 2019)
6	Background Page 4, Line 42	The section of the paragraph “Specifically, this research aimed to provide evidence around key informant perspectives…” would be better moved to the end of the introduction, as it summarises and outlines the aims of the research being undertaken for the reader.	We have moved this section to the end of the introduction.
7	Background Page 4, Line 47	Please use the full term for Therapeutic Goods Authority here, as this is the first time it is referred to in the manuscript.	The full term for Therapeutic Goods Authority is found in Background-Paragraph 4 Line 8. These changes resulted in certain medicinal cannabis products (CBD) being down regulated from a Schedule 9 (S9) - Prohibited Substances category, to a Schedule 8 (S8) - Controlled Drug category by the Australian medicines regulatory body, the Therapeutic Goods Authority (TGA),(TGA 2021).
8	Background Page 4, Line 64	Just a suggestion- the paragraph describing the DoI Framework may be more suited to go prior to the aims and objectives at the end of the introduction as it is relevant to the method of research undertaken- currently the flow of the background feels interrupted when reading.	We have applied your suggested format changes to this section, it is an improvement thank you.
9	Background Page 4, Line 62	Please can you provide appropriate Figure titles to both figures attached? It may just be a result of the article upload process that they are missing though!	Thank you we have applied titles to the figures: Figure 1 Number of Therapeutic Goods Administration Special Access Scheme Category B Approvals in Australia.

			Figure 2 The Application of Diffusion of Innovation theory to Medicinal Cannabis (MC)
10	Methods	The method section requires some clarification and reworking to inform the reader of the methods undertaken. My primary concerns are around the explanation of the recruitment strategy and inclusion criteria, key question development and explanation of thematic saturation.	Please see responses below.
11	Methods Page 7, Line 33	How were the key questions developed? In Table 1, they are presented next to themes- were these themes based on the DoI framework? The selection of key informants covers two quite separate areas- those who are involved in clinical practice and those in the development of policy for MC prescribing- what is the rationale for including those groups in the same analysis?	Thank you for this feedback. We have expanded this section to provide more clarity on the development of questions and sampling strategy.
12	Methods Page 7, Line 45	If non-prescribed artisanal products and their effects were included in the analysis, then why was recreational cannabis for health reasons considered out of scope, as they are both under the umbrella of illegal access for medicinal purposes? Or have I misinterpreted this- if so please could you clarify in the text?	Thank you for this feedback, to clarify: the difference between artisanal medicinal cannabis vs recreation. Non-prescribed artisanal products were included in the analysis as they are known to be accessed by individuals who cannot afford medicinal cannabis prescribed by clinicians,[41]. Recreational cannabis use was excluded from the analysis because this refers to a very large and heterogenous cohort, many of whom have a prior history of cannabis use for non-medical purposes. Given it is difficult to differentiate between cannabis use for recreational purposes versus use for health reasons, the scope of the informant study focused on use of cannabis unambiguously for medical purposes.

13	Methods Page 7, Line 56	Please can you elaborate on how an environmental scan and rapid review of the literature led you to select key informants? Were the professional networks used involved in medicinal cannabis research? What were the full criteria required for an informant to be selected? Was there anything that would lead to you excluding a potential informant?	Thank you for your advice. We have amended this section to provide more clarity: Key informants were selected using purposive and snowballing techniques. Initially informants were selected following an environmental scan, (Graham, Evitts et al. 2008). This approach involved the opportunistic identification of informants from already established contacts such as physicians and researchers, and more focused scoping, that involved the identification of individuals with experience in policy, prescribing, advocacy for and against medicinal cannabis. This included those from peak professional bodies, government departments and individuals who have contributed to the research evidence. Other potential key informants were identified following interviews using peer snowballing. This involved invitation of the peers of interviewees following their suggestion to do so. We excluded informants who were involved in the cannabis production industry and those who worked in or operated cannabis clinics.
14	Methods Page 8, Line 8	Please can you expand on how thematic saturation would be determined to be interviews from at least 20 key informants- whilst I assume that is to meet the pre-determined themes from the DoI model that I think you have used to develop the key questions; it is not clear why twenty informants exactly was selected?	Thank you for your advice. We have amended this section to provide more clarity: Inductive probing was employed in all interviews to facilitate response heterogenicity,(Guest, Bunce et al. 2006). Thematic saturation was ascertained after data collection, and based on saturation of new information threshold, where there was no evidence of the emergence of new themes beyond those already established.
15	Methods Page 8, Line 14	I think this is meant to read (PILS), not (PLIS). Also, was informed consent done in person or did the participant just sign the consent form?	All informants were provided a patient leaflet information statement (PLIS) and a consent form prior to the interview. Consent was provided both verbally in the interview and as a signature on the consent form.
16	Results	It appears that there was an imbalance of prescribers vs non-prescribers and policy makers. Was any attempt made to balance this? As stated above, I think this needs to be addressed in	Participants were not selected on the basis of prescriber or non-prescriber status. They were selected based on the environmental scan which highlighted clinicians who were prominent in the area of medicinal cannabis, through their clinical involvement or through their roles in regulatory or professional bodies developing medicinal cannabis policy.

		the strengths and limitations of the study. Also, a general statement regarding the supporting quotes- is it possible to attribute the quotes to either prescriber, non-prescriber or policy-maker?	Subsequent participants were approached using the snowballing technique as described earlier. We are not able to attribute quotes to prescriber, non-prescriber or policy-maker for two reasons: 1) participants were informed that the quotes would be kept anonymous and 2) there is a risk the participants could be identifiable through their quotes, given some of them had very public profiles around medicinal cannabis.
17	Results Page 8, Line 54	Were informants in SA, WA and NT sought? How was it determined that there was minimal MC prescribing in these jurisdictions- is it lack of availability or lack of willingness to prescribe? I think this needs to be expanded on slightly.	At the time of interviews there were no prescribers in SA, WA and NT. Policy makers and information from peak bodies were based in NSW, VIC, and QLD. There were no patients being prescribed medicinal cannabis in these states at the time of this study.
18	Results Page 8, Line 54	I found myself going back and forth from Figure 2, the results section and the discussion section. The authors have identified that a number of components were described by informants in relation to the model, however there are subheadings within the provided model that are not clearly explored in the results section, or absorbed into other themes.	Thank you for this feedback. We have modified diagram and subheadings for enhanced clarity.
19	Results	For example, under the Relative advantage against other medicines heading in Innovation, there is a section about the risks and harms that does not really fit in the section about advantages, and may be more suitable in a Risks heading, as per the model. Please can you review the results subheadings against the model provided and amend for clarity?	Thank you for this feedback we have reviewed the results subheadings against the model provided and amend for clarity?

20	Results	Is there a way of identifying within Figure 2 the themes that informants have identified as taking place separately from those subsequently identified as gaps in the implementation of medicinal cannabis? Or provide another Figure?	Thank you for this feedback, we have reviewed the Doi figure and the results section for enhanced clarity.
21	Results	I was surprised by the informants reporting involvement in trials of medicinal cannabis products- is this usual practice in Australia? Or does this just reflect the sampled population? This could be expanded on in the Discussion section.	At the time of the study, medical practitioners by and large were not accustomed to the prescribing process, from both a clinical and regulatory perspective. Medicinal cannabis product also was not readily available. Clinical trials were a means by which clinicians could gain experience in prescribing and observe the clinical effects and patients could access medicinal cannabis without charge.
22	Results Page 12, Line 57	I think CBD technically is psychoactive, but non-euphoriant.	Thanks you tis section has been re-written CBD is psychoactive, exhibits no effects indicative of euphoria or dependence potential
23	Results Page 14, Line 8	Implementation of the 'roll-out' of medicinal cannabis- preparedness for regulation- should this read System fit- preparedness for regulation?	Thank you for this feedback, we have reviewed results section for enhanced clarity as advised.
24	Discussion Page 16, Line 48	Please review this sentence. I think there is a bracket in the wrong place. What are 'distributer resources' and how are they catergorised into System antecedents?	'Distributor Resources' are the resources that medicinal cannabis companies use to market their product to clinicians, we have changed the terminology to MC Company Resources
25	Discussion Page 17, Line 36	Can you please explain the Medicare item number? I admit that I have some discomfort about the idea of a financial incentive related to prescribing a specific medication, even as an innovation- who would benefit from such an incentive? How does this balance against evidence-based prescribing?	Thank you for this feedback. We have modified this section as per below. Levers used to promote the diffusion of a new therapeutic, often incorporate a blend of financial and non-financial incentives can include direct remuneration, performance feedback and the delivery of information technology systems. For example, financial incentives could incorporate the inclusion of a general practice (GP) remuneration for the reporting and monitoring of medicinal cannabis prescribing. Similarly, workflow tools, such as GP software for Electronic Medical Records (EMR) that facilitate the reporting of effectiveness and adverse events of medicinal cannabis are other

			important instruments that have the potential to leverage the safe monitoring of medicinal cannabis access.
26	Discussion Page 18, Line 2	What is meant by the term “relevance is threatened’ in regards to medical colleges and regulatory bodies? Is the pressure to change how they operate substantiated?	The relevance of regulatory bodies and medical colleges has been a question of debate and continues to be so, as public opinion runs ahead of other novel therapeutics emerging in the community (e.g. e-cigarettes, psychedelics). This is a broad debate and explored in more detail in the reference provided in our manuscript for readers who wish to know more about this issue.
27	Discussion Page 18, Line 26	Whilst the informants were “comfortable with the increasing trend for consumer-led advocacy”, I am not sure if this is generalisable to the physicians as a whole, and reinforces the need for a clearly defined informant population.	We have amended this sentence to ‘several, but not all, of the informants: Several, but not all, informants were comfortable with the increasing trend for consumer-lead health advocacy in the medicinal cannabis space
28	Discussion Page 18, Line 41	The sentence ‘Substantial collaboration is therefore needed moving forwards with MC,’ is redundant, as the following sentence repeats this expands on the what is needed. There is no mention of any study limitations within the discussion, and a short paragraph addressing these would add to the validity of the study (if it cannot be expanded fully in the earlier sections of the paper).	The redundant phrase is removed. A paragraph on limitations is now included in the main body of the manuscript.

VERSION 2 – REVIEW

REVIEWER	Wagstaff, Duncan University College London Research Department of Epidemiology and Public Health
REVIEW RETURNED	18-Sep-2021

GENERAL COMMENTS	Many thanks for this revision. The extra text you have added regarding methods is very helpful and I believe this manuscript should now be accepted for publication.

REVIEWER	Kisa , Adnan Kristiania University College
REVIEW RETURNED	19-Sep-2021

GENERAL COMMENTS	Thank you for revision

REVIEWER	Oldfield, Karen Medical Research Institute of New Zealand
REVIEW RETURNED	03-Oct-2021

GENERAL COMMENTS	Thank you for taking the time to revise your manuscript. I commend the hard work that you have put into undertaking the revision and find the resulting manuscript reads with much greater clarity. All my concerns have been satisfactorily addressed and I have no further comments at this time. Thanks.