PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Adherence to Clinical Practice Guidelines (CPGs) for the treatment of cancers in Australia and the factors associated with adherence: A systematic review protocol
AUTHORS	Bierbaum, Mia; Rapport, Frances; Arnolda, Gaston; Tran, Yvonne; Nic Giolla Easpaig, Bróna; Ludlow, Kristiana; Braithwaite, Jeffrey

VERSION 1 – REVIEW

REVIEWER	Toivonen, Kirsti University of Calgary, Psychology
REVIEW RETURNED	10-May-2021

GENERAL COMMENTS	Overall this is an important topic that warrants review. I have made some requests to increase clarity of reporting: Introduction: 1. Can you strengthen the rationale for the review in the introduction? in the introduction you have outlined several factors that have been demonstrated to be associated with adherence to CPGs – what are the limits of these studies or limits their generalizability to CPGs in Australia. Methods: 2. The PRISMA statement has an updated 2020 version, please plan to report according to that instead of the 2009 statement 3. Inclusion criteria – will you be looking at primary cancer treatment only or also including adjuvant treatments? 4. Page 10, line 28 – how will the authors determine if adherence is defined, will they accept any measure of adherence (e.g., subjective or objective measures) or just specific types of measures 5. Page 11 – under screening, point 2: will full texts be independently screened by more than one reviewer so that inter-rater reliability can be assessed for the full text screening stage? This would be a methodological strength, however please state if you are also not planning to do this. 6. Page 12 – how many authors will extract data? And are there predetermined rules for how much inconsistency with the 10% data abstraction reviewed by the second consider is acceptable – and what will be done if it does not meet this goal? 7. Are you able to outline the criteria that will be assessed for the risk of bias assessment? 8. Is this review going to also include factors that were assessed but found not to be significantly associated with adherence to CPGs? Or will it just report factors found to be significantly associated with CPGs? Please specify

	9. Please include as an appendix a detailed search strategy for at least one of the databases, including search terms and planned limits

REVIEWER	Price, Sarah N. University of Arizona, Psychology
REVIEW RETURNED	09-Jun-2021

GENERAL COMMENTS	Overall, this is a well-written and detailed review protocol. Specific strengths include the use of 5 reviewers and assessments of inter-rater reliability, the use of the WHO's adherence framework, and assessments of study heterogeneity and potential publication bias. A few minor additions/clarifications may help to strengthen this protocol for publication: 1) The protocol would benefit from a brief explanation as to how the window of 2000-2021 was generated for this review and how this relates to the guidelines in consideration. What are the strengths and limitations of choosing this specific time frame? As a non-Australian, I find myself wondering whether there were any large-scale contextual changes taking place during the 21-year review window that may influence the guidelines themselves as well as CPG adherence (such as changing incentive structures). Although perhaps beyond the scope of the protocol itself, the authors should consider the degree to which the CPGs in consideration have changed during the review time frame and how certain large-scale contextual factors (in addition to factors measured in individual studies) might influence adherence over time. 2) I am curious as to how the authors decided on selecting only 1% of title abstracts for joint review and assessment of inter-rater reliability. A rationale or citation here may be beneficial for the reader to understand why such a seemingly small percentage of the abstracts will be assessed for reliability and whether this practice is standard. Will the results of the inter-rater reliability assessment be reported in the review itself? What about the results of the data extraction check? 3) The screening section (page 9) may benefit from adding more information about how many reviewers will review each selected full text and how any disagreements following full-text review will be resolved- will the same procedures that will be used to review abstracts be used to review full texts? What is meant by "experienced" when describing the reviewers? 4) Please state the plan for documenting important protocol amendments and indicate the page number for this plan on the PRISMA-P checklist. 5) Will the data abstraction tool be piloted by one or more reviewers first prior to use on all included studies? If so, please describe the plan for piloting and revising the data abstraction tool. 6) The authors plan to exclude conference abstracts and gray literature; the authors may consider discussing this as a limitation.

	7) Please provide a full search strategy for at least one electronic database, including planned searched terms. Currently there is not enough detail for a search to be repeated. Addressing these comments may strengthen the manuscript for publication and provide greater detail and transparency for the reader; in its current form it is missing justification for a few methodological choices as well as some procedural details.

REVIEWER	Rayson, Daniel QEII Health Sciences Centre Foundation, Medical Oncology
REVIEW RETURNED	14-Jun-2021

GENERAL COMMENTS	This has the making of an important contribution to the CPG literature in the Australian context. A few comments: I would suggest including the fact that you will be employing PRISMA methodology in your abstract, similarly, include it in bullet 3 of the itemized 'Strengths and limitations of this study' if you are keeping this section. It seems out of place to me and would likely be better incorporated into a separate paragraph within the body of the manuscript rather than at the end of the abstract. The Ethics and Dissemination section should specify that only anonymized data will be employed thus further justifying REB waiver. There should be a knowledge translation explanation/description as, ultimately, the benefits of this research will be actualized only if funders and health care administrators actually pay attention. Ideally there should be a statement regarding how this could/will be achieved. In the Introduction, it would be worth expanding on the goal of CPGs beyond '..to reduce clinical variation (line 10)..' It should be more explicitly stated that the ultimate goal is to standardize clinical practice in the context of best evidence to achieve optimal clinical outcomes. Please clarify inclusion and exclusion criteria: in Inclusion you state '..restricted to the care of patients in Australia.' yet the exclusion criteria ;..do not include patients in Australia..' suggests that you would include international studies that included AU patients vs being exclusive to AU. This isn't clear to this reviewer. It would be helpful for the readership to understand which 'cancer streams' you are planning to include as well as to see a complete list of variables/factors that will be explored (e.g Charlson Comorbidity Index) and how you will be examining Socioeconomic status and race effects. In the 'Screening' section, you reference that 1% of the abstracts will be jointly reviewed..it this correct? Finally, can you clarify clearly what the key primary and secondary objectives of this work are? It will be important to have defined objectives given the likely heterogeneity of the data you will be attempting to examine.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Ms. Kirsti Toivonen, University of Calgary
Comments to the Author:
Overall this is an important topic that warrants review. I have made some requests to increase clarity of reporting:

RESPONSE: Thank you for your well-considered and comprehensive review. Your comments have been valuable and will enhance the protocol.

Introduction:
1. Can you strengthen the rationale for the review in the introduction? in the introduction you have outlined several factors that have been demonstrated to be associated with adherence to CPGs – what are the limits of these studies or limits their generalizability to CPGs in Australia.

RESPONSE: That's a good point, thank you. Please see amendments at the end of the Introduction. "It is unknown whether these factors are associated with cancer treatment CPG adherence in Australia, and if there are similar patterns across cancer streams. Successful implementation of CPGs needs to be context- specific. Therefore, the identification of factors specific to the Australian cancer treatment context is warranted in order to enable future CPG development, implementation and dissemination to be tailored according to identified facilitators and barriers of adherence."

Methods:
2. The PRISMA statement has an updated 2020 version, please plan to report according to that instead of the 2009 statement

RESPONSE: Thank you for highlighting this. We will follow the updated PRISMA checklist and have updated the reference accordingly in the first paragraph of the 'Methods and analysis' section.

3. Inclusion criteria – will you be looking at primary cancer treatment only or also including adjuvant treatments?

RESPONSE: The review will look at neoadjuvant, principal and adjuvant treatments. Please see amendment in the 'Inclusion criteria' section in the Methods.

4. Page 10, line 28 – how will the authors determine if adherence is defined, will they accept any measure of adherence (e.g., subjective or objective measures) or just specific types of measures

RESPONSE: We will include all measures of adherence, so long as they are clearly described. Please see amendment to the 'Additional full text inclusion criteria' section in the Methods.

5. Page 11 – under screening, point 2: will full texts be independently screened by more than one reviewer so that inter-rater reliability can be assessed for the full text screening stage? This would be a methodological strength, however please state if you are also not planning to do this.

RESPONSE: Thank you for highlighting this. Yes, we intend to conduct a double review of all full text papers. Please see amendment to point 2 of the 'Screening' section in the Methods. We have also revised the 'Strengths and limitations' section at the beginning of the manuscript to reflect this, as recommended.

6. Page 12 – how many authors will extract data? And are there predetermined rules for how much inconsistency with the 10% data abstraction reviewed by the second consider is acceptable – and what will be done if it does not meet this goal?

RESPONSE: Two reviewers will extract data from all of the selected studies. The manuscript has been updated accordingly. Please see amendment to point two of the 'Data extraction' section in the Methods.

7. Are you able to outline the criteria that will be assessed for the risk of bias assessment?

RESPONSE: We have provided the questions asked in The Joanna Briggs Institute Critical Appraisal Checklist for analytical cross sectional studies. See amendments in the 'Risk of Bias and strength of evidence assessment' section in the Methods.

8. Is this review going to also include factors that were assessed but found not to be significantly associated with adherence to CPGs? Or will it just report factors found to be significantly associated with CPGs? Please specify

RESPONSE: Our review will extract data on all factors that have been found to be associated with CPG adherence, whether they are significant or not. Please see amendment to the 'Strategy for data synthesis' section in the Methods.

9. Please include as an appendix a detailed search strategy for at least one of the databases, including search terms and planned limits

RESPONSE: Please see included appendix (online supplementary file 2) and reference to this file, in the 'Search strategy' section in the Methods.

Reviewer: 2
Dr. Sarah N. Price, University of Arizona
Comments to the Author:
Overall, this is a well-written and detailed review protocol. Specific strengths include the use of 5 reviewers and assessments of inter-rater reliability, the use of the WHO's adherence framework, and assessments of study heterogeneity and potential publication bias. A few minor additions/clarifications may help to strengthen this protocol for publication:

RESPONSE: Your review is greatly appreciated, and your suggested amendments have enhanced the document.

1) The protocol would benefit from a brief explanation as to how the window of 2000-2021 was generated for this review and how this relates to the guidelines in consideration. What are the strengths and limitations of choosing this specific time frame? As a non-Australian, I find myself wondering whether there were any large-scale contextual changes taking place during the 21-year review window that may influence the guidelines themselves as well as CPG adherence (such as changing incentive structures). Although perhaps beyond the scope of the protocol itself, the authors should consider the degree to which the CPGs in consideration have changed during the review time frame and how certain large-scale contextual factors (in addition to factors measured in individual studies) might influence adherence over time.

RESPONSE: Thank you. The team agree with your point and have updated the search terms to reflect no publication time limit. Please see amendments to the 'Inclusion criteria' section in the

Methods, and provision of the search strategy in supplementary file 2, referenced in the 'Search strategy' in the Methods. Reflecting on potential contextual factors regarding CPG development and their influence on CPG adherence over time would be interesting and valuable. The authors will keep this in mind during the analysis of the systematic review.

2) I am curious as to how the authors decided on selecting only 1% o0f title abstracts for joint review and assessment of inter-rater reliability. A rationale or citation here may be beneficial for the reader to understand why such a seemingly small percentage of the abstracts will be assessed for reliability and whether this practice is standard. Will the results of the inter-rater reliability assessment be reported in the review itself? What about the results of the data extraction check?

RESPONSE: Thank you for highlighting this. We have rewritten the 'Screening' and 'Data extraction' sections in the Methods to improve clarity and methodological rigour.

3) The screening section (page 9) may benefit from adding more information about how many reviewers will review each selected full text and how any disagreements following full-text review will be resolved- will the same procedures that will be used to review abstracts be used to review full texts? What is meant by "experienced" when describing the reviewers?

RESPONSE: Please see amendments to the 'Screening' section in the Methods.

4) Please state the plan for documenting important protocol amendments and indicate the page number for this plan on the PRISMA-P checklist.

RESPONSE: Please see amendments to the Supplementary file 1-the PRISMA-P checklist with reference to this added into the first paragraph of the 'Methods and Analysis'.

5) Will the data abstraction tool be piloted by one or more reviewers first prior to use on all included studies? If so, please describe the plan for piloting and revising the data abstraction tool.

RESPONSE: Yes, the tool will be piloted by two reviewers, and revised if necessary. Please see amendments to the 'Data extraction' section in the Methods.

6) The authors plan to exclude conference abstracts and gray literature; the authors may consider discussing this as a limitation.

RESPONSE: Please see amendments to the 'Strengths and limitations' section. We have added this to the list of limitations and will discuss it further in the review manuscript.

7) Please provide a full search strategy for at least one electronic database, including planned searched terms. Currently there is not enough detail for a search to be repeated.

RESPONSE: Please see included appendix (online supplementary file 2) and reference to this file, in the 'Search strategy' section in the Methods.

Addressing these comments may strengthen the manuscript for publication and provide greater detail and transparency for the reader; in its current form it is missing justification for a few methodological choices as well as some procedural details.

Reviewer: 3
Dr. Daniel Rayson, QEII Health Sciences Centre Foundation
Comments to the Author:
This has the making of an important contribution to the CPG literature in the Australian context.

RESPONSE: The authors would like to thank you for your review of this work, and are greatly appreciative of your insights and the helpful suggestions made.

A few comments:
I would suggest including the fact that you will be employing PRISMA methodology in your abstract, similarly, include it in bullet 3 of the itemized 'Strengths and limitations of this study' if you are keeping this section. It seems out of place to me and would likely be better incorporated into a separate paragraph within the body of the manuscript rather than at the end of the abstract.

RESPONSE: Thank you. The abstract has been amended accordingly. BMJ open require the 'Strengths and Limitations' section to be placed after the abstract. This section has also been amended as suggested.

The Ethics and Dissemination section should specify that only anonymized data will be employed thus further justifying REB waiver.

RESPONSE: Good point. Please see amendments to the 'Ethics and dissemination' section to reflect this.

There should be a knowledge translation explanation/description as, ultimately, the benefits of this research will be actualized only if funders and health care administrators actually pay attention. Ideally there should be a statement regarding how this could/will be achieved.

RESPONSE: Please see amendments to the 'Ethics and dissemination' section.
"To translate the research into action, the findings from this work will be distributed to peak guideline development bodies, clinical societies involved in cancer treatment in Australia, and stakeholders involved in policy development and implementation in oncology."
In the Introduction, it would be worth expanding on the goal of CPGs beyond '..to reduce clinical variation (line 10)..' It should be more explicitly stated that the ultimate goal is to standardize clinical practice in the context of best evidence to achieve optimal clinical outcomes.

RESPONSE: Thank you for highlighting that. Please see amendments to the Introduction.
"Clinical Practice Guidelines (CPGs) synthesise the latest evidence to support clinical and patient decision-making, and are designed to reduce clinical variation, through standardising clinical practice in line with best evidence, to ultimately enhance clinical outcomes."

Please clarify inclusion and exclusion criteria: in Inclusion you state '..restricted to the care of patients in Australia.' yet the exclusion criteria ;..do not include patients in Australia..' suggests that you would include international studies that included AU patients vs being exclusive to AU. This isn't clear to this reviewer.

RESPONSE: Please see amendments to the 'Inclusion criteria' and the 'Exclusion criteria' sections in

the Methods.
“Studies that do not include patients care within Australia and studies focusing on diseases other than cancer will also be excluded. Studies that report data from both Australia and other countries will be excluded if the Australian data is not reported separately.”

It would be helpful for the readership to understand which 'cancer streams' you are planning to include as well as to see a complete list of variables/factors that will be explored (e.g Charlson Comorbidity Index) and how you will be examining Socioeconomic status and race effects.

RESPONSE: The review will include studies looking at any cancer stream, and will describe all factors reported by those studies that are significantly associated with adherence. We have included some examples (patient Charlson Comorbidity Index, Socioeconomic Status, geographic remoteness, Country of Birth, Eastern Cooperative Oncology Group (ECOG) performance status, clinician case load, or hospital case load). We will look at Aboriginal and Torres Strait Islander Status if it is available, however other than that data, race is not routinely collected in Australia. If available, we will look at factors related to Culturally and Linguistically Diverse populations or Country of Birth variables. Please see amendments to point one of the ‘Data extraction’ section, in the Methods.

In the 'Screening' section, you reference that 1% of the abstracts will be jointly reviewed..it this correct?

RESPONSE: Please see amendments to the planned review of title abstracts by multiple reviewers, in the ‘Screening’ section in the Methods

Finally, can you clarify clearly what the key primary and secondary objectives of this work are? It will be important to have defined objectives given the likely heterogeneity of the data you will be attempting to examine.

RESPONSE: Thank you. We have edited the ‘Objectives’ section to make the primary and secondary objectives clearer.

VERSION 2 – REVIEW

REVIEWER	Toivonen, Kirsti University of Calgary, Psychology
REVIEW RETURNED	22-Aug-2021

GENERAL COMMENTS	Thank you for your revised manuscript. My questions have been addressed.

REVIEWER	Price, Sarah N. University of Arizona, Psychology
REVIEW RETURNED	07-Aug-2021

GENERAL COMMENTS	Overall, I am satisfied with the changes made by the authors in this first round of revisions. One remaining concern is that in an earlier comment, I asked if the authors could provide a rationale for their choice of 2000 as the earliest publication date included in this systematic review (e.g. does this date hold any specific significance such as coinciding with landmark changes in existing guidelines/practices, major

	updates, or introduction of new guidelines? Is there a lack of published literature on clinical practice guideline adherence before this date?). Instead of directly addressing this question, it appears that the window for included studies has been eliminated altogether. Does this mean that there will be no date restrictions on searches and that all published literature meeting criteria (including studies published prior to 2000) will be included? Clarification would be helpful.

REVIEWER	Rayson, Daniel QEII Health Sciences Centre Foundation, Medical Oncology
REVIEW RETURNED	09-Aug-2021

GENERAL COMMENTS	Thank you for your responses to the reviewer comments, all of which have been addressed satisfactorily. A few minor comments for consideration to improve phraseology and clarity: Para 1, lines 2-3, suggest: '..through standardization of clinical practice...' Para 1, line 7, suggest: '..justified to account for individual patient characteristics and preferences.' Para 2, line 6, suggest: '...therapy and treatment access...' Para 2, line 10, suggest: 'as well as receiving care at a different facility from the initial treatment centre.' Para 2, lines 13-16, suggest: ...Patient and clinician characteristics associated with CPG adherence include older age, race, gender, comorbid conditions, private health insurance and socioeconomic status as well as clinician specialty practice and caseload. Last line of Introduction, suggest:'...barriers of adherence within the country.' Inclusion criteria: the word 'principal' in the second line will be poorly understood..suggest- '(including primary surgery, adjuvant and neoadjuvant systemic therapy). Exclusion criteria: not sure what is meant by 'Non-empirical research including conference abstracts..' is meant to convey. Just state that 'Conference abstracts, editorials and opinion pieces as well as purely qualitative research will be excluded.' Ethics and dissemination, line 6: Not sure what is meant by '...peak guideline development bodies...'

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Ms. Kirsti Toivonen, University of Calgary
Comments to the Author:
Thank you for your revised manuscript. My questions have been addressed.
RESONSE: Thank you.

Reviewer: 2
Dr. Sarah N. Price, University of Arizona
Comments to the Author:
Overall, I am satisfied with the changes made by the authors in this first round of revisions.

One remaining concern is that in an earlier comment, I asked if the authors could provide a rationale for their choice of 2000 as the earliest publication date included in this systematic review (e.g. does this date hold any specific significance such as coinciding with landmark changes in existing guidelines/practices, major updates, or introduction of new guidelines? Is there a lack of published literature on clinical practice guideline adherence before this date?). Instead of directly addressing this question, it appears that the window for included studies has been eliminated altogether. Does this mean that there will be no date restrictions on searches and that all published literature meeting criteria (including studies published prior to 2000) will be included? Clarification would be helpful.

RESPONSE: Thank you for your second review of this manuscript. Your initial query prompted reconsideration of the time restrictions and we have since concluded that there is not a strong enough rationale to restrict the search. We thank the reviewer for raising this issue, and have since amended the text to make this revision explicit. The publication date restriction has been removed, and now all studies meeting criteria (including studies published prior to 2000) will be included. In the inclusion criteria, we have added ‘no date restrictions will be applied’.

Reviewer: 3
Dr. Daniel Rayson, QEII Health Sciences Centre Foundation
Comments to the Author:
Thank you for your responses to the reviewer comments, all of which have been addressed satisfactorily.
RESPONSE: Thank you for your thorough second review of this manuscript.

A few minor comments for consideration to improve phraseology and clarity:

Para 1, lines 2-3, suggest: '..through standardization of clinical practice...'
RESPONSE: Thank you. Amended as suggested.

Para 1, line 7, suggest: '..justified to account for individual patient characteristics and preferences.'
RESPONSE: Thank you. Amended as suggested.

Para 2, line 6, suggest: '...therapy and treatment access...'
RESPONSE: Thank you. Amended as suggested.

Para 2, line 10, suggest: 'as well as receiving care at a different facility from the initial treatment centre.'
RESPONSE: Thank you. Amended as suggested.

Para 2, lines 13-16, suggest: ...Patient and clinician characteristics associated with CPG adherence include older age, race, gender, comorbid conditions, private health insurance and socioeconomic status as well as clinician specialty practice and caseload.
RESPONSE: Thank you. Amended as suggested.

Last line of Introduction, suggest:'...barriers of adherence within the country.'
RESPONSE: Thank you. Amended as suggested.

Inclusion criteria: the word 'principal' in the second line will be poorly understood..suggest- '(including primary surgery, adjuvant and neoadjuvant systemic therapy).
RESPONSE: We thank reviewer 3 (Dr Rayson) for their suggestion. As the phrasing ‘primary surgery, adjuvant and neoadjuvant systemic therapy’ may imply that surgery is the only primary therapy, and

neo-adjuvant and adjuvant therapies are only systemic (chemotherapy), excluding radiotherapy, we have instead used the phrase “primary treatment, and neoadjuvant and adjuvant treatments”.

Exclusion criteria: not sure what is meant by 'Non-empirical research including conference abstracts..' is meant to convey. Just state that 'Conference abstracts, editorials and opinion pieces as well as purely qualitative research will be excluded.'
RESPONSE: Thank you. Amended as suggested.

Ethics and dissemination, line 6: Not sure what is meant by '...peak guideline development bodies...'
RESPONSE: Thank you. The word ‘peak’ has been removed.

VERSION 3 – REVIEW

REVIEWER	Price, Sarah N. University of Arizona, Psychology
REVIEW RETURNED	30-Aug-2021

GENERAL COMMENTS	Thank you for your revised manuscript. My questions have been addressed.

REVIEWER	Rayson, Daniel QEII Health Sciences Centre Foundation, Medical Oncology
REVIEW RETURNED	06-Sep-2021

GENERAL COMMENTS	Thank you for addressing all queries. Good luck with your work.