PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	A protocol for a discrete choice experiment: understanding patient medicine preferences for managing chronic non-cancer pain
AUTHORS	Shanahan , Marian; Larance, Briony; Nielsen, Suzanne; Cohen, Milton; Schaffer, Maria; Campbell, Gabrielle

VERSION 1 – REVIEW

REVIEWER	Cary Reid Weill Cornell Medical College New York, NY USA
REVIEW RETURNED	31-Dec-2018

GENERAL COMMENTS	This is manuscript describes the protocol for an ongoing study focused on a very important topic, i.e., eliciting patient preferences regarding various treatments for the management of chronic non-cancer pain. This is a topic that has been under explored in the literature. Kudos to the authors for addressing the subject. Despite this strength, there are several important limitations that need to be addressed: 1) Not clear where the data come from to populate the attributes for the various scenarios 2) The authors do not provide any information on what the final model results will look like. Clinicians will want to know what types of results are generated and in what form? How useful will this approach be for general practice? 3) Not clear that a sample of 16 patients and 8 clinicians is sufficient to ensure that you have determined the entire universe of attributes and levels. Did you look for thematic saturation when generating your results. 4) I am surprised that pain mitigation and likelihood of generating a meaningful result (from a given treatment) were not attributes. What about ability to continue to work (important given the age range of your intended sample?) 5) NO rationale given as to why you will conduct the study in two discrete samples, one taking opioids and the other not taking opioids. 6) HOw assured are the authors that 8 scenarios will be sufficient to determine patient preferences? Other issues that require attention 1) There seems to be a fair amount of attention directed to out of pocket costs. Since these are quite variable across countries (and types of insurances), how important will this attribute be in countries outside of Australia, i.e., concerns about generalizability of your results.

	2) Page 4, line 54. You state that cost and availability of alternative treatments may affect patients' treatment choices, which is true but these factors also impact providers' recommendations as well. 3) Page 9, line 21. How were the results of refined as a result of the pilot study? 4) HOw many of the treatment scenarios compare a drug versus non-drug treatment option? Given the panoply of treatment options (both drug and non-drug) it is not clear to me whether 8 scenarios will be sufficient to completely cover patients' preferences in this setting 5) To what extend will age be examined as a explanatory factor. My sense is that many older patients may struggle with this approach, thereby limiting the reach of the tool if found helpful.

REVIEWER	Roger Knaggs University of Nottingham United Kingdom Researcher in similar area
REVIEW RETURNED	04-Jan-2019

GENERAL COMMENTS	General comments The background is rather focused on some of the challenges in the use of prescription opioids for chronic pain. However, the first aim relates to preferences for medicines for pain in general. Patients already taking opioids are probably a self-selecting subgroup with complex co-morbid psychological conditions and social circumstances. It is interesting that only pharmacological treatments have been considered and the role of other treatments have not been included. Perhaps the title should be modified to reflect that it largely relates to choices about medicines. I would recommend generally using the word ‘medicine’ rather than ‘medication’. Introduction Page 4 line 14-15 clarify the period over which overdoses have occurred Page 5 line 34 tolerability may be a more preferable word than toleration Aims Page 5 Line 55 The first aim states preferences for medicines, although the introduction and one of the patient groups have specifically taken opioids. Page 6 Line 6 it is unclear how this aim will be addressed in the criteria used in the discrete choice experiment Overview of DCE Page 7 line 52 clarify meaning of ‘national peak body’ (repeated Page 10 line 43) Page 8 line 21 and line 26 More details of the results from the literature review and qualitative interviews and focus group could be presented or referenced if published elsewhere to demonstrate how they influenced design of DCE. Pilot study The pilot testing was undertaken in people prescribed opioids. The authors draw attention to the fact that the attribute ‘risk of addiction to pain medications’ was reduced to two levels. As opioids may induce dependence and addiction, consideration should be given

	to whether this is equally applicable to patients who may not have been prescribed opioids Proposed study Page 11 line 3 – it appears that the groups will be administered the DCE in different formats; the POINT cohort as part of a pre-planned interview and the CNCP group as an online survey. Please provide clarification as to the steps to ensure that it is interpreted in the same way between the groups. Data analysis Page 11 line 15 Although, it is intended to analyse results from the prospective 'opioid' cohort study and online survey separately, people prescribed opioids may still be included from the online survey, hence be more similar to the cohort from the POINT study. It would be interesting to compare the results from people prescribed opioids and those that have not been prescribed opioids, so the authors may wish to re-consider the inclusion criteria.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

1) Not clear where the data come from to populate the attributes for the various scenarios

Author response: The data (attributes and levels of the attributes) were obtained from a range of sources, this included an initial literature review and focus groups conducted with patients and clinicians. This is explained on page 8 of the manuscript.

The final list of attributes included in the DCE experiment were generated using a detailed iterative process. The first phase involved a literature review undertaken by MSh to inform the development of list of possible factors previously identified as influencing patient choice of pain treatments. This list was reviewed and further developed among the broader POINT study investigators who include pain and addiction specialists, pharmacists and epidemiologists.

These attributes developed in the first phase of the study became the basis of (a) focus group discussions with patients and (b) telephone interviews with clinicians. Two authors (MSh and GC) reviewed the recorded transcripts separately and independently analysed data thematically. Attributes generated at this second phase included the following themes: potential side effects; concurrent medications; necessity to work / care for others; barriers; complementary medicine; multi-modal therapies; costs; time to onset of effect; adherence/compliance; risk of addiction; co-morbidities; and self-management.

In the final phase, this broader list was reviewed by the broader POINT study investigator team, and a final list of attributes (and their levels) was agreed. Attributes (and number of levels) selected were number of medications (4), risk of addiction (4), side effects (2), pain interference (4), activity goals, source of information on pain (4), provider of pain care (4) and out of pocket costs (4).

2) The authors do not provide any information on what the final model results will look like. Clinicians will want to know what types of results are generated and in what form? How useful will this approach be for general practice?

Author response:

The following text has been added

"The responses to the DCE will be analysed using mixed logit and latent class models permitting an assessment of heterogeneity of response. Tables of coefficients for the levels and covariates will be presented with relevant statistical measures including pseudo r-squared, log likelihood test, and the AIC to test for goodness of fit of the model. In addition, the marginal rate of substitution (the negative

ratio between any two estimated coefficients) will be calculated. This will allow policy makers and clinicians to understand the relative importance of different attributes, and the respondents' willingness to give up some amount of one attribute in order to obtain more of another."
3) Not clear that a sample of 16 patients and 8 clinicians is sufficient to ensure that you have determined the entire universe of attributes and levels. Did you look for thematic saturation when generating your results.
Author response: We have included the paragraph below for clarification
"Typically, a sample of 20-30 participants is sufficient for thematic analyses in qualitative research (the current study's sample size was N=24). The triangulation of data from multiple sources (literature review, investigator meetings, telephone interviews with clinicians and focus groups with patients) further increases our confidence that we reached saturation of themes."

4) I am surprised that pain mitigation and likelihood of generating a meaningful result (from a given treatment) were not attributes. What about ability to continue to work (important given the age range of your intended sample?)
Author response: Pain and reduction in pain is not considered by leading clinicians and researchers to be the main outcome of pain management. The main outcomes of pain treatment include improvements in physical, emotional and social functioning, and improvements in activities of daily living. In the focus groups conducted with people living with pain, participants noted that pain would continue to be a part of their lives, and that it was more important that functioning and ability to participate in daily activities improved. In the current study, the included attribute of functioning was included as this was most likely to address this issue.

5) No rationale given as to why you will conduct the study in two discrete samples, one taking opioids and the other not taking opioids.
Author response: The decision to use two samples is to assess whether the preferences of the POINT cohort which was recruited into the cohort study because they were on opioids for chronic pain and is different from a community sample which may or may not be taking on opioid medicines for their pain. We wanted to include both samples to understand treatment preferences among two different populations. We have included more information regarding this;
"To examine the possibility of different treatment preferences in people living with CNCP we included two distinct groups. The POINT cohort consist of participants who have been prescribed opioids for CNCP and have been on long-term opioids for an average of seven years at the time of the current study. The other sample includes CNCP recruited online. These participants are not necessarily prescribed opioids and we will examine the differences in treatment preferences between people prescribed and not prescribed opioids for CNCP."

6) How assured are the authors that 8 scenarios will be sufficient to determine patient preferences?
Author response: Although each person only sees 8 scenarios, there are a total of 80 scenarios (10 blocks of 8) which have been generated by statistical software. This is standard in DCE. As it is not feasible to present all possible options to participants, the software generates the most statistically efficient design possible given the parameters, number of levels and attributes. The range of number of scenarios typically presented to participants ranges from 2 to 16; 8 was selected for this study as the context is complex and it was felt that asking participants to complete additional scenarios might place a significant burden on some of them who are quite elderly and infirm.

7) There seems to be a fair amount of attention directed to out of pocket costs. Since these are quite variable across countries (and types of insurances), how important will this attribute be in countries outside of Australia, i.e., concerns about generalizability of your results.
Author response: These findings are likely to be generalizable to countries with healthcare systems similar to those in Australia however it is not clear whether the results are generalizable to resource-poor settings or countries without universal healthcare systems. However, although the actual

monetary values will change across countries, the information on the marginal willingness to pay (or not) for preferred attribute levels will be transferrable and useful more generally to policy makers.
We have added to the following text
"Although the marginal willingness to pay for preferred attributes will assist policy makers generally, some of the results may not be generalizable to resource-poor settings or countries without universal healthcare systems."
8) Page 4, line 54. You state that cost and availability of alternative treatments may affect patients' treatment choices, which is true but these factors also impact providers' recommendations as well.
Author response: The aim of the study was to evaluate patient choices. Although we agree that prescriber recommendations may inform patient choices, understanding prescribers' preferences in terms of attributes and levels was beyond the scope of the current study
3) Page 9, line 21. How were the results of refined as a result of the pilot study?
Author response: The key change was in decreasing the number of levels for dependency; the coefficients generated from the analysis were used to improve the efficiency of the statistical design for the final survey

9) How many of the treatment scenarios compare a drug versus non-drug treatment option? Given the panoply of treatment options (both drug and non-drug) it is not clear to me whether 8 scenarios will be sufficient to completely cover patients' preferences in this setting
Author response: The analysis of the DCE assesses the preferences for the individual attributes not the preferences for individual scenarios.

10) To what extend will age be examined as a explanatory factor. My sense is that many older patients may struggle with this approach, thereby limiting the reach of the tool if found helpful.
Author response: Age will be a covariate in the analysis

Reviewer: 2
The background is rather focused on some of the challenges in the use of prescription opioids for chronic pain. However, the first aim relates to preferences for medicines for pain in general. Patients already taking opioids are probably a self-selecting subgroup with complex co-morbid psychological conditions and social circumstances.
It is interesting that only pharmacological treatments have been considered and the role of other treatments have not been included. Perhaps the title should be modified to reflect that it largely relates to choices about medicines.
Author response: We have amended the title to "A protocol for a discrete choice experiment: understanding patient medicine preferences for managing chronic non-cancer pain"

1) I would recommend generally using the word 'medicine' rather than 'medication'.
Author response: we have changed this throughout the manuscript

2) Page 4 line 14-15 clarify the period over which overdoses have occurred Page 5 line 34 tolerability may be a more preferable word than toleration
Author response: this has been amended

3) Page 5 Line 55 The first aim states preferences for medicines, although the introduction and one of the patient groups have specifically taken opioids.
Author response: A key issue of interest is whether the choice to continue opioids is as a result of the lack of funding for alternative programs (i.e. psychologist, ongoing exercise programs). Although the POINT cohort was recruited while on opioids, not all are currently taking opioids, and many have cycled on and off of opioids in the five years of follow-up. As mentioned above, the self-selected community sample identifying as having chronic non-cancer may or may not be taking opioids

however their history of current and previous opioid use will be collected and included as a covariate in the analysis.

4) Page 6 Line 6 it is unclear how this aim will be addressed in the criteria used in the discrete choice experiment
Author response: It is not clear to what the reviewer is referring to however each of the aims related to one of the attributes. Both the sign on the coefficients for each level, and the marginal rate of substitution between the levels and costs will be used to assess each aim.

5) Page 7 line 52 clarify meaning of 'national peak body' (repeated Page 10 line 43) Page 8 line 21 and line 26
Author response: Pain Australia is Australia's leading pain advocacy body. Representing the interests of a membership that includes health, medical, research and consumer organisations it works to improve the quality of life of people living with pain and to facilitate implementation of the National Pain Strategy Australia-wide.
The text has been amended to reflect this
6) More details of the results from the literature review and qualitative interviews and focus group could be presented or referenced if published elsewhere to demonstrate how they influenced design of DCE.
Author response: As our response to reviewer 1 above. A list of possible attributes and levels were generated from (a) an initial literature review, (b) meeting involving all authors, and (c) thematic analyses of qualitative data obtained from phone interviews with clinicians and focus groups with patients. The total pool of attributes and levels were reviewed by all investigators/ authors, and the final pool of attributes and levels were selected.

7) The pilot testing was undertaken in people prescribed opioids. The authors draw attention to the fact that the attribute 'risk of addiction to pain medications' was reduced to two levels. As opioids may induce dependence and addiction, consideration should be given to whether this is equally applicable to patients who may not have been prescribed opioids
Author response: This will be an attribute in all scenarios seen by the participants, and with wording phrased as to whether they are aware of the risk. Previous and current opioid status will be a covariate in the analysis.

8) Page 11 line 3 – it appears that the groups will be administered the DCE in different formats; the POINT cohort as part of a pre-planned interview and the CNCP group as an online survey. Please provide clarification as to the steps to ensure that it is interpreted in the same way between the groups.
Author response: The POINT participants were sent the information and DCE scenarios in the mail before their interview. After the participants had completed the pre-planned interview, the interviewer asked the participant to read out their preferences so that they could be recorded. Therefore, the procedure of reading and selecting the preferred scenario by participants was essentially the same in both groups. It was the recording, i.e. online or by an interviewer that was different. It is possible that the interviewers were able to assist the POINT participants, however, the interviewers have been trained to only ask questions from the survey as they appear, without providing context or additional information. This ensures that all participants are administered the interview in the same way and the interviewer does not provide any individual participants with additional information that may affect their response.

9) Page 11 line 15 Although, it is intended to analyse results from the prospective 'opioid' cohort study and online survey separately, people prescribed opioids may still be included from the online survey, hence be more similar to the cohort from the POINT study. It would be interesting to compare the

results from people prescribed opioids and those that have not been prescribed opioids, so the authors may wish to re-consider the inclusion criteria.
Authors response: The respondents past and present opioid use will be included as a covariate in the analysis. If enough of the community group have not been prescribed opioid their data may be analysed separately. It is our preference to not limit the community sample to only those who have never been prescribed opioid medicines.

VERSION 2 – REVIEW

REVIEWER	MC Reid Weill Cornell Medical College USA
REVIEW RETURNED	27-Mar-2019

GENERAL COMMENTS	The authors have been largely responsive to the concerns raised by the reviewers. While I agree with the authors that 'leading' clinicians and researchers advocate for a focus on functional improvement in studies of pain patients, the vast majority of studies that have queried patients about their goals indicate that pain mitigation is by far the most important outcome. It is important not to lose sight of patients' preferences and goals.

REVIEWER	Roger Knaggs University of Nottingham, United Kingdom Reseacher in similar field
REVIEW RETURNED	01-Apr-2019

GENERAL COMMENTS	Many thanks for the opportunity to review the revision of this manuscript. The authors have addressed issues raised by previous reviews. In my previous review I recommended that the word medication is replaced with medicine throughout to make reading more accessible. Although the authors claim this has been done the revised manuscript still contains the word medication on numerous occasions. I reiterate my previous comment.

VERSION 2 – AUTHOR RESPONSE

Reviewer comments

Reviewer 1

1. The authors have been largely responsive to the concerns raised by the reviewers. While I agree with the authors that 'leading' clinicians and researchers advocate for a focus on functional improvement in studies of pain patients, the vast majority of studies that have queried patients about their goals indicate that pain mitigation is by far the most important outcome. It is important not to lose sight of patients' preferences and goals.

Author response: We agree with the reviewer. From the focus groups it was apparent that patients were aware that they may continue to live with pain, but they were interested in treatments which reduced the impact of pain on their daily lives, hence the inclusion of pain interference as an attribute as opposed to pain severity.

Reviewer 2

1 The authors have addressed issues raised by previous reviews. In my previous review I recommended that the word medication is replaced with medicine throughout to make reading more accessible. Although the authors claim this has been done the revised manuscript still contains the word medication on numerous occasions. I reiterate my previous comment.

Author response: We apologise for the oversight, we have amended the manuscript where possible. However, in some cases we have left the word medication as this is what has been used in the questionnaires and we present them here as they were presented to participants.