PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	The Current Understanding of Precision Medicine and Personalised Medicine in Selected Research Disciplines – Study Protocol of a Systematic Concept Analysis
AUTHORS	Brew-Sam, Nicola; Parkinson, Anne; Lueck, Christian; Brown, Ellen; Brown, Karen; Bruestle, Anne; Chisholm, Katrina; Collins, Simone; Cook, Matthew; Daskalaki, Eleni; Drew, Janet; Ebbeck, Harry; Elisha, Mark; Fanning, Vanessa; Henschke, Adam; Herron, Jessica; Matthews, Emma; Murugappan, Krishnan; Neshev, Dragomir; Nolan, Christopher; Pedley, Lachlan; Phillips, Christine; Suominen, Hanna; Tricoli, Antonio; Wright, Kristine; Desborough, Jane

VERSION 1 – REVIEW

REVIEWER	Cobo, Erik Universitat Politecnica Catalunya, Statistics and Operational Research
REVIEW RETURNED	31-Jan-2022

GENERAL COMMENTS	Disclosures: I'm a biostatistician expert on clinical trials and reporting guidelines. I'm not expert in Concept analysis. I apologize for my poor English. I think this is a well-written protocol addressing an interesting question that follows the PRISMA-P statement and should be published provided experts on concept analysis have no major objections. Personally, I wonder about the evidence on PM benefits and risks -- which relies on the unproven assumption of treatment heterogeneity within the boundaries of eligibility criteria, as my student review published here(1) tried to highlight. I only have some minor suggestions. As such, the authors may argue to consider or not. Minor suggestions: I think this review can be better classified as a scoping review or similar, nor as a systematic review. Please consider deleting "systematic" throughout the title and text. In the actual wording your methodology is open to lather interpretations, opening the way to selective reporting bias. Please, consider either to further clarify your methods or, according to an exploratory view, specify on the discussion that your aim is more to suggest than to confirm. In your PRISMA table you only talk about not quantitative synthesis. Please consider some dimensionality reduction methods, such us cluster or correspondence analyses, for example. In your own benefit, to save time, please consider the next options: 1) You may further specify your methodology in the last sentences of page 12. For example, further clarify which exclusions will be made looking only to the abstract, and the ones that will need a deeper

reading -this might also enhance reproducibility.
2) You may consider a pilot search to further specify your search, your extraction and synthesis methods, and the performance of the MMAT tool in your study (I'm confused about its benefits as a Risk of Bias tool in a concept review).
3) If your search return too many (how many is too many?) papers, consider a random sample (how many for each stratum?).
Other considerations:
Please, be careful with verb tenses. For example, I wonder if your sentence (P4L53) "our study contributes to the clarification…" should be "our study will contribute to the clarification…" or "may" or similar. Also, in P5L8, "..their interpretation (…) application (…) are…", I wonder if "are" should be "is"?
Also, please consider changing in P4L55 "…it is not possible for our analysis to deliver,,," for "…it is not our objective to deliver…".
Erik Cobo, Barcelona-Tech
(1) https://f1000research.com/articles/7-30

REVIEWER	Delles, Christian University of Glasgow, Institute of Cardiovascular and Medical Sciences
REVIEW RETURNED	26-Feb-2022

GENERAL COMMENTS	This is a well written protocol paper and I do not have any specific concerns. The project appears entirely doable and the presentation of the planned work is clear. You may want to consider a few points though: 1. The abstract is not particularly meaningful. It says that current understanding will be examined but it is not easy to understand that this project is based on literature review rather than e.g. a survey to relevant stakeholders. Please try to use the space wisely – there is certainly no need to mention all 6 of Rodger's steps. 2. I wonder how you will handle publications that cannot be unanimously allocated to one specific discipline (e.g. chemistry, engineering etc.). Particularly in the field of precision medicine there are many cross-cutting projects. 3. It is reasonable to restrict the search to papers from 2016 to 2022. As much as this will provide insight into the understanding of relevant position papers such as the Precision Medicine Initiative there is, however, a risk that authors do not develop their own views and simply cite the relevant definition from major statements. I am not sure if this will help with assessment of "understanding" and would expect a number of publications that just word-by-work cite from the big reports. I assume you have thought about this.

REVIEWER	Rakićević, Ljiljana University of Belgrade
REVIEW RETURNED	05-Mar-2022

GENERAL COMMENTS	Review of the Manuscript The Current Understanding of Precision Medicine and Personalised Medicine in Selected Research Disciplines – Study Protocol of a Systematic Concept Analysis (ID bmjopen-2021-060326) : The authors considered the current understanding of the concepts

	"precision medicine" and "peresonalised medicine" in order to determine how these two concepts are distinguished in selected research disciplines and potential subdisciplines. Theoretical consideration of these concepts is very rare in studies and because of that the manuscript might have significance for the scientific community and medical science and practice.

REVIEWER	Van de Velde, Dominique Ghent University, occupational therapy
REVIEW RETURNED	11-May-2022

GENERAL COMMENTS	This is an interesting article in which a protocol is proposed to differentiate between "precision medicine" and "personalised medicine". The protocol is described in a way that a researcher that is not involved in this study could start with this project and is therefore reproducible. It is a strong point that this protocol is based on the concept analysis of Rodgers, which is a more inductive approach than the other methods for concept analyses. I have two concerns that should be clarified. 1 also the following literature will be included: physics, chemistry, engineering; machine learning, and artificial intelligence. Why? This is a bit strange and will possibly create more difficulties to obtain a clear description of both concepts because these disciplines might have a totally different view on the concepts under investigation. How can the authors be sure that the attributes will be applicable for clinical medicine, biomedicine and health services? 2. The most difficult one; how will the authors operationalize the following inlcusion criterium for articles: Having a main focus on clarifying at least one of the concepts "precision medicine" or "personalised medicine", and contributing to a deeper understanding of the concept(s) using theoretical or empirical studies – publications that do not deliver any substantial contribution regarding the clarification of the concepts are to be excluded. How will be defined that the article provides a deeper understanding of one of the concepts? Will this be based on definitions, on explanations, descriptions of the concept, theoretical understandings. And what level of evidence is expected. Will theoretical attibutes, without supporting evidence or validation of the concept also be included? good luck with the study

VERSION 1 – AUTHOR RESPONSE

Reviewer 1: Dr. Erik Cobo, Universitat Politecnica Catalunya	
I'm a biostatistician expert on clinical trials and reporting guidelines. I'm not expert in Concept analysis. I think this is a well-written protocol addressing an interesting question that follows the PRISMA-P statement and should be published provided experts on concept analysis have no major objections.	Thank you for your supportive comments

I think this review can be better classified as a scoping review or similar, nor as a systematic review. Please consider deleting "systematic" throughout the title and text.	We have considered this carefully and respectfully disagree, as the strength of Rodger's exploratory concept analysis methodology is that it is systematic and incorporates a systematic review of the literature. As the journal requires that the title clearly describe the methodology used, we have included 'systematic' in the title.
In the actual wording your methodology is open to other interpretations, opening the way to selective reporting bias. Please consider either to further clarify your methods or, according to an exploratory view, specify on the discussion that your aim is more to suggest than to confirm.	To clarify this we have included the following in the Objectives section: *"As concepts are constantly developing and their meanings change over time it is not our objective to deliver an unequivocal definition."* and also as a limitation: *"Concepts are constantly developing and their meanings change over time, and hence it is not our objective to deliver an unequivocal definition."*
In your PRISMA table you only talk about non quantitative synthesis. Please consider some dimensionality reduction methods, such us cluster or correspondence analyses, for example.	We understand your inquiry regarding the use of quantitative methods, although in line with Rodgers concept analysis methods, we are using an inductive approach, which does not include quantitative methods such as these. At the same time, in response to your comment, we have looked at correspondence analysis methods and find it very interesting. If we feel this may add to the rigour and quality of the analysis, we will use this method and report this diversion from the methods described in this protocol and the associated results in the published paper.
You may further specify your methodology in the last sentences of page 12. For example, further clarify which exclusions will be made looking only to the abstract, and the ones that will need a deeper reading -this might also enhance reproducibility.	We have further clarified: *"We recognise that due to the nature of our inquiry, it may not be apparent at the abstract and title screening stage whether articles discuss concepts in detail; this will be determined at the full text screening stage."*
You may consider a pilot search to further specify your search, your extraction and synthesis methods, and the performance of the MMAT tool in your study (I'm confused about its benefits as a Risk of Bias tool in a concept review).	An initial exploratory search of the literature was conducted to inform our selection of search terms and highlighted the need to search for the terms beyond the title and abstract for the truncated terms 'defin*' and 'concept*' to enable capture of relevant articles. We have clarified this in the section describing the search strategy: we have added, *"The search strategy, developed after an initial exploratory search of the literature…."* Although unlikely, we may identify one or more empirical studies for inclusion in our final analysis. As per our inclusion criteria, *"Empirical studies will be included if they serve the purpose of concept clarification (e.g., hybrid concept analysis which combines empirical research with the analysis of a concept)"* For this reason, we have incorporated the MMAT to add rigour to our systematic approach to searching the literature as it enables an assessment of empirical studies to signal any flaws or limitations in their design. As this is a protocol and we have yet to conduct the literature search we will be able to determine how many empirical studies the analysis will include (after the search). From there we will be able to

	conclude if the use of MMAT is reasonable.
If your search return too many (how many is too many?) papers, consider a random sample (how many for each stratum?).	We have added the following to the manuscript: *"Guidance from Rodgers advises that each discipline should be represented by approximately 20 percent of the overall included references. If a larger number of relevant studies are returned in our search results, we will reduce the number for analysis in each discipline by selecting, for example, every fifth article starting from a random article."*
Please, be careful with verb tenses. (P4L53) "our study contributes to the clarification…" should be "our study will contribute to the clarification…" or "may" or similar. P5L8, "...their interpretation (…) application (…) are…", I wonder if "are" should be "is"? P4L55 "…it is not possible for our analysis to deliver…" for "…it is not our objective to deliver…".	Thank you for picking this up, we have amended the manuscript as suggested
Reviewer 2: Prof. Christian Delles, University of Glasgow	
This is a well-written protocol paper and I do not have any specific concerns. The project appears entirely doable and the presentation of the planned work is clear.	Thank you for your supportive comments
The abstract is not particularly meaningful. It says that current understanding will be examined but it is not easy to understand that this project is based on literature review rather than e.g. a survey to relevant stakeholders. Please try to use the space wisely – there is certainly no need to mention all 6 of Rodger's steps.	Thank you for this feedback. We have included additional information about the literature search and approach to analysis to clarify the approach to be taken.
I wonder how you will handle publications that cannot be unanimously allocated to one specific discipline (e.g. chemistry, engineering etc.). Particularly in the field of precision medicine, there are many cross cutting projects.	We recognise that overlap will occur. A paper by Tofthagen and Fagerstrom 2010 (https://doi.org/10.1111/j.1471-6712.2010.00845.x addresses this using the example of databases and references for medical and nursing science articles overlapping. Their suggested solution is to consider whether the discipline is defined according to the first author's educational background, the chosen publication's profile, or the study's theoretical foundation. We will define the relevant discipline of a publication according to the profile allocated in Scopus (www.scopus.com). Scopus provides a detailed categorisation and classification of journals into disciplines (see steps 2 and 3 of our analysis).
It is reasonable to restrict the search to papers from 2016 to 2022. As much as this will provide insight into the	Thank you for raising this issue. We will only include those papers with a main focus on clarifying at least one of the concepts and contributing to a deeper understanding of the concept(s). Articles that do not offer any substantial (theoretical) basis underlying the

understanding of relevant position papers such as the Precision Medicine Initiative there is, however, a risk that authors do not develop their own views and simply cite the relevant definition from major statements. I am not sure if this will help with assessment of "understanding" and would expect a number of publications that just word-by-work cite from the big reports. I assume you have thought about this	clarification of the concepts will be excluded. The process will enable us to identify if your concerns have any basis and will be reported in our results and discussion.

Reviewer 3: Dr Ljiljana Rakicevic, University of Belgrade

The authors considered the current understanding of the concepts "precision medicine" and "personalised medicine" in order to determine how these two concepts are distinguished in selected research disciplines and potential sub-disciplines. Theoretical consideration of these concepts is very rare in studies and because of that, the manuscript might have significance for the scientific community and medical science and practice.	Thank you for your support

Reviewer 4: Prof Dominique Van de Velde, Ghent University

This is an interesting article in which a protocol is proposed to differentiate between "precision medicine" and "personalised medicine". The protocol is described in a way that a researcher that is not involved in this study could start with this project and is therefore reproducible. It is a strong point that this protocol is based on the concept analysis of Rodgers, which is a more inductive approach than the other methods for concept analyses.	Thank you for your supportive comments
The following literature will be included: physics, chemistry, engineering; machine learning, and artificial intelligence. Why? This is a bit strange and will possibly create more difficulties to obtain a clear description of both concepts because these	As described in the *Setting, sample, and data source selection and data collection* section, the disciplines selected are all related to aspects of personalised and precision medicine research and are reflective of the large, interdisciplinary team that we represent (including clinicians, health services researchers, machine learning experts, engineers, experts in physics and chemistry).

disciplines might have a totally different view on the concepts under investigation. How can the authors be sure that the attributes will be applicable for clinical medicine, biomedicine and health services?	Our analysis aims to draw out differences to gain a better understanding of how these concepts are understood among different disciplines and to inform our collective approach to research in this field. We have also revised our presentation of this information to better reflect which disciplines we focus on, and added a Table 3 that lists the data bases/relevant disciplines that were considered and later excluded and the reasons for exclusion.

How will the authors operationalize the following inclusion criterium for articles:
 	
Having a main focus on clarifying at least one of the concepts "precision medicine" or "personalised medicine", and contributing to a deeper understanding of the concept(s) using theoretical or empirical studies – publications that do not deliver any substantial contribution regarding the clarification of the concepts are to be excluded.
 	
  • How will it be defined that the article provides a deeper understanding of one of the concepts?
  • Will this be based on definitions, on explanations, descriptions of the concept, theoretical understandings.
  • And what level of evidence is expected.
  • Will theoretical attributes, without supporting evidence or validation of the concept also be included?
	Thank you for asking for clarity regarding this. We will read identified articles closely and make an informed decision. Articles that merely reproduce a standard definition (e.g. from the US Precision Medicine Initiative) will be excluded as we are seeking articles that examine/discuss the concepts and their meaning. We will take a broad approach to "deeper" understanding and will include any discussion/reflection on clarification of the concepts. However, again, it must go beyond a simple definition. We have clarified this in the inclusion criteria:
	    *"Having a main focus on clarifying at least one of the concepts "precision medicine" or "personalised medicine", **beyond that of a simple definition**, and contributing to a deeper understanding of the concept(s) using theoretical or empirical studies – publications that do not deliver any substantial contribution regarding the clarification of the concepts are to be excluded"*
	
	While we do not expect to identify empirical studies, they will be included if they serve the purpose of concept clarification (e.g., hybrid concept analysis which combines empirical research with the analysis of a concept). Our discussion and analysis will identify and tease out the very points you have raised.

VERSION 2 – REVIEW

REVIEWER	Van de Velde, Dominique Ghent University, occupational therapy
REVIEW RETURNED	15-Jul-2022

GENERAL COMMENTS	Dear Authors, thank you for this reveised version. You have considered all comments and forme this is OK.