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The current understanding of precision medicine and personalised medicine in selected research disciplines: study protocol of a systematic concept analysis

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ABSTRACT

Introduction The terms 'precision medicine' and 'personalised medicine' have become key terms in health-related research and in science-related public communication. However, the application of these two concepts and their interpretation in various disciplines are heterogeneous, which also affects research translation and public awareness. This leads to confusion regarding the use and distinction of the two concepts. Our aim is to provide a snapshot of the current understanding of these concepts.

Methods and analysis Our study will use Rodgers' evolutionary concept analysis to systematically examine the current understanding of the concepts 'precision medicine' and 'personalised medicine' in clinical medicine, biomedicine (incorporating genomics and bioinformatics), health services research, physics, chemistry, engineering, machine learning and artificial intelligence, and to identify their respective attributes (clusters of characteristics) and surrogate and related terms. A systematic search of the literature will be conducted for 2016–2022 using databases relevant to each of these disciplines: ACM Digital Library, CINAHL, Cochrane Library, F1000Research, IEEE Xplore, PubMed/Medline, Science Direct, Scopus and Web of Science. These are among the most representative databases for the included disciplines. We will examine similarities and differences in definitions of 'precision medicine' and 'personalised medicine' in the respective disciplines and across (sub)disciplines, including attributes of each term. This will enable us to determine how these two concepts are distinguished.

Ethics and dissemination Following ethical and research standards, we will comprehensively report the methodology for a systematic analysis following Rodgers' concept analysis method. Our systematic concept analysis will contribute to the clarification of the two concepts and distinction in their application in given settings and circumstances. Such a broad concept analysis will contribute to non-systematic syntheses of the concepts, or occasional systematic reviews on one of the concepts that have been published in specific disciplines, in order to facilitate interdisciplinary communication, translational medical research and implementation science.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ In contrast to previous studies, we examine the definitions of 'precision medicine' and 'personalised medicine' in specific selected disciplines in order to facilitate interdisciplinary communication, translational medical research and implementation science.
⇒ Moreover, we analyse these two concepts systematically and base our review on renowned concept analysis methodology.
⇒ Our study will contribute to the clarification of the two concepts, their attributes and differences in various disciplines.
⇒ Concepts are constantly developing and their meanings change over time, and hence, it is not our objective to deliver an unequivocal definition.

INTRODUCTION

The terms 'precision medicine' and 'personalised medicine' are increasingly used in health-related research. However, the interpretation of these concepts and their application in various disciplines is heterogeneous.[1 2] The terms are often used in relation to specific diseases (eg, cancer) with an applied focus but without a detailed definition or specification of the underlying concepts. Non-systematic syntheses of (one of) the concepts[3 4] or occasional systematic reviews on (one or other of) the concepts have been published in specific

disciplines.[5 6] But, so far, understanding of the concepts has not been systematically clarified and compared across disciplines. Erikainen and Chan[3] report that disciplines have inconsistent, and potentially contrary, understandings of precision medicine or personalised medicine, as well as differing preferences of terms describing similar entities (for an exemplary variety of definitions see table 1).

For example, discussion in biomedical literature has relatively early started to express criticism of the term 'personalised medicine' arguing that this term implies unrealistic optimism and promises in relation to what biomedical technology will be able to deliver. According to Schleidgen *et al*[5] 'personalised medicine' wrongly implies a focus on the interests and preferences of an individual and the provision of patient-centred medicine through personalised medicine alone. A similar statement was put forward by the United States National Academies.[7] Schleidgen *et al*[5] recommended the use of the term 'stratified medicine' instead of 'personalised medicine' to present a more realistic vision of the underlying concept.[3] Similarly, 'precision' promises a level of certainty[8] 'that is unlikely to be reflected in the realities of precision medicine'.[7]

However, other disciplines (including medical ethics, critical studies of biosciences, patient-centred research) have criticised Schleidgen *et al*'s view, suggesting it can only be applied in a biomedical context, emphasising that 'personalised medicine' should be clearly distinguished from 'patient-centred care'[3]

Schleidgen *et al*'s definition can be seen as privileging the biological and molecular interpretation of 'personalisation' as group-level treatment stratification, to the explicit and purposeful exclusion of patient-centred interpretations.[3]

To summarise, the understanding and use of the concepts 'personalised' and 'precision' medicine is discipline dependent, which may also influence discussions on a policy level.[9–12] The latter can be shown by country-specific preferences at a policy level. For example, while the discussion is mostly focusing on precision medicine in the USA since the Precision Medicine Initiative was launched in 2015,[11] the European Union set up an International Consortium for Personalised Medicine (ICPerMed) in 2016.[13] Yet, the distinction of the two concepts is not clear enough to argue how the two terms differ. Preferences and an understanding largely depend on historical developments of the terms in specific contexts, leading to varying interpretations (eg, on a research and a policy level). This variety in interpretations, going along with the use of different terms, can have negative consequences, including the creation of different representations or beliefs in people when using a variety of terms, or a reinforcement of inaccuracies in definitions.[14]

A first step towards more clarity is an understanding of current differences and similarities regarding precision and personalised medicine across disciplines in research. Further research can then examine how these current interpretations developed historically (concept revisions) and how they influence(d) policy.

Our Health in Our Hands (OHIOH) is a multidisciplinary research project at the Australian National University which brings together the disciplines of clinical medicine, biomedicine (incorporating genomics and bioinformatics) and health services research; physics, chemistry and engineering; machine learning and artificial intelligence. These disciplines are the focus of this paper. OHIOH aims to advance digitalisation and personalisation of healthcare using a coproduction approach with partners from research, lived experience, healthcare professionals and health services.[15] OHIOH research includes studies on the experiences of people living with multiple sclerosis (MS)[16] and type 1 diabetes.[17] A recently published OHIOH paper[18] discusses the understanding and experiences of people living with MS in order to emphasise the importance of personalised medicine in MS treatment and care. In the course of drafting the manuscript, discussions around 'personalised' and 'precision' medicine revealed that the understanding of these two concepts varied greatly between the researchers in the various disciplines involved in OHIOH.

Objective

The aim of this study is to examine the current understanding of the concepts 'precision medicine' and 'personalised medicine' in clinical medicine, biomedicine (incorporating genomics and bioinformatics) and health services research; physics, chemistry and engineering; machine learning and artificial intelligence using Rodgers'[19] concept analysis to identify concept attributes (clusters of characteristics) and to determine how these two concepts are distinguished in these selected disciplines and potential subdisciplines. We will answer the following research questions (RQ):

RQ1: What is the current understanding of 'precision medicine' and 'personalised medicine' in clinical medicine, biomedicine (incorporating genomics and bioinformatics) and health services research; physics, chemistry and engineering; machine learning and artificial intelligence, and what are similarities and differences in definitions in the respective disciplines and across different (sub)disciplines?

RQ2: What are the related and surrogate terms for 'precision medicine' and 'personalised medicine' in each of the selected disciplines?

It is important to understand how the two concepts are currently interpreted and understood in the individual disciplines in order to be able to create consistent understanding of the concept interpretations and to reduce ambiguity in the literature. This current interpretation does not include concept revisions over time which could be examined in follow-up research. As concepts are constantly developing and their meanings change over time, it is not our objective to deliver an unequivocal definition.

Table 1 Variety of definitions of 'precision medicine' and 'personalised medicine'— examples

Concept	Year	Authors, journal/source	Discipline (Scopus)*	Definition
Precision medicine	2017	Marson *et al*, *Frontiers in Pharmacology*[32]	Medicine: pharmacology; pharmacology, toxicology, pharmaceutics: pharmacology	In precision medicine, the individual is understood "as a response to the interrelation between environment, lifestyle, and genetic factors".
	2020	Elemento, *Emerging Topics in Life Sciences*[33]	Biochemistry, genetics and molecular biology: general biochemistry, genetics and molecular biology	Precision medicine is "personalized medicine enhanced by technology".
	2020	Ho *et al*, *Trends in Biotechnology*[34]	Biochemistry, genetics and molecular biology: biotechnology; chemical engineering: bioengineering	"From an engineering perspective, precision medicine involves the use of technologies to acquire and validate population-wise data, such as omics-based single-cell analysis and biomarker discovery, for subsequent application on the individual patient level."
	2021	Ong *et al*, *Asian Bioethics Review*[35]	Arts and humanities: philosophy; social sciences: health; medicine: health policy	"Precision medicine (PM) aims to improve healthcare with the use of genomic analyses and data analytics to develop tailored approaches to predicting disease progression and treatment responses for individual patients."
	2021	US National Library of Medicine[36]	(Medicine)	"Clinical, therapeutic and diagnostic approaches to optimal disease management based on individual variations in a patient's genetic profile."
Personalised medicine	2013	Schleidgen *et al*, *BMC Medical Ethics*[5]	Nursing: ethics and legal aspects; social sciences: health; medicine: health policy	Personalized medicine "is not medicine with a special focus on the interests and preferences of the individual patient" and it "is not related to the term patient-centered medicine".
	2017	Marson *et al*, *Frontiers in Pharmacology*[32]	Medicine: pharmacology; pharmacology, toxicology, pharmaceutics: pharmacology	Personalized medicine is "the treatment directed at the symptoms, and this treatment is adjusted depending on the patient's phenotype".
	2015/2020	Council of the European Union/European Commission[9 13]	(Health policy)	"Personalised medicine refers to a medical model using characterisation of individuals' phenotypes and genotypes (eg, molecular profiling, medical imaging, lifestyle data) for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention. Personalised medicine relates to the broader concept of patient-centred care, which takes into account that, in general, healthcare systems need to better respond to patient needs."
	2020	Ho *et al*, *Trends in Biotechnology*[34]	Biochemistry, genetics and molecular biology: biotechnology; chemical engineering: bioengineering	"Personalized medicine involves the use of technologies to seriously acquire and assess an individual's own data for only their own treatment. For example, this may involve the use of artificial intelligence (AI) to both design a drug combination based on a patient's own biopsy and follow with N-of-1 dosing protocols."
	2021	Fournier *et al*, *Journal of Personalized Medicine*[14]	Medicine: medicine (miscellaneous)	"PM seems to have a wide scope, encompassing many practices, including targeted therapies (TT)… It seems there are several terms used to name PM… Indeed, it is possible to define PM as 'targeted therapy', 'pharmacogenomics' or 'precision medicine' depending on the author, the domain or the definition"…

*For discipline categorisation, the 'source details' in Scopus are used for information on the respective journals (www.scopus.com).

METHODS AND ANALYSIS

Protocol development

We used the 17 Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) throughout the development of our study protocol[20] (see online supplemental file 1). Our systematic data collection and analysis will similarly follow the subsequent PRISMA.[21] Amendments to the study protocol will be reported in the final published systematic concept analysis manuscript.

Concept analysis approach

A concept analysis aims to clarify a concept (eg, attributes, antecedents, consequences).[19] Such a concept clarification enables assessment of a concept's strengths and weaknesses.[22] Based on Walker and Avant's[23] traditional approach who view concepts as static entities which are independent of context and have clear boundaries – derived from Wilson's method[24] which is based on realism (deductive analysis) – Rodgers[19] developed an evolutionary concept analysis based on relativism (inductive analysis). Rodgers[19] viewed concepts as dynamic and evolving phenomena without strict boundaries. This took account of the fact that concepts are constantly developing and their meanings change over time, and hence it is not possible for an analysis to deliver an unequivocal definition.[22] Moreover, concepts are understood differently in different disciplines due to what Rodgers[19] calls 'enculturation' within individual disciplines. Thus, it is important to clarify the selection of disciplines being focused on when using Rodgers' approach to a concept analysis.

Bearing in mind the changing and non-static understanding of the terms 'precision medicine' and 'personalised medicine' over time, Rodgers' approach appears to be a good fit for analysis. Our analysis of 'personalised' and 'precision' medicine will only represent a snapshot of the current understanding of these concepts in the literature pertaining to clinical medicine, biomedicine (incorporating genomics and bioinformatics) and health services research; physics, chemistry and engineering; machine learning and artificial intelligence. Nevertheless, it is essential to highlight any differences and similarities between disciplines to inform current and future research, aiming to standardise and generate a uniform approach if at all possible. We will not look into revisions of definitions over time, the focus is on the current understanding of the two concepts.

Rodgers'[19] concept analysis has generated a lot of attention in the healthcare context and has become a recognised method of concept clarification. For example, Hudon *et al*[25] used Rodgers' concept analysis approach to analyse 'enablement' in a healthcare context. In Rodgers' method of concept analysis,[19] concepts are considered to be abstractions that are expressed in an arbitrary form. They constitute a mental (re)grouping of a number of attributes. Hudon *et al*[25] define attributes as characteristics of concepts that must be present for the recognition of the concept as an entity. Concept analyses are employed in developing valid measuring instruments which can evaluate the attributes of a concept (determining whether there is good content validity).[25]

Concept analysis procedure

Rodgers'[19] concept analysis is divided into six steps, comprising (1) the identification of the concepts of interest and associated expressions and background, (2) the selection of an appropriate realm for data collection (setting, sample and data sources), (3) the collection of data relevant to identifying concept attributes and the contextual concept basis, (4) the analysis and data summary regarding the concept characteristics, (5) the identification of concept examples and (6) the identification of implications for further concept development.

Concept identification (step 1)

By way of example, Viana *et al*[26] state that 'precision medicine' and 'precision health' are not identical:

> Distinct from precision medicine, precision health takes a lifespan perspective in health monitoring, identifying actionable risks and intervening early.[26]

Our systematic concept analysis will focus on the clarification of the two concepts 'precision medicine' and 'personalised medicine'. Surrogate and related terms will not be identified in advance: surrogate terms are other terms used to describe identical concepts, while related terms describe entities that are not identical but have something in common with the concepts under analysis.[19] The exploration of these will be conducted at a later step in the full-text analysis of the included papers (eg Pueyo-Garrigues *et al*[27]). Related (but not identical) concepts such as individualised care, stratified medicine, P4 (predictive, preventive, personalised and participatory) medicine, genomic medicine or patient-centred care will be collected in the systematic review alongside definitions and interpretations derived from analysis of the full texts. Similarly, replacement terms for 'medicine' in 'precision/personalised medicine' such as 'health(-care)', 'treatment', 'therapy/therapeutics', 'medical care' or similar composite terms[28] will be collected during full-text analysis. Since related concepts are not identical with precision or personalised medicine, these are not central to the focus of this study. The main focus will be on the two terms 'precision medicine' and 'personalised medicine'.

Setting, sample and data source selection and data collection (steps 2 and 3)

As above, the disciplines of clinical medicine, biomedicine (incorporating genomics and bioinformatics) and health services research; physics, chemistry and engineering; machine learning and artificial intelligence were selected for analysis due to their key roles in OHIOH, which is an interdisciplinary research collaboration. The analysis might also reveal diverse understandings of the concepts

Table 2 Collection of databases for the selected disciplines

Database	Disciplines
Association for Computing Machinery Digital Library	Machine learning and artificial intelligence
CINAHL	Clinical medicine Health services research
Cochrane Library	All included disciplines
F1000Research	Biomedicine
IEEE Xplore Digital Library	Machine learning and artificial intelligence
PubMed/Medline	Clinical medicine Biomedicine Health services research Medical informatics
Science Direct	All included disciplines
Scopus	Clinical medicine Health services research Medical informatics Physics Chemistry Engineering
Web of Science	Clinical medicine Health services research Physics Chemistry Engineering

in subdisciplines of the selected disciplines. This will be considered adequately in the analysis.

The search strategy will be used to search a number of databases relevant to each of these disciplines. We will use the databases Association for Computing Machinery (ACM) Digital Library, CINAHL, Cochrane Library, F1000Research, IEEE Xplore Digital Library, PubMed/Medline, Science Direct, Scopus and Web of Science (table 2). These are among the most representative and commonly used databases for the included disciplines. They were selected based on a more extensive list of databases from which several were excluded for reasons as specified in table 3.

Once identified, the relevant discipline of a given publication will be defined according to the chosen publication's profile in Scopus (www.scopus.com). Scopus delivers a detailed categorisation and classification of journals into disciplines.

Additional manual hand searching will be carried out to identify potentially relevant articles that might have been missed in the searches of the above databases (eg, references of papers).

The search strategy, developed after an initial exploratory search of the literature, will look for articles that mention 'precision medicine' and/or 'personalised medicine' in their titles in addition to 'defin*' (definition/define) or 'concept*' in the full text. Both British and American spelling will be accepted ('personalised'/'personalized' medicine). As an example, a PubMed search string for precision and personalised medicine will include:

((precision medicine[Title]) OR (personalised medicine[Title]) OR (personalized medicine[Title])) AND ((defin*[Text Word]) OR (concept*[Text Word])).

The search will be limited to scientific research papers in English language published in peer-reviewed academic journals. Moreover, the search will be limited to articles published from 2016 to 2022 in order to capture the current understanding of these concepts following the introduction of major initiatives such as the Precision Medicine Initiative[11] or the International Consortium for Personalised Medicine (ICPerMed) in 2015 and 2016.[13]

Guidance from Rodgers advises that each discipline should be represented by approximately 20% 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 every fifth article starting from a random article.

Table 3 Considered but excluded databases

Database	Disciplines	Exclusion reason
ACL Anthology	Machine learning and artificial intelligence	Poster and conference proceedings
arXiv (Cornell University)	Machine learning and artificial intelligence	Pre-print server
DBLP Computer Science Bibliography	Machine learning and artificial intelligence	Limited search options (by publication only) Pilot searches returned poor results
EMBASE	Biomedicine	Unable to access
Google Scholar	Clinical medicine Health services research Physics Chemistry Engineering Machine learning and artificial intelligence	Searches difficult to refine Large volume of irrelevant results
Papers With Code	Machine learning and artificial intelligence	No advanced search option Could not restrict to peer reviewed journal papers
Research Square	Biomedicine	Mainly preprints No advanced search option No export option

Box 1 Eligibility criteria for articles

- ⇒ Publications in peer-reviewed academic journals.
- ⇒ Published in the disciplines of clinical medicine, biomedicine (incorporating genomics and bioinformatics) and health services research; physics, chemistry and engineering; machine learning and artificial intelligence (discipline defined by the chosen publication's profile in Scopus).
- ⇒ Published between 2016 and 2022 (including papers under review).
- ⇒ Published in English language.
- ⇒ 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.
- ⇒ Empirical studies will be included if they serve the purpose of concept clarification (eg, hybrid concept analysis which combines empirical research with the analysis of a concept).

Any articles with a main focus on clarifying at least one of the concepts, beyond that of a simple definition and contributing to a deeper understanding of the concept(s) will be included (box 1). Articles that do not offer any substantial (theoretical) basis underlying the clarification of the concepts will be excluded. Empirical studies will be included if they serve the purpose of concept clarification (eg, hybrid concept analysis which combines empirical research/fieldwork such as expert interviews with the analysis of a concept[29]).

Analysis, data summary and identification of examples (steps 4 and 5)

The study selection procedure will follow standard practice, that is, an initial first search by one researcher who will remove any duplicates, followed by screening of titles and abstracts and then full article screening, by several researchers from the included disciplines. 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. Any disagreements regarding article inclusion will be resolved through discussion with additional researchers.

Search and inclusion results will be displayed using a PRISMA flow diagram. A search/study log book will be used to support study reliability estimation, with notes about the search and data collection procedure taken by the researchers throughout the data collection.

Data will be managed using a reference manager (Endnote), an Excel list with study details and data extraction summaries and the systematic review management programme Covidence to organise data collection and analysis steps.

For full-text analysis, every included article will be read with a focus on extracting information relevant to the interpretation and definition of the two concepts, as well as their contextual basis, their attributes and any related and/or surrogate terms (table 4). Data extracted from the eligible papers will include the journal name, research discipline/context (including subdiscipline), authors, year, citation, study aim, definitions of the concepts, attributes/characteristics, concept differences/similarities, related and surrogate terms, quality appraisal and further notes. For empirical studies—if the final analysis will include these—risk of bias will be assessed using the Mixed Methods Appraisal Tool.[30]

Several researchers with expertise in cooperating across the included disciplines (who participated in the abstract and full article screening) will initially extract data from five to ten papers for the extraction to be compared in order to reach consensus for the further extraction. The subjectivity of the views of involved researchers will be identified and discussed through intercoder comparisons, and differences will be resolved through discussion with additional researchers, if necessary. In the following, data will be extracted from all remaining included articles by the same researchers.

Rodgers' concept analysis method will guide a narrative synthesis, an example can be found in Miles and Huberman.[31] The findings will be compared, with (dis) similarities within the disciplines analysed.[22] Through this process, patterns will be revealed and main themes will be identified. This is a continuous process of data analysis, the data being reorganised until a descriptive pattern of themes is reached.[19] A data summary requires consensus regarding the concepts and their attributes, and (practical) examples from the included articles are

Table 4 Questions to explain the categories for analysis

Concept attribute	What are the concept's characteristics?
Concept definition	Which definitions are presented in the data material?
Concept differences/similarities	Are specific concept differences or similarities mentioned in the data material?
Contextual basis	In which context is the concept presented (research discipline)?
Example	Are examples of the concept described in the data material?
Related term	Do other words have something in common with the concept?
Surrogate term	Do other words say the same thing as the chosen concept?

Based on Tofthagen and Fagerstrom.[22]

used for concept explanation and illustration.[19 22] Several researchers will be involved in the data analysis in order to avoid subjective interpretation.

Identification of implications for further concept development (step 6)

Rodgers[19] suggests that, based on the data analysis, further questions and hypotheses are presented, rather than an attempt to generate a 'final' definition of the concepts involved, since this is not possible due to the dynamic nature of concepts. Suggestions will be made in relation to directing future research and helping guide further concept development and analysis.

Patient and public involvement

OHIOH is a project that spans several disciplines and is underpinned by a participatory coproduction model of research that is characterised by close collaboration with clinicians and with people living with MS or type 1 diabetes in research planning and in conducting the research. Our coproduction partners have been involved in the development of this protocol and will continue to be involved throughout the research project. After finalising the data collection and data analysis, the results will be discussed with our partners and the OHIOH teams in order to put the results in an OHIOH context. For each discipline, the respective OHIOH team will review the resulting understanding of personalised and precision medicine from their scientific perspective.

Ethics and dissemination

Following ethical and research standards, we will comprehensively report the methodology for a concept analysis following Rodgers.[19] Ethical approval is not required for this research because our study collects publicly available and theoretical data about the concepts underlying 'precision medicine' and 'personalised medicine'. The results of this study will be disseminated through publication in peer-reviewed academic journals and at scientific conferences. Our findings will contribute to clarification of the underlying concepts and so help guide future research.

Potential study limitations

Potentially relevant articles might be missed using any specific search strategy. However, the inclusion of several databases and additional hand searching as part of a systematic approach is likely to minimise the risk of missing significant literature. Difficulties arising in an application of concept analysis to precision/personalised medicine could include that in contrast to other theoretical concepts (eg, enablement), precision/personalised medicine are mostly practical medical terms rather than mere theoretical concepts.

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist

Section and topic	Item No		Checklist item	
ADMINISTRATIVE INFORMATION				
Title:				
Identification	1a	✔	Identify the report as a protocol of a systematic review	Title of manuscript, p.1
Update	1b	x	If the protocol is for an update of a previous systematic review, identify as such	
Registration	2	x	If registered, provide the name of the registry (such as PROSPERO) and registration number	N/A
Authors:				
Contact	3a	✔	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Title page, p.1
Contributions	3b	✔	Describe contributions of protocol authors and identify the guarantor of the review	Author contributions, p.14
Amendments	4	✔	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Methods - protocol development, p.7
Support:				
Sources	5a	✔	Indicate sources of financial or other support for the review	Funding statement, p.14
Sponsor	5b	✔	Provide name for the review funder and/or sponsor	
Role of sponsor or funder	5c	✔	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	
INTRODUCTION				
Rationale	6	✔	Describe the rationale for the review in the context of what is already known	Introduction/objective, p.3-6
Objectives	7	✔	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Research questions, p.6
METHODS				
Eligibility criteria	8	✔	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Methods, p.8-12
Information sources	9	✔	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Methods, p.8-12
Search strategy	10	✔	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Methods, p.8-12
Study records:				
Data management	11a	✔	Describe the mechanism(s) that will be used to manage records and data throughout the review	Methods, p.8-12

Selection process	11b	✔	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Methods, p.8-12
Data collection process	11c	✔	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Methods, p.8-12
Data items	12	✔	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Methods, p.8-12
Outcomes and prioritization	13	x	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	N/A
Risk of bias in individual studies	14	✔	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Methods, p.12
Data synthesis	15a	x	Describe criteria under which study data will be quantitatively synthesised	N/A
	15b	x	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	
	15c	x	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	
	15d	✔	If quantitative synthesis is not appropriate, describe the type of summary planned	Methods, p.12
Meta-bias(es)	16	x	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	
Confidence in cumulative evidence	17	x	Describe how the strength of the body of evidence will be assessed (such as GRADE)	N/A

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.