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# Cost Effectiveness of Treatment Optimization with Biomarkers for Immunotherapy in Solid Tumors: A Systematic Review Protocol

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| Complete List of Authors: | Mucherino, Sara; CIRFF, Center of Pharmacoeconomics and Drug utilization Research , Department of Pharmacy, University of Naples Federico II<br>Lorenzoni, Valentina; Institute of Management, Scuola Superiore Sant'Anna<br>Orlando, Valentina; CIRFF, Center of Pharmacoeconomics and Drug utilization Research , Department of Pharmacy, University of Naples Federico II<br>Triulzi, Isotta; Institute of Management , Scuola Superiore Sant'Anna<br>Del Re, Marzia; Unit of Clinical Pharmacology and Pharmacogenetics , University Hospital of Pisa<br>Capuano, Annalisa; Department of Experimental Medicine , Section of Pharmacology 'L. Donatelli', University of Campania 'L. Vanvitelli'<br>Danesi, Romano; Unit of Clinical Pharmacology and Pharmacogenetics, University Hospital of Pisa<br>Turchetti, Giuseppe; Institute of Management , Scuola Superiore Sant'Anna<br>Menditto, Enrica; CIRFF, Center of Pharmacoeconomics and Drug utilization Research, Department of Pharmacy, University of Naples Federico II |
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# Cost Effectiveness of Treatment Optimization with Biomarkers for Immunotherapy in Solid Tumors: A Systematic Review Protocol

Sara Mucherino [1], Valentina Lorenzoni [2], Valentina Orlando[1], Isotta Triulzi [2], Marzia Del Re[3], Annalisa Capuano[4], Romano Danesi[3], Giuseppe Turchetti[2], Enrica Menditto[1,*]

**Affiliations:**

[1] CIRFF, Center of Pharmacoeconomics and Drug utilization Research, Department of Pharmacy, University of Naples Federico II, Naples, Italy

[2] Institute of Management, Scuola Superiore Sant'Anna, Pisa, Italy

[3] Unit of Clinical Pharmacology and Pharmacogenetics, University Hospital of Pisa, Pisa, Italy

[4] Department of Experimental Medicine, Section of Pharmacology 'L. Donatelli', University of Campania 'L. Vanvitelli', Naples, Italy

***Correspondence to:**

Prof. Enrica Menditto, PharmD, PhD

CIRFF, Department of Pharmacy, University of Naples Federico II

Via Montesano, 49

80131, Naples

Email: enrica.menditto@unina.it

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## ABSTRACT

**Introduction:** The combination of biomarkers and drugs is the subject of growing interest both from regulators, physicians and companies. This study protocol of a systematic review is aimed to describe available literature evidences about the cost-effectiveness, cost-utility or net-monetary benefit of the use of biomarkers in solid tumour as tools for customizing immunotherapy to identify what further research needs.

**Methods and analysis:** A systematic review of the literature will be carried out according to the PRISMA statement guidelines. PubMed and Embase will be queried from June 2010 to June 2020. The PICO Model will be applied: the patients target will be with solid tumours treated with immunotherapy; the interventions (I) will be the use of predictive biomarkers; the comparator (C) will be any other strategies; the outcomes (O) will be expressed in terms of cost-effectiveness, cost-utility, net-monetary benefit, life years gained and quality of life. The quality of the evidence was graded according to GRADE (Grading of Recommendations Assessment, Development and Evaluation).

**Ethics and dissemination:** This systematic review will assess the cost effectiveness implications of using blood-based biomarkers in the immunotherapy, which may help to understand whether this approach is widespread in real clinical practice. This research is exempt from ethics approval because the work is carried out on published documents. We will disseminate this protocol in a related peer-reviewed journal.

**PROSPERO registration number:** CRD42020201549

## ARTICLE SUMMARY

### Strengths and limitations of this study

- The use of predictive biomarkers in the immunotherapy can help target therapy in some solid tumors, hence, the combination of biomarkers and drugs is the subject of growing interest both from regulators, physicians and companies.
- This is the first systematic review which will specifically describe and synthetize available literature evidences about the cost-effectiveness, cost-utility or net-monetary benefit of the use of biomarkers in solid tumor as tools for customizing immunotherapy to identify what further research needs.
- An in-depth search strategy will be applied to two major scientific databases, without geographic or language restrictions, and conducted by a multidisciplinary team with expertise in the field.
- The literature will be carefully assessed for quality using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) tool.

## Introduction

In recent years, the pharmaceutical industry has seen a shift from the blockbuster model, in which drugs are developed for an ideal patient, to a nichebuster model, in which drugs developed specifically for specific patient groups [1,2]. In this context, the combination of biomarkers and drugs is the subject of growing interest both from regulators, physicians and companies [3-7].

The US Food and Drug Administration (FDA) publishes and updates a list of drugs for which it is suggested or mandatory to associate a genetic-molecular test [8]. The importance of predictive biomarkers is related to optimizing patient benefits, reducing the risk of toxicity and leading combined approaches [9]. Particularly, for some drugs the test result defines whether or not to administer, for others it establishes the most appropriate dosage of therapy.

Only in 29% of cases (48 combinations) the use of the biomarker has an impact on the doctor's choice to prescribe or not prescribe a specific drug [10]. In Italy, 34 of the 48 combinations are approved for use and of these, about 80% find application in oncology particularly for solid tumors treatment [10]. The clinical development of checkpoint inhibitor-based immunotherapy has ushered in an exciting era of anticancer therapy. The importance of predictive biomarkers is related to the optimization of benefits in patients treated with immunotherapy, by reducing the risk of toxicity and leading combined approaches. Durable responses have been observed in patients with various malignant neoplasms [11].

This study protocol is part of a funded Italian National Research Project based on the hypothesis that the identification of predictive biomarkers can improve the understanding of the mechanisms underlying the complex interactions between the immune system and cancer, and can help clinicians optimize therapy with monoclonal anti-PD-1 and anti-PD-L1 antibodies. Hence, among the already known biomarkers, the overexpression of PD-L1 is an important and widely explored predictive biomarker for the response to PD-1/PD-L1 antibodies [4,12]. Direct assessment of PD-L1

expression on tumor cells is a logical biomarker for the prediction of treatment response to anti-PD-1 or anti-PD-L1 therapies [13,14]. The use of PD-1 and PDL-1 as predictive biomarkers can help target therapy in some solid tumors, including renal and non-small cell lung cancer (NSCLC) [15-17]. Nivolumab and pembrolizumab (two PD-1 inhibitors) and an PD-L1 inhibitor, atezolizumab, have been approved by the Italian Medicines Agency (AIFA), for the treatment of patients with NSCLC [18-20].

A targeted approach to treatment using predictive biomarkers has the potential not only to maximize clinical benefit, but also to improve cost-effectiveness and reduce the economic burden of the disease [21]. As the global impact of these types of cancers continues to grow, the implementation of new and more effective therapies becomes important but also overly expensive [22]. Therefore, the analysis of the cost-effectiveness and economic impact of the use of biomarkers upstream of the choice of the specific therapy represents an imperative to validate its effectiveness, the eventual relationship with the quality of life and patient reported outcomes (PROMs), and sustainability [23]. However, there is no existing peer-reviewed or published synthesis assessing the impact in terms of cost-effectiveness and quality of life of predictive biomarkers use in oncological treatment.

This is the protocol of a systematic review aimed to describe and synthetize available literature evidences about the cost-effectiveness, cost-utility or net-monetary benefit of the use of biomarkers in solid tumor as tools for customizing immunotherapy to identify what further research needs.

## Methods and Analysis

### Information sources

A systematic review of the literature will be carried out according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement guidelines [24]. For the

present review, the identification of relevant studies will be achieved by searching electronic databases of the published literature, which will include the following: Medical Literature Analysis and Retrieval System Online (via PubMed/MEDLINE) and Embase (via Ovid), queried from June 2010 to June 2020.

**Search strategy**

First, the search strategy will be developed and completed in PubMed, and then the same strategy will be applied to Embase. More in detail, the search strategy will combine headings and keywords identifying according to the PICO Model. They will be searched as Mesh Term (PubMed) or Emtree (Embase) and in title and abstract (antibodies, immunotherapy, nivolumab, durvalumab, avelumab, atezolizumab, nivolumab, pembrolizumab, neoplasms, cancer, carcinoma, biomarkers, PD-1, programmed death 1, PD-L1, programmed death ligand 1, IL-6, interleukin-6; cost benefit analysis; cost effectiveness; cost utility; economic evaluation; quality of life). The Boolean operators used will be AND/OR. The full search strategy that will be used is reported in Table 1. More in detail, the search syntax for the two databases are presented in the online Supplementary Appendix 1.

**Elegibility criteria**

The inclusion criteria are based on compliance with the PICO. Particularly, we will identify:

- the patients target (P) will be with solid tumors treated with immunotherapy;
- the interventions (I) will be related to the use of predictive biomarkers before the choice of therapeutic approach;
- the comparator (C) will be any other strategies;
- the outcomes (O) will be expressed in terms of cost-effectiveness, cost-utility, net-monetary benefit, life years gained and quality of life.

All studies responding to the PICO will be included in the research. Hence, peer-reviewed original articles, published between June 2010 to June 2020, will be included. Particularly, all studies about health economics evaluation performed within clinical trials or observational studies related to biomarkers use published will be included (inclusion criteria).

On the other hand, conference proceedings, rationale and/or design, letters, editorials, commentaries, case reports, case study, case series, review, consensus, guidelines, expert opinions will be not included (exclusion criteria). Any identified literature reviews will be used as a source for finding additional articles not present in our dataset. Moreover, no language restriction will be applied to the research, but, fundamental to the eligibility of the study will be the availability of the papers' full text published in English.

**Selection and data process**

The references will be collected using the software program Reference Manager, ver. 12 (Institute for Scientific Information, Berkeley, CA). All references will be screened for relevance and, those potentially eligible will be assessed, according the inclusion/exclusion criteria, accepted or rejected, as appropriate.

Four researchers will screen titles and abstract to discard irrelevant ones in the first screening phase, then they will assess full texts for eligibility defining which references to include in the qualitative analysis. The references obtained will be validated by expert researchers in the fields of pharmacology, immunotherapy, pharmacovigilance, pharmacoeconomic. Reference lists from included records will be also screened to identify additional papers. Full texts of relevant studies will be retrieved and reviewed for eligibility in accordance with the inclusion criteria.

From each reference included in the qualitative analysis information which will be extracted in an Excel file are reported in Table 2. Finally, the quality of the evidence was graded according to

GRADE (Grading of Recommendations Assessment, Development and Evaluation) system [25], assessing heterogeneity, consistency and risk of bias. Quality of evidence and recommendation for All studies and their individual elements will be graded in terms of adequacy of the study regarding the research question, risk of selection bias, measurement of exposure and assessment of outcomes. Disagreements will be resolved by third reviewers.

**Study registration**

The study is prospectively registered in PROSPERO, the International Prospective Register of Systematic Reviews (CRD42020201549).

## Ethics and dissemination

This review will systematically describe the extent of available evidences investigating the predictive biomarkers used in immunotherapy and their health-economic impact. The use of biomarkers to monitor the clinical outcome of patients treated with immune check-point inhibitors may help to reduce the incidence of adverse events related to the immune system thus also improving quality of life. Furthermore, from the pharmaco-economic evaluations already conducted on these immune biomarkers we expect to find that their use is associated with better cost/effectiveness (or cost-utility, net-monetary benefit) ratio due to their improved ability to predict clinical outcome and to redirect non-reactive patients towards alternative and more effective and cost/effective therapeutic approaches.

Accordingly, main strength of the present work will consist in having an overview on what is already know on blood-based immune biomarkers use to realize treatment personalization of cancer patients. Also, we will try to gather considerations about the diffusion of their real use through economic evaluations that report their outcomes in terms of cost effectiveness ratio or cost utility ratio and patients' health related quality of life.

Other systematic reviews on biomarkers were already published evaluating cost-related aspects but they are specifically focused on a cancer condition and the pertaining biomarker [26-29]. To the best of our knowledge this is the first systematic review published broadly exploring the health-economic impact of biomarkers.

A potential limitation relates to the heterogeneity associated to the study conducted on biomarkers. Accordingly, between-study heterogeneity may not support the conduct of quantitative meta-analysis.

Results of the systematic review will be published in a peer-reviewed journal and disseminated at a range of health research conferences. The systematic review is part of a larger project funded by PRIN 2017 whose aims include the identification of biomarkers able to predict immunotherapeutic-related adverse drug reactions and the potential cost-effectiveness and quality of life of personalized therapies based on advanced tools.

Finally, this systematic review will assess the cost effectiveness implications of using blood-based biomarkers is in the immunotherapy, which may help to understand whether or not this approach is widespread in real clinical practice and how the customization of therapy, can actually affect a decrease in costs for the health care systems.

## Author contributions

E.M. designed and conceptualised this review. S.M., V.O., V.L., I.T. drafted the protocol. All authors were involved in checking various steps of the search strategy, including keywords, as well as the final version of the protocol. S.M, V.L. and I.T. were involved in the statistical strategy for data analysis. M.D.R., A.C., R.D. and G.T. were involved in establishing eligibility criteria and data extraction forms. G.T. and E.M. supervised all work stages. R.D. was the funding acquisition supervisor. All authors reviewed and agreed the final version of the manuscript.

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## Conflicts of interest

The authors have no conflicts of interest to declare.

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# Tables

## Table 1. Search strategy

| Query | Keywords (MeshTerms/Emtree OR Title and Abstract) |
|---|---|
| **#1** | Antibodies, monoclonal |
| **#2** | Immunotherapy |
| **#3** | (nivolumab/ipilimumab[Title/Abstract]) OR ipilimumab[Title/Abstract]) OR durvalumab[Title/Abstract]) OR atezolizumab[Title/Abstract]) OR nivolumab[Title/Abstract]) OR pembrolizumab[Title/Abstract]) OR "Ipilimumab"[Mesh]) OR "durvalumab" [Supplementary Concept]) OR "avelumab" [Supplementary Concept]) OR "atezolizumab" [Supplementary Concept]) OR "Nivolumab"[Mesh]) OR "pembrolizumab" [Supplementary Concept] |
| **#4** | Neoplasms |
| **#5** | Cancer |
| **#6** | Carcinoma |
| **#7** | Biomarkers OR PD1 OR Programmed Death 1 OR PD-L1 OR Programmed Death Ligand 1 OR IL-6 OR Interleukin-6 |
| **#8** | Cost benefit analysis |
| **#9** | Cost effectiveness |
| **#10** | Cost utility |
| **#11** | Economic evaluation |
| **#12** | Quality of life |
| **#13** | 1 AND 2 AND 3 |
| **#14** | 4 OR 5 OR 6 |
| **#15** | 8 OR 9 OR 10 OR 11 OR 12 |
| **#16** | 13 AND 14 |
| **#17** | 16 AND 7 |
| **#18** | 17 AND 15 |

**Table 2. Data extraction and analysis process**

| Data extraction | Description |
|---|---|
| Reference | All paper identification details |
| Year | Year of publication of the paper |
| Study design | In the case of economic evaluations, specific technique used and source of the clinical data, e.g. RCT, expert panel |
| Analysis perspective | National health service, society, government, patient |
| Type of costs | Direct healthcare costs, direct non-health costs, indirect costs, intangible costs |
| Reference year of costs | Specific year of reference of costs if reported |
| Patient Diagnosis | Type of solid tumor studied |
| Patient (P) | Solid tumors treated with immunotherapy |
| Intervention (I) | The use of predictive biomarkers before the choice of therapeutic approach |
| Comparator (C) | Any other strategies |
| Outcomes (O) | Cost-effectiveness, cost-utility, net-monetary benefit, life years gained (LYG) and quality of life (QALY) |

# Appendix 1

Search syntax in different databases

PubMed

((((((Antibodies, monoclonal[MeSH Terms]) OR (Antibodies, monoclonal[Title/Abstract])) AND ((immunotherapy[MeSH Terms]) OR (immunotherapy[Title/Abstract]))) AND ((nivolumab/ipilimumab[Title/Abstract]) OR ipilimumab[Title/Abstract]) OR durvalumab[Title/Abstract]) OR atezolizumab[Title/Abstract]) OR nivolumab[Title/Abstract]) OR pembrolizumab[Title/Abstract]) OR "Ipilimumab"[Mesh]) OR "durvalumab" [Supplementary Concept]) OR "avelumab" [Supplementary Concept]) OR "atezolizumab" [Supplementary Concept]) OR "Nivolumab"[Mesh]) OR "pembrolizumab" [Supplementary Concept])) AND ((((cancer[Title/Abstract]) OR (cancer[MeSH Terms])) OR ((carcinoma[Title/Abstract]) OR (carcinoma[MeSH Terms]))) OR ((neoplasm[Title/Abstract]) OR (neoplasm[MeSH Terms])))) AND ((((((((((PD1[Title/Abstract]) OR (PD1[MeSH Terms])) OR (Programmed Death 1[MeSH Terms])) OR (Programmed Death 1[Title/Abstract])) OR (PD-L1[Title/Abstract])) OR (PD-L1[MeSH Terms])) OR (Programmed Death Ligand 1[MeSH Terms])) OR (Programmed Death Ligand 1[Title/Abstract])) OR (IL-6[Title/Abstract])) OR (IL-6[MeSH Terms])) OR ((biomarker[Title/Abstract]) OR (biomarker[MeSH Terms])))) AND ((((((cost benefit analysis[Title/Abstract]) OR (cost benefit analysis[MeSH Terms])) OR ((cost effectiveness[MeSH Terms]) OR (cost effectiveness[Title/Abstract]))) OR ((cost utility[Title/Abstract]) OR (cost utility[MeSH Terms]))) OR ((economic evaluation[Title/Abstract]) OR (economic evaluation[MeSH Terms]))) OR ((quality of life[Title/Abstract]) OR (quality of life[MeSH Terms]))) Sort by: Publication Date

Embase

(('cost benefit analysis':ti,ab,kw OR 'cost benefit analysis'/exp) AND [embase]/lim OR (('cost effectiveness':ti,ab,kw OR 'cost effectiveness'/exp) AND [embase]/lim) OR (('cost utility':ti,ab,kw OR 'cost utility'/exp) AND [embase]/lim) OR (('economic evaluation':ti,ab,kw OR 'economic evaluation'/exp) AND [embase]/lim) OR (('quality of life':ti,ab,kw OR 'quality of life'/exp) AND [embase]/lim)) AND ('biomarkers':ti,ab,kw OR 'biomarkers'/exp OR 'pd1':ti,ab,kw OR 'pd1'/exp OR 'programmed death 1':ti,ab,kw OR 'programmed death 1'/exp OR 'pd-l1':ti,ab,kw OR 'pd-l1' OR 'programmed death ligand 1':ti,ab,kw OR 'programmed death ligand 1'/exp OR 'il-6':ti,ab,kw OR 'il-6'/exp OR 'interleukin-6':ti,ab,kw OR 'interleukin-6'/exp) AND ('antibodies monoclonal':ti,ab,kw OR 'antibodies monoclonal'/exp) AND ('immunotherapy':ti,ab,kw OR 'immunotherapy'/exp) AND ('pembrolizumab':ti,ab,kw OR 'nivolumab/ipilimumab' OR 'ipilimumab' OR 'durvalumab' OR 'avelumab' OR 'atezolizumab' OR 'nivolumab' OR 'pembrolizumab'/exp) AND [embase]/lim AND (('neoplasms':ti,ab,kw OR 'neoplasms'/exp) AND [embase]/lim OR (('cancer':ti,ab,kw OR 'cancer'/exp) AND [embase]/lim) OR (('carcinoma':ti,ab,kw OR 'carcinoma'/exp) AND [embase]/lim))

# Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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| | | Reporting Item | Page Number |
|---|---|---|---|
| **Title** | | | |
| Identification | #1a | Identify the report as a protocol of a systematic review | 1 |
| Update | #1b | If the protocol is for an update of a previous systematic review, identify as such | 1 |

| | | | |
|---|---|---|---|
| **Registration** | | | |
| | #2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | 2 |
| **Authors** | | | |
| Contact | #3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contribution | #3b | Describe contributions of protocol authors and identify the guarantor of the review | 9 |
| **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 | 5-6 |
| **Support** | | | |
| Sources | #5a | Indicate sources of financial or other support for the review | 10 |
| Sponsor | #5b | Provide name for the review funder and / or sponsor | 10 |
| Role of sponsor or funder | #5c | Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol | 10 |
| **Introduction** | | | |

| | | | |
|---|---|---|---|
| Rationale | #6 | Describe the rationale for the review in the context of what is already known | 4-5 |
| Objectives | #7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 5 |
| **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 | 6-7 |
| 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 | 5-6 |
| 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 | 6 |
| Study records - data management | #11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 7-8 |
| Study records - 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) | 7-8 |

| | | | |
|---|---|---|---|
| Study records - 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 | 7-8 |
| 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 | 6-7 |
| Outcomes and prioritization | #13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 6-7 |
| 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 | 7-8 |
| Data synthesis | #15a | Describe criteria under which study data will be quantitatively synthesised | 7-8 |
| Data synthesis | #15b | 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 I2, Kendall's τ) | 7-8 |
| Data synthesis | #15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 7-8 |

| | | | |
|---|---|---|---|
| Data synthesis | #15d | If quantitative synthesis is not appropriate, describe the type of summary planned | 7-8 |
| Meta-bias(es) | #16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | 7-8 |
| Confidence in cumulative evidence | #17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 7-8 |

BMJ Open

# Cost Effectiveness of Treatment Optimization with Biomarkers for Immunotherapy in Solid Tumors: A Systematic Review Protocol

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# Cost Effectiveness of Treatment Optimization with Biomarkers for Immunotherapy in Solid Tumors: A Systematic Review Protocol

Sara Mucherino [1], Valentina Lorenzoni [2], Valentina Orlando[1], Isotta Triulzi [2], Marzia Del Re[3], Annalisa Capuano[4], Romano Danesi[3], Giuseppe Turchetti[2], Enrica Menditto[1,*]

**Affiliations:**

[1] CIRFF, Center of Pharmacoeconomics and Drug utilization Research, Department of Pharmacy, University of Naples Federico II, Naples, Italy

[2] Institute of Management, Scuola Superiore Sant'Anna, Pisa, Italy

[3] Unit of Clinical Pharmacology and Pharmacogenetics, University Hospital of Pisa, Pisa, Italy

[4] Department of Experimental Medicine, Section of Pharmacology 'L. Donatelli', University of Campania 'L. Vanvitelli', Naples, Italy

***Correspondence to:**

Prof. Enrica Menditto, PharmD, PhD

CIRFF, Department of Pharmacy, University of Naples Federico II

Via Montesano, 49

80131, Naples

Email: enrica.menditto@unina.it

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**Keywords:** Immunotherapy; Biomarkers; Cost effectiveness; Economic evaluation; Quality of life

## ABSTRACT

**Introduction:** The combination of biomarkers and drugs is the subject of growing interest both from regulators, physicians and companies. This study protocol of a systematic review is aimed to describe available literature evidences about the cost-effectiveness, cost-utility or net-monetary benefit of the use of biomarkers in solid tumour as tools for customizing immunotherapy to identify what further research needs.

**Methods and analysis:** A systematic review of the literature will be carried out according to the PRISMA statement guidelines. PubMed and Embase will be queried from June 2010 to June 2021. The PICOS Model will be applied: target population (P) will be patients with solid tumors treated with immune checkpoint inhibitors (ICIs); the interventions (I) will be test of the immune checkpoint predictive biomarkers; the comparator (C) will be any other targeted or non-targeted therapy; outcomes evaluated will be health economic and clinical implications assessed in terms of incremental cost-effectiveness ratio (ICERs), net health benefit, net monetary benefit, life years gained (LYG) , quality of life (QALY), etc. (O); study (S) considered will be economic evaluations reporting cost-effectiveness analysis, cost-utility analysis, net-monetary benefit. The quality of the evidence will be graded according to GRADE (Grading of Recommendations Assessment, Development and Evaluation).

**Ethics and dissemination:** This systematic review will assess the cost effectiveness implications of using biomarkers in the immunotherapy with ICIs, which may help to understand whether this approach is widespread in real clinical practice. This research is exempt from ethics approval because the work is carried out on published documents. We will disseminate this protocol in a related peer-reviewed journal.

**PROSPERO registration number:** CRD42020201549

## ARTICLE SUMMARY

### Strengths and limitations of this study

- The use of predictive biomarkers in the therapy with immune checkpoint inhibitors can help target therapy in some solid tumors, hence, the combination of biomarkers and drugs is the subject of growing interest both from regulators, physicians and companies.
- This is the first systematic review which will specifically describe available literature evidences about the cost-effectiveness, cost-utility or net-monetary benefit of the use of biomarkers in solid tumor as tools for customizing immunotherapy to identify what further research needs.
- An in-depth search strategy will be applied to two major scientific databases, without geographic and conducted by a multidisciplinary team with expertise in the field.
- The quality of studies included and related level of evidence will be assessed quality using the Consolidated Health Economic Evaluation Reporting Standard (CHEERS) checklist and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool.

## Introduction

In recent years, the pharmaceutical industry has seen a shift from the blockbuster model, in which drugs are developed for an ideal patient, to a nichebuster model, in which drugs developed specifically for specific patient groups [1,2]. In this context, the combination of biomarkers and drugs is the subject of growing interest both from regulators, physicians and companies [3-7].

The US Food and Drug Administration (FDA) regularly publishes and updates a list of drugs for which it is suggested or mandatory to associate a genetic-molecular test [8]. The importance of predictive biomarkers is related to optimizing patient benefits, reducing the risk of toxicity and leading combined approaches [9]. Particularly, for some drugs the test result defines whether or not to administer, for others it establishes the most appropriate dosage of therapy. Among the 166 biomarker-drug combinations reported by the FDA, in only 29% (48 combinations) of cases, results obtained from biomarker test have an impact on the physician's choice to prescribe or not prescribe a particular drug. [10]. In Italy, 34 of those 48 combinations are approved for use and among these, about 80% find application in oncology particularly for solid tumors treatment [10]. The clinical development of checkpoint inhibitor-based immunotherapy has ushered in an exciting era of anticancer therapy. Since the FDA approval of ipilimumab (human IgG1 k anti-CTLA-4 monoclonal antibody) in 2011, six more immune checkpoint inhibitors (ICIs) have been approved for cancer therapy. Programmed Death-1 (PD-1) inhibitors nivolumab, pembrolizumab, cemiplimab and Programmed Death Ligand-1 (PDL-1) inhibitors atezolizumab, avelumab, and durvalumab are in the current list of the approved agents in addition to ipilimumab [11]. The importance of predictive biomarkers is related to the optimization of benefits in patients treated with immunotherapy, by reducing the risk of toxicity and leading combined approaches. Durable responses have been observed in patients with various malignant neoplasms [12].

This study protocol is part of a funded Italian National Research Project based on the hypothesis that the identification of predictive biomarkers can improve the understanding of the mechanisms underlying the complex interactions between the immune system and cancer thus guiding clinicians to optimize therapy with monoclonal anti-PD-1 and anti-PD-L1 antibodies. Hence, among the already known biomarkers, the overexpression of PD-L1 is an important and widely explored predictive biomarker for the response to PD-1/PD-L1 antibodies [4,13]. Direct assessment of PD-L1 expression on tumor cells is a logical biomarker for the prediction of treatment response to anti-PD-1 or anti-PD-L1 therapies [14,15]. The use of PD-1 and PDL-1 as predictive biomarkers can help target therapy in some solid tumors, including renal and non-small cell lung cancer (NSCLC) [16-18]. Nivolumab and pembrolizumab and an PD-L1 inhibitor, atezolizumab, have also been approved by the Italian Medicines Agency (AIFA), for the treatment of patients with NSCLC [19-21].

A targeted approach to treatment using predictive biomarkers has the potential not only to maximize clinical benefit in respect to not-targeted therapy, but also to improve cost-effectiveness and reduce the economic burden of the disease [22]. As the global impact of these types of cancers continues to grow, the implementation of new and more effective therapies becomes important but also overly expensive [23]. Therefore, the analysis of the cost-effectiveness and economic impact of the use of biomarkers upstream of the choice of the specific therapy represents an imperative to validate its effectiveness, the eventual relationship with the quality of life, patient reported outcomes (PROMs), and sustainability [24]. However, there is no existing peer-reviewed or published synthesis summarizing the impact of predictive biomarkers use in oncological treatment in health-economics terms.

This is the protocol of a systematic review aimed at describing available literature about the cost-effectiveness, cost-utility or net-monetary benefit of the use of predictive biomarkers in solid tumor treated with ICIs as tools for customizing immunotherapy; the final goal of the study is to

help decision-makers and clinicians identify the most effective and sustainable options and identify further research needs.

## Methods and Analysis

The PRISMA-P 2015 (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist was used to develop the present study protocol. Modifications in the item sequencies were done where appropriate [25].

**Information sources**

A systematic review of the literature will be carried out according to the PRISMA 2020 (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement guidelines [26]. For the present review, the identification of relevant studies will be achieved by searching electronic databases of the published literature. In details Medical Literature Analysis and Retrieval System Online (via PubMed/MEDLINE) and Embase (via Ovid) were queried from June 2010 to June 2021.

**Search strategy**

First, the search strategy will be developed and completed in PubMed, and then the same strategy will be applied to Embase. The search strategy was developed according to the PICOS model and based on the existing literature and finally revised by clinicians. More in detail, the search strategy will combine headings and keywords listed in Table 1 answering each questions of the PICOS Model. Those terms combined with boolean operators AND/OR will be searched both as Mesh Term (PubMed) or Emtree (Embase) both in title and abstract. The full search strategy that will be used is reported in Table 1. More in detail, the search syntax for the two databases are presented in the online Supplementary Appendix 1.

**Elegibility criteria**

The inclusion criteria are based on compliance with the PICOS. Particularly, we will identify:

- Patient (P): Patients with solid tumors treated with immune checkpoint inhibitors (monotherapy or combination therapy): nivolumab, pembrolizumab, ipilimumab, atezolizumab, durvalumab, avelumab, cemiplimab;
- Intervention (I): Test of the immune checkpoint predictive biomarkers, such as PD1, PDL-1 CTLA4, IL-6.
- Comparator (C): Any other targeted or non-targeted therapy
- Outcomes (O): health-economic outcomes (Incremental Cost-effectiveness, ICERs, net health benefit, net monetary benefit, life years,LYs, quality adjusted life years, QALYs, etc.) will be evaluated between immune checkpoint inhibitors therapy
- Study design (S): health-economic evaluations reporting cost-effectiveness analysis, cost-utility analysis, net-monetary benefit.and conducted within clinical trials or observational studies.

All peer-reviewed original articles about health economics evaluation related to biomarkers use published between June 2010 to June 2021 and responding to the PICOS will be considered for inclusion in the study. On the other hand, conference proceedings, rationale and/or study protocol, letters, editorials, commentaries, case reports, case study, case series, review, consensus, guidelines, expert opinions and grey literature will be not included (exclusion criteria). Moreover, language restriction will be applied to the research, as fundamental to the eligibility of the study will be the availability of the papers' full text published in English.

Any identified literature reviews will be used as a source for finding additional articles not present in our dataset.

Inclusion and exclusion criteria are summarized in Table 2.

The quality of the economic evaluations that will be included in the study will be assessed through the CHEERS checklist [27].

**Selection and data process**

The references will be collected using the software program Reference Manager, ver. 12 (Institute for Scientific Information, Berkeley, CA). All references will be screened for relevance and, those potentially eligible will be assessed, according to the inclusion/exclusion criteria, accepted or rejected, as appropriate.

Four researchers will double screen titles and abstract to discard irrelevant ones in the first screening phase. Then, full texts of the records selected from the previous step will be retrieved and double screened to assess the eligibility for the inclusion in the qualitative analysis. Finally, the references obtained will be validated by clinicians and researchers in the fields of pharmacology, immunotherapy, pharmacovigilance, pharmacoeconomics. Reference lists from included records will be also screened to identify additional papers (backward reference searching) as for other studies citing that paper (forward citation searching).

The type of information that will be extracted from each reference included in the qualitative analysis and collected into a dedicated file are reported in Table 3. The structure of the table that will be used to describe results obtained is shown in Appendix 2. Changes to the variables in the table could be made in the final revision based on the evidence that emerged. Quality of studies will be assessed using the Cheers checklist and finally, the quality of the evidence will be graded according to GRADE (Grading of Recommendations Assessment, Development and Evaluation) system [28], assessing heterogeneity, consistency and risk of bias.

All studies and their individual elements will be graded in terms of adequacy of the study regarding the research question, risk of selection bias, measurement of exposure and assessment of outcomes. Disagreements will be resolved by third reviewers.

**Study registration**

The study is prospectively registered in PROSPERO, the International Prospective Register of Systematic Reviews (CRD42020201549).

**Data description**

This review will systematically describe the extent of available evidences investigating the predictive biomarkers used in immunotherapy and their health-economic impact. The use of biomarkers to monitor the clinical outcome of patients treated with immune check-point inhibitors (ICIs) may help to reduce the incidence of adverse events related to the immune system thus also improving quality of life. Furthermore, from the pharmaco-economic evaluations already conducted on these immune biomarkers we expect to find that their use is associated with better cost-effectiveness (or cost-utility, net-monetary benefit) ratio due to their improved ability to predict clinical outcome and to redirect non-reactive patients towards alternative and more effective and cost-effective therapeutic approaches.

Accordingly, main strength of the present work will consist in having an overview on what is already know on immune biomarkers use to guide choice and personalization of treatment for cancer patients treated with ICIs. Also, we will try to gather considerations about the diffusion of their real use through economic evaluations that report their outcomes in terms of incremental cost effectiveness ratio or cost utility ratio and patients' health related quality of life. So, results expected from the systematic review will strictly depend on the study design used. We aim to consider the study design such as cost-effectiveness analysis, cost-utility analysis, budget impact analysis, highlighting first the methodology used in the study and to report for each biomarker used in cancer patients their cost-effectiveness, willingness to pay (WTP) with the reference threshold. Appendix 1 shows the hypothetical structure of the data synthesis.

Other systematic reviews on biomarkers were already published evaluating cost-related aspects but they are specifically focused on a cancer condition and the pertaining biomarker [29-32].

Particularly, our study differs to that of Oosterhoff et al [29] as they aimed to widely investigate the methodological characteristics of economic evaluations on biomarkers and examine economic aspect. To the best of our knowledge this is the first systematic review published broadly exploring the health-economic impact of predictive biomarkers specifically used in treatment of solid tumors with ICIs comparing them with other targeted and non-targeted therapeutic strategies that do not include the use of the reference biomarker.

A potential limitation relates to the heterogeneity associated to the study conducted on biomarkers. Accordingly, between-study heterogeneity may not support the conduct of quantitative meta-analysis. Based on the results obtained, any heterogeneity of the studies will be managed by grouping, if feasible, the included records into different classes such as solid tumor type (e.g. breast cancer, bladder cancer, cervical cancer, colon cancer, head and neck cancer, hodgkin lymphoma, liver cancer, lung cancer, renal cell cancer, skin cancer, stomach cancer, rectal cancer) and study design type (e.g. cost-effectiveness analysis, cost-utility analysis, net-monetary benefit). The same variables present in Appendix 2 will be evaluated for each group and subgroup.

**Patient and Public Involvement**

No patients involved.

## Ethics and dissemination

Results of the systematic review will be published in a peer-reviewed journal and disseminated at a range of health research conferences. The systematic review is part of a larger project funded by PRIN 2017 whose aims include the identification of biomarkers able to predict immunotherapeutic-related adverse drug reactions and the potential cost-effectiveness and quality of life of personalized therapies based on advanced tools.

Finally, this systematic review will assess the cost effectiveness implications of using biomarkers in in cancer patients treated with ICIs compared to any other target therapy or conventional therapy without the use of biomarkers. This review may help to understand if this approach may be cost-effective in clinical practice and how the customization of therapy, can actually affect a decrease in costs for the health care systems.

## Author contributions

E.M. designed and conceptualised this review. S.M., V.O., V.L., I.T. drafted the protocol. All authors were involved in checking various steps of the search strategy, including keywords, as well as the final version of the protocol. S.M, V.L. and I.T. were involved in the definition of specific criteria for the extraction of information from studies included and in the development of the strategy for the qualitative data analysis. M.D.R., A.C., R.D. and G.T. were involved in establishing eligibility criteria and data extraction forms. G.T. and E.M. supervised all work stages. R.D. was the funding acquisition supervisor. All authors reviewed and agreed the final version of the manuscript.

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## Conflicts of interest

The authors have no conflicts of interest to declare.

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# Tables

**Table 1. Search strategy**

| Query | Keywords (MeshTerms/Emtree OR Title and Abstract) |
|---|---|
| **#1** | Antibodies, monoclonal |
| **#2** | Immunotherapy |
| **#3** | (nivolumab/ipilimumab[Title/Abstract]) OR ipilimumab[Title/Abstract]) OR durvalumab[Title/Abstract]) OR atezolizumab[Title/Abstract]) OR nivolumab[Title/Abstract]) OR pembrolizumab[Title/Abstract]) OR "Ipilimumab"[Mesh]) OR "durvalumab" [Supplementary Concept]) OR "avelumab" [Supplementary Concept]) OR "atezolizumab" [Supplementary Concept]) OR "Nivolumab"[Mesh]) OR "pembrolizumab" [Supplementary Concept] |
| **#4** | Immune checkpoint inhibitor |
| **#5** | Neoplasms |
| **#6** | Cancer |
| **#7** | Carcinoma |
| **#8** | Tumor OR Toumor |
| **#9** | Target therapy OR Chemotherapy |
| **#10** | Biomarkers OR PD-1 OR Programmed Death 1 OR PD-L1 OR Programmed Death Ligand 1 OR IL-6 OR Interleukin-6 OR CTLA-4 |
| **#11** | Cost benefit analysis |
| **#12** | Cost effectiveness |
| **#13** | Cost utility |
| **#14** | Economic evaluation |
| **#15** | Quality of life |
| **#16** | 1 OR 2 OR 3 OR 4 |
| **#17** | 5 OR 6 OR 7 OR 8 |
| **#18** | 11 OR 12 OR 13 OR 14 OR 15 |
| **#19** | 16 AND 17 |
| **#20** | 19 AND 9 AND 10 |
| **#21** | 20 AND 18 |

**Table 2. Synthesis of inclusion and exclusion criteria**

| Selection Criteria | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| Language study type | English | Non-English |
| Time limit (years) | 2010 – 2021 | < 2010 |
| Study design | Published and peer-reviewed health economi evalutations | Conference proceedings, rationale and/or design, letters, editorials, commentaries, case reports, case study, case series, review, consensus, guidelines, expert opinions, grey literature |

**Table 3. Data extraction and analysis process**

| Data extraction | Description |
|---|---|
| Reference | All paper identification details |
| Publication year | Year of publication of the paper |
| Perspective of the analysis | National health service, society, government, patient |
| Type of costs | Direct healthcare costs, direct non-health costs, indirect costs, intangible costs |
| Reference year of costs | Specific year of reference of costs if reported |
| Patient Diagnosis | Each status of: breast cancer, bladder cancer, cervical cancer, colon cancer, head and neck cancer, hodgkin lymphoma, liver cancer, lung cancer, renal cell cancer (a type of kidney cancer), skin cancer, stomach cancer, rectal cancer and any solid tumor that is not able to repair errors in its DNA that occur when the DNA is copied. |
| Patient (P) | Patients with solid tumors treated with immune checkpoint inhibitors (monotherapy or combination therapy): nivolumab, pembrolizumab, ipilimumab, atezolizumab, durvalumab, avelumab, cemiplimab |
| Intervention (I) | Test of the immune checkpoint predictive biomarkers, such as PD1, PDL-1 CTLA4, IL-6. |
| Comparator (C) | Any other targeted or non-targeted therapy |
| Outcomes (O) | health-economic outcomes (Incremental cost-effectiveness ratio, ICERs, net health benefit, net monetary benefit, LYs, QALYs) |
| Study design (S) | Health-economic evaluations reporting cost-effectiveness analysis, cost-utility analysis, net-monetary benefit |

# Appendix 1

## Search syntax in different databases

### PubMed

((((((Antibodies, monoclonal[MeSH Terms]) OR (Antibodies, monoclonal[Title/Abstract])) OR ((immunotherapy[MeSH Terms]) OR (immunotherapy[Title/Abstract]))) OR ((nivolumab/ipilimumab[Title/Abstract]) OR ipilimumab[Title/Abstract]) OR durvalumab[Title/Abstract]) OR atezolizumab[Title/Abstract]) OR nivolumab[Title/Abstract]) OR pembrolizumab[Title/Abstract]) OR "Ipilimumab"[Mesh]) OR "durvalumab" [Supplementary Concept]) OR "avelumab" [Supplementary Concept]) OR "atezolizumab" [Supplementary Concept]) OR "Nivolumab"[Mesh]) OR "pembrolizumab" [Supplementary Concept]) OR “immune checkpoint inhibitor[Title/Abstract])) AND ((((cancer[Title/Abstract]) OR (cancer[MeSH Terms])) OR ((carcinoma[Title/Abstract]) OR (carcinoma[MeSH Terms]))) OR ((neoplasm[Title/Abstract]) OR (neoplasm[MeSH Terms]))) OR (((tumor[Title/Abstract]) OR (tumor[MeSH Terms])) OR ((tumour[Title/Abstract]) OR (tumour[MeSH Terms])))) AND ((((((((((PD1[Title/Abstract]) OR (PD1[MeSH Terms])) OR (Programmed Death 1[MeSH Terms])) OR (Programmed Death 1[Title/Abstract])) OR (PD-L1[Title/Abstract])) OR (PD-L1[MeSH Terms])) OR (Programmed Death Ligand 1[MeSH Terms])) OR (Programmed Death Ligand 1[Title/Abstract])) OR (IL-6[Title/Abstract])) OR (IL-6[MeSH Terms])) OR ((biomarker[Title/Abstract]) OR (biomarker[MeSH Terms]))))) AND (((Target therapy [Title/Abstract]) OR (Target therapy [MeSH Terms])) OR ((Chemotherapy [Title/Abstract]) OR (Chemotherapy [MeSH Terms]))) AND ((((((cost benefit analysis[Title/Abstract]) OR (cost benefit analysis[MeSH Terms])) OR ((cost effectiveness[MeSH Terms]) OR (cost effectiveness[Title/Abstract]))) OR ((cost utility[Title/Abstract]) OR (cost utility[MeSH Terms]))) OR ((economic evaluation[Title/Abstract]) OR (economic evaluation[MeSH

Terms]))) OR ((quality of life[Title/Abstract]) OR (quality of life[MeSH Terms]))) Sort by: Publication Date

**Embase**

(('cost benefit analysis':ti,ab,kw OR 'cost benefit analysis'/exp) AND [embase]/lim OR (('cost effectiveness':ti,ab,kw OR 'cost effectiveness'/exp) AND [embase]/lim) OR (('cost utility':ti,ab,kw OR 'cost utility'/exp) AND [embase]/lim) OR (('economic evaluation':ti,ab,kw OR 'economic evaluation'/exp) AND [embase]/lim) OR (('quality of life':ti,ab,kw OR 'quality of life'/exp) AND [embase]/lim)) AND ('biomarkers':ti,ab,kw OR 'biomarkers'/exp OR 'pd1':ti,ab,kw OR 'pd1'/exp OR 'programmed death 1':ti,ab,kw OR 'programmed death 1'/exp OR 'pd-l1':ti,ab,kw OR 'pd-l1' OR 'programmed death ligand 1':ti,ab,kw OR 'programmed death ligand 1'/exp OR 'il-6':ti,ab,kw OR 'il-6'/exp OR 'interleukin-6':ti,ab,kw OR 'interleukin-6'/exp) OR (‘target therapy’: ti,ab,kw OR 'target therapy’/exp OR ‘chemotherapy’: ti,ab,kw OR ‘chemotherapy’/exp) AND ('antibodies monoclonal':ti,ab,kw OR 'antibodies monoclonal'/exp) AND ('immunotherapy':ti,ab,kw OR 'immunotherapy'/exp) AND ('pembrolizumab':ti,ab,kw OR 'nivolumab/ipilimumab' OR 'ipilimumab' OR 'durvalumab' OR 'avelumab' OR 'atezolizumab' OR 'nivolumab' OR 'pembrolizumab'/exp) AND ('immune checkpoint inhibitor':ti,ab,kw OR 'immune checkpoint inhibitor'/exp) AND [embase]/lim AND (('neoplasms':ti,ab,kw OR 'neoplasms'/exp) AND [embase]/lim OR (('cancer':ti,ab,kw OR 'cancer'/exp) AND [embase]/lim OR (('tumor':ti,ab,kw OR 'tumor'/exp) AND [embase]/lim OR (('tumour':ti,ab,kw OR 'tumour'/exp) AND [embase]/lim) OR (('carcinoma':ti,ab,kw OR 'carcinoma'/exp) AND [embase]/lim))

# Appendix 2

## Assumed tables structure for data synthesis

### Appendix Table 1. Characteristics of included studies

| Study Reference | Publication year | Country | Population | Comparators | Type of biomarker | Health-economic outcomes | Threshold (WTP) | Conclusions |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| | | | | | | | | |

### Appendix Table 2. Methodology of the included studies

| Study Reference | Study design | Type of Economic evaluation | Perspective used in the analysis | Type of costs included | Reference year of costs | Effectiveness measures |
|---|---|---|---|---|---|---|
| | | | | | | |
| | | | | | | |

# Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Preporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

| | | Reporting Item | Page Number |
|---|---|---|---|
| **Title** | | | |
| Identification | #1a | Identify the report as a protocol of a systematic review | 1 |
| Update | #1b | If the protocol is for an update of a previous systematic review, identify as such | 1 |

| | | | |
|---|---|---|---|
| **Registration** | | | |
| | #2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | 2 |
| **Authors** | | | |
| Contact | #3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | 1 |
| Contribution | #3b | Describe contributions of protocol authors and identify the guarantor of the review | 9 |
| **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 | 5-6 |
| **Support** | | | |
| Sources | #5a | Indicate sources of financial or other support for the review | 10 |
| Sponsor | #5b | Provide name for the review funder and / or sponsor | 10 |
| Role of sponsor or funder | #5c | Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol | 10 |
| **Introduction** | | | |

| | | | |
|---|---|---|---|
| Rationale | #6 | Describe the rationale for the review in the context of what is already known | 4-5 |
| Objectives | #7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 5 |
| **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 | 6-7 |
| 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 | 5-6 |
| 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 | 6 |
| Study records - data management | #11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | 7-8 |
| Study records - 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) | 7-8 |

| | | | |
|---|---|---|---|
| Study records - 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 | 7-8 |
| 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 | 6-7 |
| Outcomes and prioritization | #13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 6-7 |
| 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 | 7-8 |
| Data synthesis | #15a | Describe criteria under which study data will be quantitatively synthesised | 7-8 |
| Data synthesis | #15b | 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 I2, Kendall's τ) | 7-8 |
| Data synthesis | #15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 7-8 |

| | | | |
|---|---|---|---|
| Data synthesis | #15d | If quantitative synthesis is not appropriate, describe the type of summary planned | 7-8 |
| Meta-bias(es) | #16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | 7-8 |
| Confidence in cumulative evidence | #17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 7-8 |