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# Cost and Cost-Effectiveness of mHealth interventions for the prevention and control of Type 2 Diabetes Mellitus: A protocol for a Systematic Review



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# Cost and Cost-Effectiveness of mHealth interventions for the prevention and control of Type 2 Diabetes Mellitus: A protocol for a Systematic Review

Giulia Rinaldi[1] , Alexa Hijazi[2], Hassan Haghparast-Bidgoli[2]

[1]St.George's University of London, London, UK
[2]Institute for Global Health, University College London, London, UK

**Authors' emails:**
GR: m1401237@sgul.ac.uk
AH: alexahijazi@gmail.com
HHB: h.haghparast-bidgoli@ucl.ac.uk

§ Corresponding author:
Hassan Haghparast-Bidgoli
Address: University College London, Institute for Global Health, 30 Guilford Street, London WC1N 1EH, UK
Email: h.haghparast-bidgoli@ucl.ac.uk
Tel: +44 (0) 20 7905 2779

## Abstract

**Introduction**: Type 2 Diabetes Mellitus (T2DM) remains one of the most common chronic diseases of adulthood which creates high degrees of morbidity and mortality worldwide. The incidence of T2DM continues to rise and recently, mHealth interventions have been increasingly used in the prevention, monitoring and management of T2DM. The aim of this study is to systematically review and evaluate the cost and cost-effectiveness of these interventions.

**Methods & Analysis**: A comprehensive review of PubMed, EMBASE and Web of Science of articles published until October 2018 will be conducted. Included studies will be partial or full economic evaluations which provide cost or cost-effectiveness outcomes for mHealth interventions targeting individuals diagnosed with, or at risk of, T2DM. The quality of reporting evidence will be evaluated using the CHEERS checklist. Results will be presented using a flowchart following the PRISMA-P guidelines. Graphical and tabulated representations of the results will be created for both descriptive and numerical results. The cost and cost-effectiveness values will be presented as reported by the original studies as well as converted into international dollars to allow comparability.

**Ethics and Dissemination**: No formal approval or review of ethics is required for this systematic review as it will involve the collection and analysis of secondary data. This protocol follows the current Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines. The review will provide information on the cost and cost-effectiveness of mHealth interventions targeting T2DM. These results will be disseminated through publication and submission to conferences for presentations and posters.




## Strengths and Limitations

- This review will address a gap in the literature regarding the cost and cost-effectiveness of mHealth interventions for patients with or at risk of T2DM
- We will use a CHEERS checklist to assess the quality of reporting evidence by the included studies.
- This protocol is written according to the most recent PRISMA-P guidelines

- The inclusion of only peer-reviewed published studies and only in the English-language may result in some relevant studies being excluded
- Key words: diabetes, mhealth, systematic review, telemedicine, T2DM

## Introduction

### Description of the Condition:

Type 2 Diabetes Mellitus (T2DM) is a chronic endocrine disease where the patient becomes progressively resistant to insulin causing a tendency to develop high blood sugars and symptomatic cardiovascular disease[1]. In poorly controlled patients, diabetes creates high amounts of morbidity and mortality due to cardiovascular, ocular and nephrogenic complications[2].The prevalence of diabetes is increasing with 422 million adults thought to be living with the condition in 2014, that is, around 8.5% of the adult population[1]. In 2015, diabetes was the sixth highest cause for disability worldwide[3]. The loss of productivity due to diabetes and its health consequences causes an economic burden to patients, healthcare providers and country's economy, mounting to 1.8% of the global gross domestic product(GDP)[4]. Moreover, more than 80% of the yearly deaths due to diabetes occur in developing countries where the economic consequences of diabetes are greater than in developed counterparts[5].

The prevention and management of the diabetes consists of lifestyle modifications (including weight, exercise and nutritional changes) and, if unsuccessful, the pharmacological control of hyperglycemia[6]. For many patients, the diagnosis and management of the condition challenges their long term lifestyle habits including exercise and diet[7]. Motivational interviewing has become a commonly prescribed person-centered form of counselling thought to reinforce patients healthy lifestyle modifications. However, it has proven to have variable results across T2DM populations with many patients still demonstrating low willingness to change their unhealthy lifestyle habits[7, 8]. To overcome these barriers, technology has demonstrated encouraging potential in supporting patients' behavioral changes by providing an empowering, portable every-day reminder of their diabetes management plan[9].

### Description of the Intervention:

Currently it is estimated that 96.8% of adults worldwide have access to a mobile phone, whilst, 43.4% of individuals worldwide are using the internet[10], this increases to 94.4% of internet

users if solely describing high-income countries[11]. The large growth of wireless connection usage has created a platform for technology-based opportunities in healthcare combining patient empowerment with the convenience of mobile devices.

mHealth can be defined as the integration of mobile devices, personal digital assistants, and other technological wireless systems to improve the health of individuals [12]. Importantly, it can help to equilibrate the disparities in health care access and quality by diminishing barriers for patients to access healthcare advice and monitoring[13]. mHealth programs consist of a myriad of different interventions targeting a variety of medical specialties in all of preventative, curative and chronic medicine. The use of mHealth has increased exponentially throughout the last two decades and the the literature focused on mHealth has increased significantly with only 33 relevant articles published before 2007 to a total of 289 articles published between the years of 2012-2014[14]. Early research consisted mostly of pilot studies, whilst, current research is increasingly structured and evidence-based[15].

## Diabetes and mHealth

The studies evaluating the clinical effectiveness of mHealth interventions targeting diabetes have demonstrated clinical usefulness in the prevention and the control of diabetes utilizing lifestyle modification and blood glucose monitoring applications [16–18]. A meta-analysis review demonstrated that there is a statistically significant reduction in blood glucose levels amongst patients using mobile phone interventions[19]. Additionally, a systematic review evaluating the effectiveness of mHealth interventions in glycemic control found that the effects are amplified when two different methods are used in conjunction with one another, such as text reminders and blood glucose record keeping [20].

mHealth interventions have been shown to be low costs and cost-effective across non-communicable medical specialties, such as cardiovascular and renal medicine; however, specific evidence for T2DM is still lacking[13]. Consequently, there are significant gaps in the literature addressing the cost and cost-effectiveness of mHealth interventions targeted at individuals with or at risk of type 2 diabetes mellitus. One recent review, has shown that digital behavior counselling for patients at risk of diabetes both significantly reduces their risk of diabetes and cardiovascular disease and provides a positive return on investment costs [21].

## Why do this review?

mHealth for diabetes shows clinical promise, however, there is a lack of cost and cost-effectiveness evidence in regard to mHealth interventions. A systematic review evaluating the cost and cost-effectiveness of mHealth interventions targeting T2DM is required to close a gap in the literature.

## Aim

The aim of this study is to systematically review the published evidence on the cost and cost-effectiveness of mHealth interventions for T2DM. It also aims to analyze the quality of reporting of this evidence.

## Specific Objectives

1. To identify and summarize the cost and cost-effectiveness evidence for mHealth interventions targeting T2DM
2. To evaluate the quality of reporting of the evidence
3. To summarize the cost and cost-effectiveness results and discuss their possible policy implications

## Methods

### Types of Studies

All partial and full economic evaluation studies presenting data for mHealth interventions directed at patients diagnosed or at risk of T2DM will be included. Partial economic evaluations are defined as evaluations that provide the cost of the intervention but do not, however, compare the costs to an alternative intervention or to the outcomes of the intervention[22]. Full economic evaluations compare the costs of the intervention to one or more alternative interventions (i.e., comparators) and relate these to the outcomes. Full economic evaluations include cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA), cost-minimization analysis (CMA), and cost-consequence analysis (CCA) [22].

### Types of Participants

Included mHealth interventions will be targeted at individuals who are diagnosed with or are at risk of developing T2DM due to impaired glucose tolerance. This review will include mHealth interventions implemented in both low- and middle- and high-income settings.

### Types of Interventions

All mHealth interventions targeting patients at risk of or with diagnosed T2DM that involve the use of the internet, mobile devices or computer-based interventions will be included in the review. We recognize that mHealth is a vast subject area and, therefore, we will attempt to categorize included mHealth interventions into relevant subgroups to facilitate comparability.

### Outcome Measures

The common outcome measures such as incremental cost effectiveness ratios (ICERs), average cost-effectiveness ratio, benefit-cost ratio and unit costs will be extracted from the selected studies.

We will report outcome measures as presented in the original studies and, for comparison, we will convert the original values to 2017 international dollars utilizing purchasing power parity.

### Exclusion Criteria

Studies will be excluded from our analysis if they are:

- Not published in a peer-reviewed journal
- Not available in the English language

- Not evaluating mHealth interventions
- Not reporting any costing data

## Locating Studies

*Electronic Searches*

We will conduct a literature search on the following online databases from inception to end of October 2018 for studies published in English on:

- MEDLINE (PubMed)
- EMBASE
- Web of Science

*Other Searches*

We will additionally review the reference lists of identified studies for any further relevant studies.

### Search Strategy

We will use the search strategy with the key words specified in Table 1 for all three online databases. We will modify the search strategy to suit all three databases.

Table 1: Search Strategy Key Words

| Search Strategy Key Words |
|---|
| ((((((((((m-health) OR ehealth) OR mhealth) OR mobile health) OR telemedicine) OR e-health) OR electronic health))<br><br>AND (((((((((diabetes) OR Type 2 Diabetes) OR Diabetes Mellitus) OR T2DM) OR DM2) OR impaired glucose tolerance) OR insulin resistance) OR pre-diabet*) OR impaired fasting tolerance)<br><br>AND ((((((((((cost effectiv*) OR cost-effetiv*) OR cost benefit) OR cost-benefit) OR cost-utility) OR cost utility) OR cost analysis) OR cost-analysis) OR economic evaluation) OR cost*) OR cost outcome))<br><br>AND ((((((((((((monitor*) OR control*) OR management) OR prevention) OR risk reduction) OR lifestyle modification) OR exercis*) OR physical fitness) OR bariatric surgery) OR metformin) OR diet) OR weight loss) OR food) OR obesity) OR BMI |

### Data Collection and Analysis

## Selection of Studies

Relevant papers will be selected in two steps: in the first step two authors (GR and AH) will independently review the titles and abstracts of the studies resulting from the above search and, in the second step, the full text of the selected papers in the first step will be screened. The search will be managed in Endnote X7 to facilitate the organization and management of the selection process. Any disagreements amongst the authors will be discussed until an agreement is reached with consultation of another experienced author (HHB). The outline of the study selection procedure will be shown in a preferred reporting items for systematic review and meta-analysis protocol (PRISMA-P) flow chart (Figure 1)[23]. After the consensus on the final studies for inclusion, the reviewers will analyze the full publications data extraction.

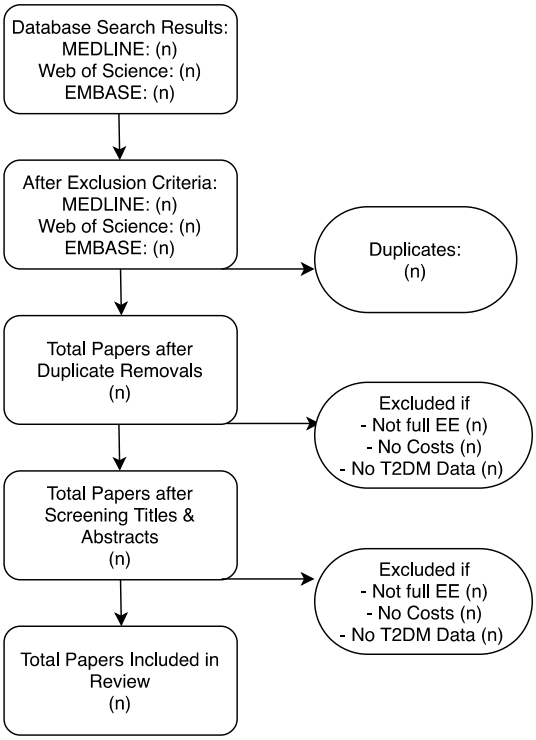


Figure 1: A schematic process of the literature search

## Data Extraction

General information and economic features will be collected from all the selected studies including date of publication, study design, type of intervention (i.e., type of mHealth), objective of the intervention, duration of the intervention, setting of the intervention (i.e., based on income level and geographical region), platform of the intervention and demographics of the participants. Furthermore, economic evaluation details such as type of analysis (i.e., CEA, CUA, CBA etc.), perspective of analysis, type of outcome measured, time horizon, type of data used (primary, secondary or mixed), type of sensitivity analysis and measures of uncertainty will be recorded. This data will be recorded and extracted using a data extraction tool designed for this purposed based on existing guidelines and other economic evaluation articles[22, 24, 25].

## Quality of reporting evidence

We will assess the quality of reporting the economic evidence presented in the selected studies using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist[26]. Two authors will use this checklist independently and any discrepancies will be discussed amongst them until a consensus is reached. If discrepancies continue then a third person will be involved to resolve these.

The checklist includes 24 items which are divided into these subheadings:

1. The Title and Abstract
2. Introduction
3. Methods
4. Results
5. Discussion

The quality of reporting of the included papers will be presented using the CHEERS checklist in both table and graph format to ensure a numerical and visual representation of the quality limitations of the studies.

## Analysis

### Summarizing Results

Results will be summarized using appropriate tables and figures to ensure a complete and objective account of our findings. We will include a general summary table quantifying the main characteristics of the included studies such as study design (RCT, before-after, modeling etc.), type of mHealth intervention, time horizon, country income setting, and outcome measure used (Refer to annex).

A more detailed account of the outcome measures will be presented and categorized via mHealth intervention type allowing the subdivision and ranking of the cost and cost-effectiveness of different mHealth interventions. For generalizability purposes, results will also be compared against the World Health Organization's (WHO) cost effectiveness threshold using the setting's GDP per capita [27]. To facilitate comparability of the results across countries and years, costs will be converted to 2017 international dollars using purchasing power parity conversion factors for each study setting.

### Addressing Bias

We will critically analyze the results of our review for possible bias. Particularly, we are aware of publication bias; often published studies demonstrate positive results and research demonstrating negative results may be lacking[28]. Additionally, we will exclude studies that are not available in the English language and which are not published in a peer-reviewed journal, therefore, we acknowledge the bias that this may introduce.

### Subgroup Analysis

If sufficient studies are included, we plan on carrying out analysis amongst subgroups. For example, one stratification method will be the subdivision of interventions by mHealth category, such as mobile phone applications or computer-based interventions. Secondly, subdividing the interventions according to their objective, for example, diabetes prevention versus diabetes control, may allow a greater generalizability of results. Another sub-analysis we may include is the evaluation of cost and cost-effectiveness results according to the countries' income level (low, middle or high) or healthcare platform used (community, hospital or primary care).

## Ethics and Dissemination

No formal ethical review or approval is needed as there will be no primary collection of data involved in this review. The results of this review will be submitted to a peer-reviewed journal for publication. The findings will also be shared at international conferences. This review will address the gap in the literature concentrating on the cost and cost-effectiveness of mHealth interventions for T2DM. We predict that this information will help to influence the policy making surrounding mHealth interventions targeting people at risk of or diagnosed with type 2 diabetics or people at risk of type 2 diabetes.

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**Competing interests:** None declared.

**Word Count:** 2100

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## Annex:

## Data Extraction Table Examples:

Table 1: Summary of economic features of the studies

| Feature | N | % |
|---|---|---|
| **Type of economic evaluation** | | |
| CEA | | |
| CUA | | |
| CBA | | |
| Cost Analysis | | |
| **Study Design** | | |
| Randomised clinical trial (RCT) | | |
| Observational | | |
| Modelling | | |
| **Country Income Setting** | | |

| | | |
|---|---|---|
| Low Income | | |
| Middle Income | | |
| High Income | | |
| **Time horizon** | | |
| <= 1 year | | |
| 1-10 years | | |
| over 10 years/lifetime | | |
| Not specified | | |
| **Type of mHealth intervention** | | |
| Primary prevention | | |
| Secondary prevention | | |
| Tertiary Prevention | | |
| **Level of Care** | | |
| Community based | | |
| Primary Care | | |
| Secondary Care | | |
| **Type of data used** | | |
| Primary data | | |
| Secondary data | | |
| Mixed | | |
| **Type of sensitivity analysis** | | |
| One-way/Univariate | | |
| Multi-way/Multivariate | | |
| Probabilistic analysis | | |
| Not performed/specified | | |

Table 2: Number of Studies fulfilling each CHEERS checklist item

| Item | | Item no. | Yes | No | Partially | N/A |
|---|---|---|---|---|---|---|
| Title and abstract | Title | 1 | | | | |
| | Abstract | 2 | | | | |
| Introduction | Background and objectives | 3a | | | | |
| | | 3b | | | | |
| Methods | Target population and subgroups | 4 | | | | |
| | Setting and location | 5 | | | | |
| | Study perspective | 6 | | | | |
| | Comparators | 7 | | | | |
| | Time horizon | 8 | | | | |
| | Discount rate | 9 | | | | |
| | Choice of health outcomes | 10 | | | | |
| | Measurement of effectiveness | 11 a) | | | | |
| | | 11 b) | | | | |
| | Measurement and valuation of preference based outcomes | 12 | | | | |
| | Estimating resources and costs | 13 a) | | | | |
| | | 13 b | | | | |
| | Currency, price date, and conversion | 14 | | | | |
| | Choice of model | 15 | | | | |
| | Assumptions | 16 | | | | |
| | Analytical methods | 17 | | | | |
| Results | Study parameters | 18 | | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| | Incremental costs and outcomes | 19 | | | | |
| | Characterising uncertainty | 20 a | | | | |
| | | 20 b | | | | |
| | Characterising heterogeneity | 21 | | | | |
| Discussion | Study findings, limitations, generalisability, and current knowledge | 22 | | | | |
| Other | Source of funding | 23 | | | | |
| | Conflicts of interest | 24 | | | | |

# 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-P reporting 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 |
|---|---|---|---|
| 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 | n/a |
| | #2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | n/a |
| 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 | 1 |
| | #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 | n/a |
| Sources | #5a | Indicate sources of financial or other support for the review | 9 |

| | | | |
|---|---|---|---|
| Sponsor | #5b | Provide name for the review funder and / or sponsor | n/a |
| Role of sponsor or funder | #5c | Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol | n/a |
| Rationale | #6 | Describe the rationale for the review in the context of what is already known | 4 |
| Objectives | #7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 4 |
| 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 | 5 |
| 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 |
| 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 | 6 |
| 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 |
| 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 | 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 | 8 |
| Outcomes and prioritization | #13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 9 |
| 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 | 9 |

| | | | |
|---|---|---|---|
| | | level, or both; state how this information will be used in data synthesis | |
| Data synthesis | #15a | Describe criteria under which study data will be quantitatively synthesised | 9 |
| | #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) | n/a |
| | #15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 9 |
| | #15d | If quantitative synthesis is not appropriate, describe the type of summary planned | 9 |
| Meta-bias(es) | #16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | n/a |
| Confidence in cumulative evidence | #17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 8 |

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| Primary Subject Heading: | Diabetes and endocrinology |
| Secondary Subject Heading: | Health economics, Health services research, Global health |
| Keywords: | General diabetes < DIABETES & ENDOCRINOLOGY, HEALTH ECONOMICS, Telemedicine < BIOTECHNOLOGY & BIOINFORMATICS, Diabetes & endocrinology < INTERNAL MEDICINE |
| | |

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Giulia Rinaldi[1] , Alexa Hijazi[2], Hassan Haghparast-Bidgoli[2]

[1]St.George's University of London, London, UK
[2]Institute for Global Health, University College London, London, UK

**Authors' emails:**
GR: m1401237@sgul.ac.uk
AH: alexahijazi@gmail.com
HHB: h.haghparast-bidgoli@ucl.ac.uk

§ Corresponding author:
Hassan Haghparast-Bidgoli
Address: University College London, Institute for Global Health, 30 Guilford Street, London WC1N 1EH, UK
Email: h.haghparast-bidgoli@ucl.ac.uk
Tel: +44 (0) 20 7905 2779

## Abstract

**Introduction**: Type 2 Diabetes Mellitus (T2DM) remains one of the most common chronic diseases of adulthood which creates high degrees of morbidity and mortality worldwide. The incidence of T2DM continues to rise and recently, mHealth interventions have been increasingly used in the prevention, monitoring and management of T2DM. The aim of this study is to systematically review the published evidence on cost and cost-effectiveness of mHealth interventions for T2DM, as well as assess the quality of reporting of the evidence.

**Methods and Analysis**: A comprehensive review of PubMed, EMBASE, Science Direct and Web of Science of articles published until January 2019 will be conducted. Included studies will be partial or full economic evaluations which provide cost or cost-effectiveness results for mHealth interventions targeting individuals diagnosed with, or at risk of, T2DM. The quality of reporting evidence will be assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. Results will be presented using a flowchart following the PRISMA-P guidelines. Graphical and tabulated representations of the results will be created for both descriptive and numerical results. The cost and cost-effectiveness values will be presented as reported by the original studies as well as converted into international dollars to allow comparability. As we are predicting heterogenous results we will conduct a narrative and interpretive analysis of the data.

**Ethics and Dissemination**: No formal approval or review of ethics is required for this systematic review as it will involve the collection and analysis of secondary data. This protocol follows the current Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines. The review will provide information on the cost and cost-effectiveness of mHealth interventions targeting T2DM. These results will be disseminated through publication and submission to conferences for presentations and posters.

PROSPERO registration number: CRD42019123476; Registered: 27/01/2019

## Strengths and Limitations

- This review will address a gap in the literature regarding the cost and cost-effectiveness of mHealth interventions for individuals with or at risk of Type 2 Diabetes Mellitus
- The protocol follows the latest PRISMA-P guidelines and we will use a CHEERS checklist to assess the quality of reporting evidence by the included studies.
- The validity and quality of the results will depend on the quality of the identified studies.
- The heterogenicity of the identified studies may complicate the narrative analysis of the results.

# Introduction

## Description of the Condition:

Type 2 Diabetes Mellitus (T2DM) is a chronic disease where the patient becomes progressively resistant to insulin causing a tendency to develop high blood sugars and symptomatic cardiovascular disease [1]. In poorly controlled patients, diabetes can cause a substantial number of morbidity and mortality due to cardiovascular, ocular and nephrogenic complications[2].The prevalence of diabetes is increasing with 425 million adults thought to be living with the condition in 2018, that is, around 8.5% of the adult population [1, 3]. In 2015, diabetes was the sixth highest cause for disability worldwide[4]. The loss of productivity due to diabetes and its health consequences causes an economic burden to patients, healthcare providers and country's economy, mounting to 1.8% of the global gross domestic product (GDP) and 12% of the global health expenditure in 2018 [3, 5]. Moreover, more than 80% of yearly deaths due to diabetes occur in developing countries where the economic consequences are greater than in developed counterparts [6].

The prevention and management of the diabetes consists of lifestyle modifications (including weight, exercise and nutritional changes) and, if unsuccessful, the pharmacological control of hyperglycemia [7]. For many patients, the diagnosis and management of the condition challenges their lifestyle habits including exercise and diet. Therefore, many patients still demonstrate low willingness to change their unhealthy lifestyle habits [8, 9]. To overcome these barriers, technology has demonstrated encouraging potential in supporting patients' behavioral changes by providing an empowering, portable every-day reminder of their diabetes management plan[10].

## Description of the Intervention:

It is estimated that 96.8% of adults worldwide have access to a mobile phone, whilst, 43.4% of individuals are using the internet[11], this increases to 94.4% if solely describing high-income countries[12]. The large growth of wireless connection has created a platform for technology-based opportunities in healthcare combining patient empowerment with the convenience of mobile devices. MHealth can be defined as the integration of mobile devices, personal digital assistants, and other technological wireless systems to improve the health of individuals [13]. Importantly, it can help to equilibrate the disparities in health care access

and quality by diminishing barriers for patients to access healthcare advice and monitoring[14]. The use of mHealth has increased exponentially throughout the last two decades with early research consisting mostly of small pilot studies, whilst, current research is increasingly structured and evidence-based[15, 16].

## Diabetes and mHealth

Studies evaluating the clinical effectiveness of mHealth interventions targeting diabetes have demonstrated clinical usefulness in the prevention and control of diabetes utilizing lifestyle modification and blood glucose monitoring applications [17–19]. A meta-analysis review demonstrated that there is a statistically significant reduction in blood glucose levels amongst patients using mobile phone interventions[20]. Additionally, a systematic review found that glycemic control results are amplified when two different methods are used in conjunction with one another, such as text reminders and blood glucose record keeping [21]. MHealth interventions have been shown to be low cost and cost-effective across medical specialties, such as cardiovascular and renal medicine, however, there are significant gaps in the economic literature addressing mHealth interventions targeted at individuals with or at risk of type 2 diabetes mellitus [14].

## Why do this review?

mHealth for diabetes shows clinical promise, however, there is a lack of cost and cost-effectiveness evidence in regard to mHealth interventions. A systematic review evaluating the cost and cost-effectiveness of mHealth interventions targeting T2DM is required to close a gap in the literature.

## Aim

The aim of this study is to systematically review the published evidence on the cost and cost-effectiveness of mHealth interventions for T2DM.

## Specific Objectives

1. To identify and summarize the cost and cost-effectiveness evidence for mHealth interventions targeting T2DM
2. To evaluate the quality of reporting of the evidence
3. To identify the main drivers of the cost and cost-effectiveness results amongst these interventions

## Methods

### Types of Studies

All partial and full economic evaluation studies presenting data for mHealth interventions directed at patients diagnosed or at risk of T2DM will be included. Partial economic evaluations are defined as evaluations that provide the cost of the intervention but do not, however, compare the costs to an alternative intervention or to the outcomes of the intervention[22]. All. studies that report cost of the intervention, either from provider (e.g., design and implementation costs), patients (e.g., subscription fee, cost of changing behavior) or societal perspectives, will be included in the review. Full economic evaluations compare the costs of the intervention to one or more alternative interventions (i.e., comparators) and relate these to the outcomes. Full economic evaluations include cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA), cost-minimization analysis (CMA), and cost-consequence analysis (CCA) [22].

### Types of Participants

Included mHealth interventions will be targeted at individuals who are diagnosed with or are at risk of developing T2DM due to impaired glucose tolerance. This review will include mHealth interventions implemented in both low- and middle- and high-income settings.

### Types of Interventions

All mHealth interventions targeting patients at risk of or with diagnosed T2DM that involve the use of the internet, mobile devices or computer-based interventions will be included in the review. We recognize that mHealth is a vast subject area and, therefore, we will attempt to categorize included mHealth interventions into relevant subgroups to facilitate comparability.

### Outcome Measures

The common outcome measures such as incremental cost effectiveness ratios (ICERs), average cost-effectiveness ratio, benefit-cost ratio and unit costs will be extracted from the selected studies. We will report outcome measures as presented in the original studies and, for comparison, we will convert the original values to 2017 international dollars utilizing purchasing power parity for the country where the study is conducted.

### Exclusion Criteria

Studies will be excluded from our analysis if they are:

- Not published in a peer reviewed journal
- Not available in the English language
- Not addressing mHealth based interventions
- Not reporting any cost or cost-effectiveness data on the interventions

## Locating Studies

*Electronic Searches*

We will conduct a literature search on the following online databases from inception to end of January 2019 for studies published in English on:

- MEDLINE (PubMed)
- EMBASE
- Web of Science
- Science Direct

*Other Searches*

We will additionally review the reference lists of identified studies for any further relevant studies.

### Search Strategy

We will use the search strategy with the key words specified in Table 1 for all four online databases. We will modify the search strategy to suit all four databases.

Table 1: Search Strategy Key Words

| Search Strategy Key Words |
|---|
| ((((((((((m-health) OR ehealth) OR mhealth) OR MeSH) OR mobile health) OR telemedicine) OR e-health) OR application) OR app) OR electronic health))<br><br>AND (((((((((diabetes) OR Type 2 Diabetes) OR Diabetes Mellitus) OR T2DM) OR DM2) OR impaired glucose tolerance) OR insulin resistance) OR pre-diabet*) OR impaired fasting tolerance)<br><br>AND ((((((((((cost effectiv*) OR cost-effetiv*) OR cost benefit) OR cost-benefit) OR cost-utility) OR cost utility) OR cost analysis) OR cost-analysis) OR economic evaluation) OR cost*) OR cost outcome))<br><br>AND ((((((((((((monitor*) OR control*) OR management) OR prevention) OR risk reduction) OR lifestyle modification) OR exercis*) OR physical fitness) OR bariatric surgery) OR metformin) OR diet) OR weight loss) OR food) OR obesity) OR BMI |

## Data Collection and Analysis

### Selection of Studies

Relevant papers will be selected in two steps: in the first step two authors (GR and AH) will independently review the titles and abstracts of the studies resulting from the above search and, in the second step, the full text of the selected papers in the first step will be screened. The search will be managed in Endnote X7 to facilitate the organization and management of the selection process. Any disagreements amongst the authors will be discussed until an agreement is reached with consultation of another experienced author (HHB). The outline of the study selection procedure will be shown in a preferred reporting items for systematic review and meta-analysis protocol (PRISMA-P) flow chart (Figure 1) [23]. After the consensus on the final studies for inclusion, the authors will analyze the full publications data extraction.

## Data Extraction

General information and economic features will be collected from all the selected studies including date of publication, study design, type of intervention (i.e., type of mHealth), objective of the intervention, duration of the intervention, setting of the intervention (i.e., based on income level and geographical region), platform of the intervention and demographics of the participants. Furthermore, economic evaluation details such as type of analysis (i.e., CEA, CUA, CBA etc.), perspective of analysis, type of outcome measured, time horizon, type of data used (primary, secondary or mixed), type of sensitivity analysis and measures of uncertainty will be recorded. This data will be recorded and extracted using a data extraction tool designed for this purposed (Additional file 1) based on existing guidelines and other economic evaluation articles[22, 24, 25].

In addition, we will evaluate the main drivers of the costs and cost-effectiveness results based on the findings from sensitivity analyses conducted by the included studies.

## Quality of reporting evidence

We will assess the quality of reporting the economic evidence presented in the selected full economic evaluation studies using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist[26]. For partial economic evaluations, we developed a tool using the relevant criteria in the CHEERS checklist, some modified, and the tools used by previous researchers [27]. Two authors (GR and AH) will use these checklists independently and any discrepancies will be discussed amongst them until a consensus is reached. If discrepancies continue then third author (HHB) will be involved to resolve these. The CHEERS checklist includes 24 items which are divided into five subheadings: title and abstract; introduction; methods; results; and discussion (Additional file 2). The checklist for partial economic evaluations or costing studies is a 16 item checklist with similar sub-headings as the CHEERS (Additional file 3). The quality of reporting of the included papers will be presented using the checklists in both table and graph format to ensure a numerical and visual representation of the quality limitations of the studies.

## Patient and Public Involvement

As this is a protocol for a systematic review, we did not have patient or public involvement throughout the design, recruitment and conduct of this protocol.

## Analysis

### Summarizing Results

Results will be summarized using appropriate tables and figures to ensure a complete and objective account of our findings. We will include a general summary table quantifying the main characteristics of the included studies such as study design (Randomized control trial, before-after, modeling etc.), type of mHealth intervention, time horizon, country income setting, and outcome measure used (refer to Additional file 1). A more detailed account of the outcome measures will be presented and categorized via mHealth intervention type allowing the subdivision and ranking of the cost and cost-effectiveness of different mHealth interventions. To facilitate comparability of the results across countries and years, costs will be converted to 2017 international dollars using purchasing power parity conversion factors for each study setting. To evaluate cost effectiveness, results will also be compared against the World Health Organization's (WHO) cost effectiveness threshold [28], as well as, an alternative threshold by Woods et al.'s [29], using the setting's GDP per capita.

### Addressing Bias

We will critically analyze the results of our review for possible bias. Particularly, we are aware of publication bias; often published studies demonstrate positive results and research demonstrating negative results may be lacking[30]. Additionally, we will exclude studies that are not available in the English language and which are not published in a peer-reviewed journal, therefore, we acknowledge the bias that this may introduce.

### Subgroup Analysis

If sufficient studies are included, we plan on carrying out analysis amongst subgroups. For example, one stratification method will be the subdivision of interventions by mHealth category, such as mobile phone applications or computer-based interventions. Secondly, subdividing the interventions according to their objective, for example, diabetes prevention versus diabetes control, may allow a greater generalizability of results. Other potential sub-analyses we may include is the evaluation of cost and cost-effectiveness results according to the study design (for example, Randomized control trial, modeling), the countries' income level (low, middle or high), or geographical region.

## Discussion

Although there is some evidence on the effectiveness of mHealth interventions in non-communicable disease such as diabetes and cardiology, evidence on cost and cost-effectiveness evidence of these interventions is limited. To the best of our knowledge, this is the first study that will systematically review the cost and cost-effectiveness of mHealth interventions targeting T2DM. Where sufficient data is available, we will also conduct subgroup analyses and explore the main drivers of costs and cost-effectiveness results.

The limitations of our study regard the quality and the heterogeneity of the selected studies. To address these limitations, we will use the CHEERS checklist and a modified CHEERS checklist to evaluate the quality of the all the included cost-effectiveness and costing studies, respectively. We anticipate heterogeneous results and predict limited scope for a meta-analysis, therefore, we will perform a narrative analysis. To contextualize and compare the heterogeneous results, we will convert the results into 2017 international dollars. Another possible limitation of this study, is its susceptibility to publication and small sample biases, which, will be considered when interpreting the results.

## Conclusion

This systematic review will provide evidence to close a significant gap in the literature addressing the costs and cost-effectiveness of mHealth interventions targeted at T2DM. Conclusions will be based upon the results from both full and partial economic evaluations. Summarizing the cost and cost-effectiveness of mhealth interventions will provide useful information for policy makers when designing and implementing these interventions.

## Ethics and Dissemination

No formal ethical review or approval is needed as there will be no primary collection of data involved in this review. The results of this review will be submitted to a peer-reviewed journal for publication. The findings will also be shared at international conferences. This review will address the gap in the literature concentrating on the cost and cost-effectiveness of mHealth interventions for T2DM. We predict that this information will help to influence the decision making surrounding mHealth interventions targeting people at risk of or diagnosed with T2DM.

**Author Contributors:** GR and HHB equally contributed in conception and design of the protocol and preparation of the first draft. GR developed the search strategy. GR and HHB developed the data extraction and quality assessment tool for partial economic evaluation studies. AH reviewed and amended the draft of the protocol. GR, HHB and AH all reviewed and approved of the final version of the manuscript submitted for publication.

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**Competing interests:** None declared.

**Word Count:** 2395

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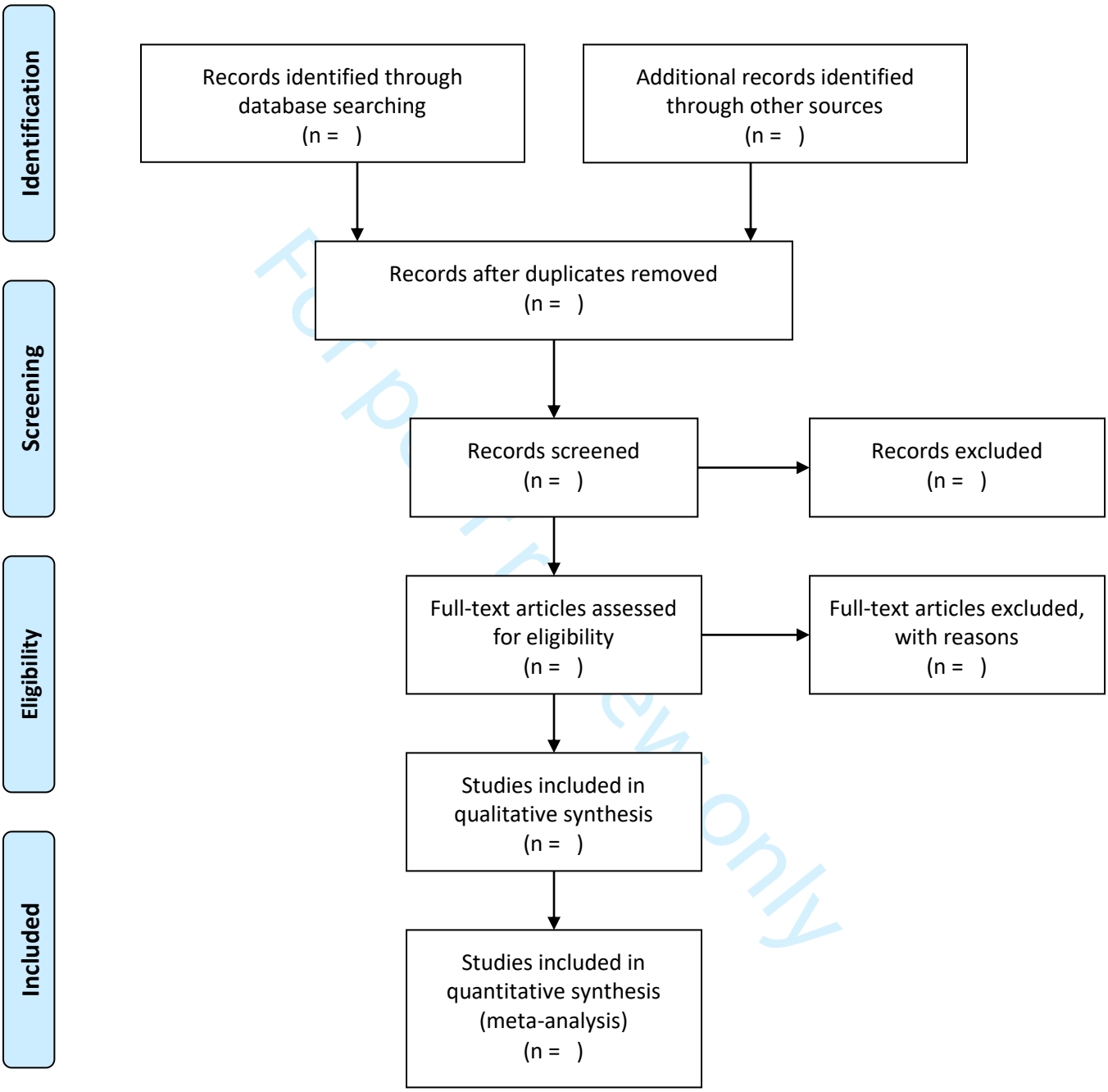
**Figures Legend:**

Figure 1: PRISMA-P Flow chart of the study selection process.

Figure 1: PRISMA Study Selection Flow Chart



Additional file 1: Tool for Extracting General and Economic Characteristics of the Selected Studies

| Paper (Author, Year) | Country | Type of Economic evaluation (CEA, CUA, ..., cost analysis) | Study Design (RTC, modeling etc.) | Perspective | Time Horizon | Outcome measures | Type of sensitivity analysis | Type of interventions (prevention, management etc.) | Description of Intervention | Type of mHealth intervention | Type and source of data used (Primary, secondary, mix) | Sample Size | Results |
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# Additional file 2: CHEERS checklist for assessing quality of reporting full economic evaluation studies

| Section/item | | Item no. | Recommendation | Yes | No | Partialy | N/A |
|---|---|---|---|---|---|---|---|
| Title and abstract | Title | 1 | Identify the study as an economic evaluation, or use more specific terms such as ''cost-effectiveness analysis'' and describe the interventions compared. | | | | |
| | Abstract | 2 | Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analyses), and conclusions. | | | | |
| Introduction | Background and objectives | 3a | Provide an explicit statement of the broader context for the study. | | | | |
| | | 3b | Present the study question and its relevance for health policy or practice decisions. | | | | |
| Methods | Target population and subgroups | 4 | Describe characteristics of the base-case population and subgroups analyzed including why they were chosen. | | | | |
| | Setting and location | 5 | State relevant aspects of the system(s) in which the decision(s) need(s) to be made. | | | | |
| | Study perspective | 6 | Describe the perspective of the study and relate this to the costs being evaluated. | | | | |
| | Comparators | 7 | Describe the interventions or strategies being compared and state why they were chosen. | | | | |
| | Time horizon | 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate. | | | | |
| | Discount rate | 9 | Report the choice of discount rate(s) used for costs and outcomes and say why appropriate. | | | | |
| | Choice of health outcomes | 10 | Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed. | | | | |
| | Measurement of effectiveness | 11 a) | Single study–based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. | | | | |
| | | 11 b) | Synthesis-based estimates: Describe fully the methods used for the identification of included studies and synthesis of clinical effectiveness data. | | | | |
| | Measurement and valuation of preference based outcomes | 12 | If applicable, describe the population and methods used to elicit preferences for outcomes. | | | | |
| | Estimating resources and costs | 13 a) | Single study–based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | 13 b | Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | | | | |
| | Currency, price date, and conversion | 14 | Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate. | | | | |
| | Choice of model | 15 | Describe and give reasons for the specific type of decision-analytic model used. Providing a figure to show model structure is strongly recommended. | | | | |
| | Assumptions | 16 | Describe all structural or other assumptions underpinning the decision-analytic model. | | | | |
| | Analytical methods | 17 | Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (e.g., half-cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty. | | | | |
| Results | Study parameters | 18 | Report the values, ranges, references, and if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended. | | | | |
| | Incremental costs and outcomes | 19 | For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios. | | | | |
| | Characterising uncertainty | 20 a | Single study–based economic evaluation: Describe the effects of sampling uncertainty for estimated incremental cost, incremental effectiveness, and incremental cost-effectiveness, together with the impact of methodological assumptions (such as discount rate, study perspective). | | | | |
| | | 20 b | Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. | | | | |
| | Characterising heterogeneity | 21 | If applicable, report differences in costs, outcomes, or cost- effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information. | | | | |
| Discussion | Study findings, limitations, generalisability, and current knowledge | 22 | Summarize key study findings and describe how they support the conclusions reached. Discuss limitations and the generalizability of the findings and how the findings fit with current knowledge | | | | |
| Other | Source of funding | 23 | Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other nonmonetary sources of support. | | | | |
| | Conflicts of interest | 24 | Describe any potential for conflict of interest among study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors' recommendations. | | | | |

Additional file 3: Modified CHEERS Checklist to assess the quality of reporting cost in partial economic evaluations

| | Section | Item Number | Criteria | Yes | No | Partly | N/A |
|---|---|---|---|---|---|---|---|
| Title and abstract | Title | 1 | Identify the study as an economic evaluation, or costing study and describe the intervention evaluated. | | | | |
| | Abstract | 2 | Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base-case and uncertainty analyses), and conclusions. | | | | |
| Introduction | Background and objectives | 3 | Provide an explicit statement of the broader context for the study.<br>Present the study question and its relevance for health policy or practice decisions. | | | | |
| Methods | Target population and subgroups | 4 | Describe characteristics of the base-case population and subgroups analysed including why they were chosen | | | | |
| | Setting and location | 5 | State relevant aspects of the system(s) in which the decision(s) need(s) to be made. | | | | |
| | Study perspective | 6 | Describe the perspective of the study and relate this to the costs being evaluated | | | | |
| | Time horizon | 7 | State the time horizon(s) over which costs are being evaluated and say why appropriate. | | | | |
| | Discount rate | 8 | Report the choice of discount rate(s) used for costs and say why appropriate. | | | | |
| | Estimating resources and costs | 9 | Describe approaches used to estimate resource use associated with the intervention. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | Currency, price date, and conversion | 10 | Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate. | | | | |
| | Analytical Methods | 11 | Describe all analytic methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments to a model; & methods for handling population heterogeneity and uncertainty. | | | | |
| Results | Presenting the costs | 12a | Provide detailed breakdown of costs incurred to develop and implement the intervention. | | | | |
| | | 12b | Express costs per person or beneficiaries covered by the intervention. | | | | |
| | Characterising uncertainty | 13 | Describe the effects of sampling uncertainty for estimated cost, together with the impact of methodological assumptions (such as discount rate, study perspective). | | | | |
| Discussion | Study findings, limitations, generalisability, and current knowledge | 14 | Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge. | | | | |
| Other | Funding | 15 | Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support. | | | | |
| | Conflicts of Interest | 16 | Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations. | | | | |

# 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-P reporting 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 |
|---|---|---|---|
| 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 | n/a |
| | #2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | n/a |
| 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 | 1 |
| | #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 | n/a |
| Sources | #5a | Indicate sources of financial or other support for the review | 9 |

| | | | |
|---|---|---|---|
| Sponsor | #5b | Provide name for the review funder and / or sponsor | n/a |
| Role of sponsor or funder | #5c | Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol | n/a |
| Rationale | #6 | Describe the rationale for the review in the context of what is already known | 4 |
| Objectives | #7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | 4 |
| 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 | 5 |
| 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 |
| 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 | 6 |
| 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 |
| 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 | 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 | 8 |
| Outcomes and prioritization | #13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | 9 |
| 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 | 9 |

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|---|---|---|---|
| | | level, or both; state how this information will be used in data synthesis | |
| Data synthesis | #15a | Describe criteria under which study data will be quantitatively synthesised | 9 |
| | #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) | n/a |
| | #15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | 9 |
| | #15d | If quantitative synthesis is not appropriate, describe the type of summary planned | 9 |
| Meta-bias(es) | #16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | n/a |
| Confidence in cumulative evidence | #17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | 8 |