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Economic evaluations of scaling up strategies of evidence-based HEALTH interventions: a systematic review Protocol

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ECONOMIC EVALUATIONS OF SCALING UP STRATEGIES OF EVIDENCE-BASED HEALTH INTERVENTIONS: A SYSTEMATIC REVIEW PROTOCOL

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Economic evaluations of scaling up strategies of evidence-based health interventions: a systematic review protocol

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Economic evaluations of scaling up strategies of evidence-based health interventions: a systematic review protocol

ABSTRACT

Introduction: Scaling up strategies can help roll out evidence-based health interventions on a wide scale to benefit more individuals. Yet, little is known on how to evaluate economic aspects of these strategies. We seek then to identify and describe the methods and issues related to economic evaluations assessing scaling up strategies of evidence-based health interventions.

Methods and analysis: Using the Joanna Briggs Institute guidance on systematic reviews, we will conduct a systematic review of characteristics and methods applied in economic evaluations in scaling up science. To be eligible for inclusion, studies must include a scaling up strategy of an evidence-based health intervention delivered and received by any individual or organization in any country and setting. They must report costs and cost-effectiveness outcomes. We will consider full or partial economic evaluations, modelling, and methodological studies. We searched peer-reviewed publications in Medline, Web of Science, Embase, Cochrane Library Database, PEDE, EconLIT, INHATA from their inception onwards. We will search grey literature from international organizations, bilateral agencies, nongovernmental organizations, consultancy firms websites and region-specific databases. Two independent reviewers will screen the records against the eligibility criteria and extract data using a pretested extraction form. We will extract data on study characteristics, scaling up strategies, economic evaluation methods and their components. We will appraise the methodological quality of included studies using the BMJ Checklist. We will narratively summarize the studies' descriptive characteristics, methodological strengths/weaknesses, and the main drivers of cost-effectiveness outcomes. This study will help identify what are the trade-offs of scaling up evidence-based interventions to allocate resources efficiently.

Ethics and dissemination: No ethics approval is required as no primary data will be collected. The results will be published in a peer-reviewed, international journal and presented at national and international conferences.

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Economic evaluations of scaling up strategies of evidence-based health interventions: a systematic review protocol

KEYWORDS: Scaling up, Spread, Economic evaluations, Evidence-based health interventions, Systematic review, Protocol

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Economic evaluations of scaling up strategies of evidence-based health interventions: a systematic review protocol

Strengths and limitations of this study

- This systematic review will be the first, to the best of our knowledge, to systematically summarize approaches used for economic evaluations of scaling up strategies of evidence-based interventions in health.
- This review will assess the completeness of reporting practices in economic evaluations of scaling up strategies of evidence-based interventions in health and will identify areas for improvement in the field.
- It is expected that a great heterogeneity of studies will be included due to the different types of evidence-based interventions in health, scaling up strategies, targeted populations, and economic evaluation approaches.
- The review may face some limitations to generalizability due to the highly context-specific nature of cost-effectiveness evaluations.

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Economic evaluations of scaling up strategies of evidence-based health interventions: a systematic review protocol

INTRODUCTION

Researchers, healthcare professionals and decision-makers are increasingly focusing on filling the gap between knowledge and practice. In recent years, growing efforts to bridge this gap have produced a vast body of knowledge on the efficacy and effectiveness of health interventions and their implementation in practice.[1-3] Most of this evidence derives from experimental studies in which interventions are delivered under optimal, or at least "best practice" conditions, generally conducted on relatively small populations and from projects done in given settings. To date, these efforts have produced a wide set of well-documented effective health interventions.[1 2 4 5] However, health decision-makers are still not systematically implementing such evidence to benefit more people on a wider scale.[1 2 4-8] One way to fill this gap is to develop and implement strategies to scale up effective evidence-based interventions in health (EBIs).[7 9]

While both efficacy and effectiveness are key to the roll out of EBIs on a large scale, other factors – such as costs and cost-effectiveness – are central to the successful scale up of EBIs.[8 10-14] As health systems face continuous strains and limited resource availability, economic evaluations can play an important role in informing health decision-makers on the trade-offs in costs health benefits of choosing and defining a scaling up strategy.[10 12 14-21] Economic evaluations are a means to both assess the value for money and inform resource allocation decision-making.[22] To do so, economic evaluations compare alternative choices in terms of both costs and consequences.[22] Alternative choices refer to the different ways in which healthcare resources can be used to improve health. The type of economic evaluations are generally defined by the number of alternatives compared, whether both costs and consequences are examined, and how the consequences are expressed.[22]

Little is known on what these evaluations should include to analyze the cost-effectiveness of scaling up strategies, as the cost-effectiveness of EBIs does not necessarily reflect the cost-effectiveness of the scaling up effort.[8 13 15-19 21 23] While not many, a small number of studies synthesized the costs and cost-effectiveness of scaling up strategies of EBIs in health. Mostly conducted in Low and Middle Income Countries (LMICs), these reviews show that included studies generally focus, among other interventions, on national

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immunization programs,[21 24 25] maternal, infant and children health programs,[20] and HIV/AIDS prevention and care interventions.[16 26] Despite being conducted in specific geographical areas and having a narrow focus on scaling up strategies of certain health interventions, these reviews provide insights into the economic evaluation research production of scaling up strategies. These reviews reveal a great variability among the included economic evaluation studies. When included, these studies vary in perspectives, scope, approaches, assumptions, cost categories, and are often not presented in a way that can be easily comparable and generalized across settings and countries.[19-21 26-28]

Oftentimes, the lack of complete availability of scaling up cost data or the use of models leads economic analysts to rely on assumptions that may not reflect the complexity of implementing scaling up strategies.[8 16-19 21 26 29 30] For example, economic evaluations may posit that scaling-up implementation costs are a fixed part of the intervention costs.[19 30 31] In reality, scaling up strategies may present additional costs to that of the intervention that can greatly vary across interventions and settings, potentially leading to both economies and/or diseconomies of scale.[29] Costs and cost-effectiveness estimates may change according to the type of intervention being expanded, the size of the targeted population, the prevalence/incidence of the disease, the relevant efficacy level of the intervention, the geography, and the financial resources available and needed.[8 13 15-17 19 29 32] Additionally, costs and estimates related to infrastructure and available human resources can vary based on the different scaling up strategy operationalization and management, the cost impacts of change, including the excess cost of service delivery as uptake changes and the opportunity costs to providers and patients participating in the activities.[8 13 15-17 19 29 32] This variability then results in a wide heterogeneity of studies and approaches when it comes to economically evaluating scaling up strategies. Costs and cost-effectiveness estimates may also vary according to different modelling approaches. For example, ex-ante economic evaluations are often used for informing pre-implementation decision-making using available evidence and modelling to simulate the costs and consequences of alternatives.[15]

We argue then that, little is known on how to evaluate the economic aspects of these strategies to understand what constitutes the trade-offs of scaling up evidence-based interventions to allocate resources efficiently.

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Thus, we seek to identify and describe the methods and issues related to economic evaluations aimed at assessing scaling up strategies of evidence-based interventions (EBIs) in health.

Objectives

Our goals are to:

- Identify and describe which economic evaluations methods are used to assess scaling up strategies of EBIs in health.
- Identify and describe the costs and cost elements adopted in such economic evaluations.
- Identify and describe environmental factors accounted for in such economic evaluations.
- Discuss the strengths and limitations of each approach and explain reasons for variation in the reporting of economic evaluations of scaling up strategies of EBIs in health.

METHODS

Study design

We are conducting a systematic review following Joanna Briggs Institute (JBI) guidance for conducting systematic review of evidence from all (i.e. partial and full) economic evaluations addressing a question(s) about scaling up health intervention strategies' cost-effectiveness.[33 34] We adopted PRISMA-P guidelines for reporting of systematic reviews protocols.[35] (Online supplementary additional file 1). We registered the protocol on Open Science Framework database (registration number osf.io/fsq84).

Eligibility criteria

Studies included in the review must adhere to the eligibility criteria described below following the PICOS as outlined in the PRISMA-P guidelines:[35]

Population: We will include studies in which the population of interest is any individual, organization, or system – directly or indirectly – involved in the delivery or receipt of any health services that was the target of the scale-up.

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Economic evaluations of scaling up strategies of evidence-based health interventions: a systematic review protocol

Intervention: We will include research studies that investigate strategies for scaling up. Included studies must evaluate a scaling up strategy of an EBI (and not the evidence-based health intervention itself). For the purposes of this systematic review, we consider:

- a health intervention to be a health service or a package of health services aimed at improving, maintaining, promoting, or restoring health;[36 37]
- evidence-based interventions (EBIs) in health as health interventions that are effective, efficacious, and ready for dissemination;[38]
- a strategy as one or more initiatives, approaches, or activities that directly aim to change the supply or demand of EBIs in health to improve reach, adoption, and sustainability of an EBI;
- scaling up in healthcare as the "deliberate efforts to increase the impact of successfully tested health interventions so as to benefit more people and to foster policy and program development on a lasting basis." [12 39 40] In other words, scaling up strategies are systematic courses of action that aim to roll out successful local health interventions to regional, national, or international levels to reach broader populations and settings over time.[39 40]

No restrictions will be made on the type of EBI or impact (effectiveness) metric chosen. The scaling up of an EBI can be implemented as a standalone intervention, or as an addition in combination with other interventions.

Comparator: There are no restrictions on the type of comparator. Included studies may report economic evaluations that compare the studied scaling up strategy to current practice (i.e., no scaling up), or to alternative scaling up strategies.

Outcomes: All reported partial or full economic evaluation outcomes are of interest. Outcomes will include measures related to costs and cost-effectiveness. Partial evaluations focused only on costs will include cost outcomes reported as monetary amounts. Full economic evaluations cost-effectiveness outcomes will include incremental cost-effectiveness ratio (ICER), incremental cost-utility ratio (ICUR), net benefit, cost-

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benefit ratio. The metric chosen to report the health gain (effectiveness) used in the economic evaluations will not be an inclusion criterion. It can include (but not restricted to) for instance cost/illness averted, cost/quality-adjusted life year (QALY) gained, or cost/disability-adjusted life year (DALY) averted. All viewpoints/analytic perspectives will be considered with no restrictions. We expect that a variety of outcomes are used in studies to report on the cost-effectiveness of scaling up EBIs. Studies in which only scaling up strategy's effectiveness, adoption, or health gain was reported will not be included.

Study design: Any study design that includes any type of empirical economic evaluation, as well as any modelling and methodological considerations will be included. We will include both full economic evaluation designs, such as cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA), and partial economic evaluation designs, such as cost minimization analysis (CMA), cost comparison/cost analysis, cost outcome descriptions, cost descriptions, and budget impact analysis. Additionally, included modelling studies can be based on a meta-analysis of data from randomised trials or using secondary data from literature and those based on observational studies or analysis of large administrative databases. Both published and unpublished grey literature will be included. We will exclude the following studies: reviews, systematic reviews, qualitative studies, clinical effectiveness studies, critical reviews, editorials, commentaries, abstracts, protocols, academic theses.

Settings: We will review studies independently of the settings, thus, including any healthcare setting (i.e., public health, primary care clinic, hospital, etc.) in both rural and urban areas. We will not restrict the inclusion criteria based on geography. Economic evaluations undertaken within any country context will be included.

Information sources

The information sources include a search of the following electronic bibliographic databases from their inception onwards: Medline, Web of Science, Embase, Cochrane Library Database, PEDE, EconLIT, INHATA. Additionally, since economic evaluation studies are often conducted for the government or by

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government agencies, we will systematically perform an internet search as this has been shown to regularly capture eligible studies not identified by other databases.[25] We will perform an extensive search strategy using free text, with no restrictions on date and year of publication. A search of web pages of international organizations, bilateral agencies, nongovernmental organizations (NGOs), and consultancy firms involved in the delivery, funding or evaluation of scaling up EBIs. Reports found to have a matching publication in the published literature will be excluded. We will search the following Internet search databases and data sources: Google, Google Scholar, INESSS (Institut national d'excellence en santé et en services sociaux), OpenGrey, Grey Literature Report, GreyNet, Canadian Evaluation Society, EuroScan, databases included in the "Grey Matters – A Practical Deep web Search Tool for Evidence based Medicine" (CADTH) Checklist, and region-specific databases (African Index Medicus, Eastern Mediterranean Literature (WHO), Index Medicus for South-East Asia Region, LILACS for Latin America). We will then conduct a webpage search of following organizations/agency/governmental websites: UNICEF, World Health Organization, GAVI Alliance, Program for Appropriate Technology in Health (PATH), Johns Hopkins School of Public Health, World Bank, Global Affairs Canada, UK Department for International Development, and United States Agency for International Development.

The search will include a combination of the following three concepts: 1) scaling up, 2) intervention, and 3) cost-effectiveness analysis basic terms: (scaling up OR uptake) AND (intervention OR innovation) AND (cost OR cost-effectiveness OR cost benefit analysis OR cost-utility analysis). No language restrictions will be applied.

Search strategy

Our information specialist (NR) developed a Medline strategy with input from the project team. An iterative process of revision was conducted by the members of the research team. Comments will be integrated for a final version of the search strategy. This final version was approved by the team members. Once validated, the information specialist (NR) translated this search strategy for each electronic database mentioned above. The present protocol only includes the search strategy conducted in Medline on October, 14th 2020 (see

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online supplementary file 2). A hand search will also be performed, and citations and bibliographies of included primary studies and relevant literature reviews will be reviewed for additional relevant articles.

Study records

Data management

In this ongoing study, we exported all citations identified from the electronic databases into Endnote X9 (citation manager software). We used EndNote X9 to remove duplicates in addition to manual checking to identify unique citations for the study selection process. Unique records were then exported into Covidence (internet-based screening and data extraction tool).

Selection process

All stages of the selection process will be performed independently by two reviewers. One reviewer (FB) developed and tested (after team validation) together with the second reviewer a pilot screening form against the eligibility criteria on a 7.5% random sample of the retrieved citations (title and abstracts) to validate the process of inclusion of articles in the review. This piloting stage ensured reviewers shared a common understanding of the eligibility criteria. At the title and abstract stage, the reviewers will independently screen the titles and abstracts with regard to the inclusion/exclusion criteria using Covidence. Studies not fulfilling the eligibility criteria will be excluded, and the full texts of the remaining studies will be retrieved for further assessment. Articles with abstracts that do not appear to meet the criteria for exclusion or are ambiguous, or that have a missing abstract, will be retained and reviewed in full. The full text of retained studies will be independently assessed for exclusion against inclusion/exclusion criteria by both reviewers. To resolve eligibility questions, we will contact the authors of the included studies to seek additional information. Discrepancies between reviewers will be solved through discussion, and – if needed – a consultation with a third reviewer. Any reasons for exclusion will be recorded in Covidence at the full text

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stage. The results of the identification, screening and inclusion process will be displayed using the PRISMA flowchart.[35]

Data collection process

A standardized data extraction template form will be piloted in duplicate by the reviewers. The extraction form will be informed by the study objectives, eligibility criteria and the JBI-ACTUARI tool.[33] This template form will allow to extract from each study information on the key characteristics, the results for the outcomes of interest, and the author conclusions.[34] The form will be tested on a 10% random sample of the included studies for data collection. This pilot test will help to identify extraction items that are missing from the template, or likely to be confusing or unnecessary. Authors' consensus will be required before the form can be modified if deemed appropriate. The investigators will use the finalized revised and agreed upon version of the data extraction form to extract data independently.

Data items

The data extracted will cover: firstly descriptive data about (i) the study general characteristics (e.g., title, short name, corresponding author name, funding source, conflict of interest), study type (published or grey literature), study population/participants, type of scaled up intervention and authors' description of intervention (including whether it was a standalone intervention or a combination of interventions), type of scaling up strategy (including scaling up level of implementation) and authors' description of strategy, its comparator(s) and outcomes; (ii) study methods including evaluation design type, analytic viewpoint(s), prices and currency used for costing, time period of analysis; sensitivity testing; source of effectiveness data, measures of resource use, cost and health effect/clinical and cost effectiveness; (iii) study context (geographical, healthcare and broader service delivery setting); secondly reported results for the resource use and/or cost and/or cost effectiveness measures; thirdly, when possible author conclusions about factors that promote and limit the cost-effectiveness of scaling up EBIs strategies.

Quality appraisal

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There is still no consensus among health economic experts on which guidelines to follow when conducting systematic reviews of economic evaluations.[41-44] We will be using Drummond and Jefferson checklist, also known as the British medical journal (BMJ) checklist, as it was designed for full economic evaluations but also applicable to partial economic evaluations, report and commentaries on economic evaluations, thus aligned to our broad inclusion criteria.[45] The BMJ tool is a Yes/No, thirty-five items checklist organized in three sections: study design, data collection, and analysis and interpretation of results.[45] If items are not applicable to a specific study, a "not appropriate" (NA) response can be stated. Critical appraisal will be undertaken independently by two individuals. If any disagreements arise, they will be discussed between the two reviewers and if need be resolved by team consensus or by a third reviewer.

Data synthesis

We will use descriptive structured narratives, statistics, and tables to identify and summarize the key features of the included economic evaluations of scaling-up strategies and the elements considered in such evaluations. Narrative synthesis will be used to summarize the methods, highlighting important characteristics of the studies when relevant, focusing on differences/similarities and methodological weaknesses, and where possible identifying the main drivers of cost-effectiveness outcomes. In particular, the synthesis will focus on:

- The assumed key theoretical trade-offs (between levels and types of resources, and levels and types of outcome) of scaling up strategies used in the included economic evaluations.
- The level and configuration of scaling up resources examined in the economic evaluations, how they are related to the levels and types of outcomes observed, and the contextual/environmental factors accounted for in these relationships.
- The conclusions regarding the relationship between the cost-effectiveness of the scaling up strategy under examination and the economic evaluation approach.
- Strengths and weaknesses of each approach for evaluating scaling up strategies of EBIs.

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We expect to include a plurality of economic evaluation studies assessing scaling up strategies of EBIs with diverse interventions, populations, and settings, thus we anticipate that there will be heterogeneity making difficult to perform a meta-analysis with interpretable results.

Patient and Public Involvement

Patients and the public were not involved in the design of this study.

DISCUSSION

The identification and description of the methods and issues related to the economic evaluations for the scaling up strategies of EBIs in health will help understand what constitutes the trade-offs of scaling up evidence-based interventions to allocate resources efficiently. It will contribute to both health economic evaluation research in scaling science and its implementation in policy and practice. Large-scale health intervention implementation warrants governmental investment, this will also require demonstrable benefits for the patients, providers, and society at large. As our world is currently hitting rock bottom by an unseen pandemic – i.e., Covid-19 – healthcare systems are in more need than ever to understand how to best reduce waste [46] and increase the roll out of what has more benefits than harms at the lowest cost. If deliberate efforts are not taken to efficiently allocate resources on a wide scale, healthcare systems will collapse.

To the best of our knowledge, this will be the first review that will systematically outline and summarize different economic evaluation approaches used in scaling up strategies of EBIs in health. The science of scale is young and has been too often either completely undermined or clustered with that of sustainability.[47] This study will offer a valuable picture of the advancements and gaps in the application of economic evaluation methods in the scaling up science arena. Earlier reviews of economic evaluations considering scaling up strategies were narrower and focused only on scaling up strategies of specific health interventions. This study can help guide future research aimed at defining costing tools and models that can be easily used in scaling up frameworks and plans. It will contribute to define the nature and selection of costs that are integral to the successful roll out of EBIs on large scale, as well as the benefits and

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disadvantages of each economic methodological approaches aimed at evaluating strategies identified in the literature. As scaling up science is becoming an increasingly relevant area for research, policy, and practice, improving the standardized reporting of costs and coverage data across studies will advance the quantity and quality of the information extractable from the evidence to inform both research and practice. We believe this review will then offer opportunities for improvement in the quality, production, reporting, and application of health economic evaluative methods to scaling up strategies.

Second, we hope that this work will support the use of economic evaluations in policies that aim to successfully implement EBIs on a large scale. While health economic evaluations are a well-established component of health technology assessments, their use in implementation science, and in particular scaling up science, remains limited.[15 32] Yet, unless there are sufficient resources, not all possible scaling up strategies can be implemented. Health decision-makers need to have a clear, evidence-based understanding of the financial implications of scaling up EBIs to make an informed choice to use resources efficiently. Without systematically examining and reporting cost and cost-effectiveness evidence the allocation of financial resources to scaling up strategies may be too high or too low. Economic evidence is then crucial for decision makers to design scaling up strategies that are affordable and that represent an efficient use of current available resources.

We plan to use passive and active dissemination strategies to disseminate our findings. First, we will publish this study's protocol and later the results of this project in leading peer-reviewed journals in health implementation and services research. We will also share our findings at local, national, and international conferences addressing audiences interested in implementation science, scaling science, and health economics. Second, findings from this project will be relevant for health administrators, decision-makers, health professionals and patients. To reach these audiences, we will use our networks with health organizations and health research groups (such as the Quebec Strategy for Patient-Oriented Research (SPOR) Unit). We will tailor the dissemination message to fit each audience and select champions to

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disseminate our results. Finally, we will use different communication channels, such as newsletters, organization websites, and webinars, to reach all relevant audiences.

Since our research project is a systematic review based on existing primary studies and methodological papers, it will not be necessary to request ethics approval.

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Author contributions: Members of the executive committee (FB, ML, HTVZ, AG, NR, and FR) contributed to the conception and design. FB drafted the protocol. All authors provided a critical review of the protocol and subsequent versions. All authors read and approved the final protocol.

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Competing interests statement: None to declare.

Abbreviations: EBIs: evidence-based interventions; LMICs: Low and Middle Income Countries; JBI: Joanna Briggs Institute; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols; CINHAL: Cumulative Index to Nursing and Allied Health Literature; EMBASE: Excerpta Medica dataBASE; MEDLINE: Medical Literature Analysis and Retrieval System Online; PEDE: Paediatric Economic Database Evaluation; INHATA: International Network of Agencies for Health Technology Assessment; INESSS: Institut national d'excellence en santé et en services sociaux; CADTH:

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Canadian Agency for |Drugs and Technologies in Health; LILACS: Literatura Latino-Americana e do Caribe em Ciências da Saúde; PICOS: Population, Intervention, Comparison, Outcomes, Study design; ICER: incremental cost-effectiveness ratio; ICUR: incremental cost-utility ratio; QALY: quality-adjusted life year; DALY: disability-adjusted life year; CEA: cost-effectiveness analysis; CUA: cost-utility analysis; CBA: cost-benefit analysis; CMA: cost minimization analysis; ACTUARI: Analysis of Cost, Technology and Utilisation Assessment and Review Instrument.

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
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	☐	☐	N.a.
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	Open Access Framework. Registration number osf.io/fsq84
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	10
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	☐	☐	N.a.
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/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

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Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
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 (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	5-6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	6-7
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	☒	☐	7, Supplementary file 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	7
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	7
Data collection process	11c	Describe planned method of extracting data from reports (e.g., 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 (e.g., 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	☐	☐	N.a.
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	8
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☐	N.a.
	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 (e.g., I^2, Kendall's tau)	☐	☐	N.a.

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Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☐	N.a.
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	Descriptive structured narratives and descriptive statistics of key features of included economic evaluations 8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., 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 (e.g., GRADE)	☐	☒	N.a.

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Table. 1 - Search strategy in Ovid MEDLINE

Medline-Ovid (2020-10-14)

Concepts	Search strategy keywords	Search
Scaling (Controlled Vocabulary)	"diffusion of innovation"/ or Organizational Innovation/	#1
Scaling (Free text)	("scal* up" or "scal* out").ab,kf,kw,ti.	#2
	(("scaling" or widespread or spread? or spreading or "rolling out" or "roll out" or "rolls out" or "rolled out" or upscaling or scalability or scalable) adj5 (innovation? or intervention? or technolog* or practice* or care or initiative* or program* or product? or therap* or service* or strateg* or change? or proces*)).ab,kf,kw,ti.	#3
	((bring* or brought or taking or take* or increas* or going or implement* or econom*) adj5 scal* adj5 (innovation? or intervention? or technolog* or practice* or care or initiative* or program* or product? or therap* or service* or strateg* or change? or proces*)).ab,kf,kw,ti.	#4
Scaling (Free text)	2 or 3 or 4	#5
Scaling	1 or 5	#6
Economic Evaluation (Controlled Vocabulary)	"costs and cost analysis"/ or cost-benefit analysis/ or Economics, Dental/ or exp Economics, Hospital/ or Economics, Medical/ or Economics, Nursing/ or Economics, Pharmaceutical/	#7
Economic Evaluation (Free text)	("cost analysis" or "cost-benefit*" or "cost comparison*" or (cost* adj2 description*) or "cost-effective*" or "cost estimat*" or "cost minimization" or "cost-utility" or "Economic analys*" or "Economic evaluation*" or "net benefit*" or overhead or (value adj3 money)).ab,kf,kw,ti.	#8
Economic Evaluation	7 or 8	#9
Scaling AND Economic Evaluation	6 and 9	#10
Scaling AND Economic Evaluation	Organizational Innovation/ec [Economics]	#11
Total Result	10 or 11	#12
Filter for abstract comment, editorial, protocol,	academic dissertation/ or clinical conference/ or clinical trial protocol/ or comment/ or editorial/ or meeting abstract/	#13

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Concepts	Search strategy keywords	Search
theses (Controlled Vocabulary)		
Filter for abstract comment, editorial, protocol, theses (Free text)	("clinical conference*" or comment* or congress* or "consensus development conference*" or editorial or "english abstract*" or lecture*).pt.	#14
	(Comment* or editorial or Protocol).ti.	#15
Filter for abstract comment, editorial, protocol, theses	13 or 14 or 15	#16
Without the filter for abstract comment, editorial, protocol, theses	12 not 16	#17
Filter for Review (Controlled Vocabulary)	META-ANALYSIS/	#18
Filter for Review (Free text)	("systematic review*" or "overview review*" or "literature review*" or "scoping review*" or meta-analy* or metaanaly* or meta-synthesis or metasynthesis or ((research or literature) adj3 synthesis)).ti.	#19
	(cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab.	#20
	("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn.	#21
	((review* or "Meta Analysis" or guideline* or "practice guideline*" or "systematic review*") not "Book review").pt.	#22
	19 or 20 or 21 or 22	#23
Filter for review	18 or 23	#24
Without the filter for review	17 not 24	#25

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BMJ Open

Economic evaluations of scaling up strategies of evidence-based HEALTH interventions: a systematic review Protocol

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Primary Subject Heading:	Evidence based practice

Secondary Subject Heading:	Health economics, Health services research
Keywords:	HEALTH ECONOMICS, HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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ECONOMIC EVALUATIONS OF SCALING UP STRATEGIES OF EVIDENCE-BASED HEALTH INTERVENTIONS: A SYSTEMATIC REVIEW PROTOCOL

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Economic evaluations of scaling up strategies of evidence-based health interventions: a systematic review protocol

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Word count: 3944 words

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Economic evaluations of scaling up strategies of evidence-based health interventions: a systematic review protocol

ABSTRACT

Introduction: Scaling science aims to help roll out evidence-based research results on a wide scale to benefit more individuals. Yet, little is known on how to evaluate economic aspects of scaling up strategies of evidence-based health interventions.

Methods and analysis: Using the Joanna Briggs Institute guidance on systematic reviews, we will conduct a systematic review of characteristics and methods applied in economic evaluations in scaling up strategies. To be eligible for inclusion, studies must include a scaling up strategy of an evidence-based health intervention delivered and received by any individual or organization in any country and setting. They must report costs and cost-effectiveness outcomes. We will consider full or partial economic evaluations, modelling, and methodological studies. We searched peer-reviewed publications in Medline, Web of Science, Embase, Cochrane Library Database, PEDE, EconLIT, INHATA from their inception onwards. We will search grey literature from international organizations, bilateral agencies, nongovernmental organizations, consultancy firms websites and region-specific databases. Two independent reviewers will screen the records against the eligibility criteria and extract data using a pretested extraction form. We will extract data on study characteristics, scaling up strategies, economic evaluation methods and their components. We will appraise the methodological quality of included studies using the BMJ Checklist. We will narratively summarize the studies' descriptive characteristics, methodological strengths/weaknesses, and the main drivers of cost-effectiveness outcomes. This study will help identify what are the trade-offs of scaling up evidence-based interventions to allocate resources efficiently.

Ethics and dissemination: No ethics approval is required as no primary data will be collected. The results will be published in a peer-reviewed, international journal and presented at national and international conferences.

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Economic evaluations of scaling up strategies of evidence-based health interventions: a systematic review protocol

KEYWORDS: Scaling up, Spread, Economic evaluations, Evidence-based health interventions, Systematic review, Protocol

Open Access Framework registration number osf.io/fsq84

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Economic evaluations of scaling up strategies of evidence-based health interventions: a systematic review protocol

Strengths and limitations of this study

- This is the first systematic review to provide evidence on economic evaluation approaches for the scaling up strategies of evidence-based interventions.
- We plan a strong, rigorous and reproducible methodology for conducting our systematic reviews of economic evaluations.
- We follow the Joanna Briggs Institute guidance for conducting systematic reviews of economic evaluations.
- A comprehensive search strategy will be employed to retrieve both peer-reviewed and grey publications.
- The review may face some limitations to generalizability due to the highly context-specific nature of economic evaluations.

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Economic evaluations of scaling up strategies of evidence-based health interventions: a systematic review protocol

INTRODUCTION

Researchers, healthcare professionals and decision-makers are increasingly focusing on filling the gap between knowledge and practice. In recent years, growing efforts to bridge this gap have produced a vast body of knowledge on the efficacy and effectiveness of health interventions and their implementation in practice.[1-3] Most of this evidence derives from experimental studies in which interventions are delivered under optimal, or at least "best practice" conditions, generally conducted on relatively small populations and from projects done in given settings. To date, these efforts have produced a wide set of well-documented effective health interventions.[1, 2, 4, 5] However, health decision-makers are still not systematically implementing such evidence to benefit more people on a wider scale.[1, 2, 4-8] One way to fill this gap is to develop and implement strategies to scale up effective evidence-based interventions in health (EBIs).[7, 9]

While both efficacy and effectiveness are key to the roll out of EBIs on a large scale, other factors – such as costs and cost-effectiveness – are central to the successful scale up of EBIs.[8, 10-14] As health systems face continuous strains and limited resource availability, economic evaluations can play an important role in informing health decision-makers on the trade-offs in costs health benefits of choosing and defining a scaling up strategy.[10, 12, 14-21] Economic evaluations are a means to both assess the value for money and inform resource allocation decision-making.[22] To do so, economic evaluations compare alternative choices in terms of both costs and consequences.[22] Alternative choices refer to the different ways in which healthcare resources can be used to improve health. The type of economic evaluations are generally defined by the number of alternatives compared, whether both costs and consequences are examined, and how the consequences are expressed.[22]

Little is known on what these evaluations should include to analyze the cost-effectiveness of scaling up strategies, as the cost-effectiveness of EBIs does not necessarily reflect the cost-effectiveness of the scaling up effort.[8, 13, 15-19, 21, 23] While not many, a small number of studies synthesized the costs and cost-effectiveness of scaling up strategies of EBIs in health. Mostly conducted in Low and Middle Income Countries (LMICs), these reviews show that included studies generally focus, among other interventions,

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on national immunization programs,[21, 24, 25] maternal, infant and children health programs,[20] and HIV/AIDS prevention and care interventions.[16, 26] Despite being conducted in specific geographical areas and having a narrow focus on scaling up strategies of certain health interventions, these reviews provide insights into the economic evaluation research production of scaling up strategies. These reviews reveal a great variability among the included economic evaluation studies. When included, these studies vary in perspectives, scope, approaches, assumptions, cost categories, and are often not presented in a way that can be easily comparable and generalized across settings and countries.[19-21, 26-28]

Oftentimes, the lack of complete availability of scaling up cost data or the use of models leads economic analysts to rely on assumptions that may not reflect the complexity of implementing scaling up strategies.[8, 16-19, 21, 26, 29, 30] For example, economic evaluations of scaling up strategies may posit that scaling up implementation costs are a fixed part of the intervention costs.[19, 30, 31] In reality, scaling up strategies may present additional costs to that of the intervention that can greatly vary across interventions and settings, potentially leading to both economies and/or diseconomies of scale.[29] Costs and cost-effectiveness estimates may change according to the type of intervention being expanded, the size of the targeted population, the prevalence/incidence of the disease, the relevant efficacy level of the intervention, the geography, and the financial resources available and needed.[8, 13, 15-17, 19, 29, 32] Specific to scaling up strategies, costs and estimates related to infrastructure and available human resources can vary based on the different scaling up strategy operationalization and management, the cost impacts of change, including the excess cost of service delivery as uptake changes and the opportunity costs to providers and patients participating in the activities.[8, 13, 15-17, 19, 29, 32] Finally, implementation and scale-up theoretical frameworks – that support thinking and interpretation of "real world" complex data – consider economic constructs in scaling up strategies in different ways. For example, some frameworks consider cost (and resource) mobilisation as a key objective,[33, 34] yet implementation frameworks consider costs as an implementation outcome.[35] Frameworks vary also in the ways they consider potential benefit or effectiveness ('Cost-benefit').[36] This variability then results in a wide heterogeneity of studies and approaches when it comes to economically evaluating scaling

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up strategies. Costs and cost-effectiveness estimates may also vary according to different modelling approaches. For example, ex-ante economic evaluations are often used for informing pre-implementation decision-making using available evidence and modelling to simulate the costs and consequences of alternatives.[15]

We argue then that little is known on how to evaluate the economic aspects of these strategies to understand what constitutes the trade-offs of scaling up evidence-based interventions to allocate resources efficiently. Thus, we seek to identify and describe the methods and issues related to economic evaluations aimed at assessing scaling up strategies of evidence-based interventions (EBIs) in health.

Objectives

Our goals are to:

- Identify and describe which economic evaluations methods are used to assess scaling up strategies of EBIs in health.
- Identify and describe the costs and cost elements adopted in such economic evaluations.
- Identify and describe environmental factors accounted for in such economic evaluations.
- Discuss the strengths and limitations of each approach and explain reasons for variation in the reporting of economic evaluations of scaling up strategies of EBIs in health.

METHODS

Study design

We are conducting a systematic review following Joanna Briggs Institute (JBI) guidance for conducting systematic review of evidence from all (i.e. partial and full) economic evaluations addressing a question(s) about scaling up health intervention strategies' cost-effectiveness.[37, 38] We adopted PRISMA-P guidelines for reporting of systematic reviews protocols.[39] (supplementary additional file 1). We registered the protocol on Open Science Framework database (registration number osf.io/fsq84).

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Eligibility criteria

Studies included in the review must adhere to the eligibility criteria described below following the PICOS as outlined in the PRISMA-P guidelines:[39]

Population: We will include studies in which the population of interest is any individual, organization, or system – directly or indirectly – involved in the delivery or receipt of any health services that was the target of the scale-up.

Intervention: We will include research studies that investigate strategies for scaling up. Included studies must evaluate a scaling up strategy of an EBI (and not the evidence-based health intervention itself). For the purposes of this systematic review, we consider:

- a health intervention to be a health service or a package of health services aimed at improving, maintaining, promoting, or restoring health;[40, 41]
- evidence-based interventions (EBIs) in health as health interventions that are effective, efficacious, and ready for dissemination;[42]
- a strategy as one or more initiatives, approaches, or activities that directly aim to change the supply or demand of EBIs in health to improve reach, adoption, and sustainability of an EBI;
- scaling up in healthcare as the "deliberate efforts to increase the impact of successfully tested health interventions so as to benefit more people and to foster policy and program development on a lasting basis." [12, 34, 43] In other words, scaling up strategies are systematic courses of action that aim to roll out successful local health interventions to regional, national, or international levels to reach broader populations and settings over time.[34, 43]

No restrictions will be made on the type of EBI or impact (effectiveness) metric chosen. The scaling up of an EBI can be implemented as a standalone intervention, or as an addition in combination with other interventions.

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Comparator: There are no restrictions on the type of comparator. Included studies may report economic evaluations that compare the studied scaling up strategy to current practice (i.e., no scaling up), or to alternative scaling up strategies.

Outcomes: All reported partial or full economic evaluation outcomes are of interest. Outcomes will include measures related to costs and cost-effectiveness. Partial evaluations focused only on costs will include cost outcomes reported as monetary amounts. Full economic evaluations cost-effectiveness outcomes will include incremental cost-effectiveness ratio (ICER), incremental cost-utility ratio (ICUR), net benefit, cost-benefit ratio. The metric chosen to report the health gain (effectiveness) used in the economic evaluations will not be an inclusion criterion. It can include (but not restricted to) for instance cost/illness averted, cost/quality-adjusted life year (QALY) gained, or cost/disability-adjusted life year (DALY) averted. All viewpoints/analytic perspectives will be considered with no restrictions. We expect that a variety of outcomes are used in studies to report on the cost-effectiveness of scaling up EBIs. Studies in which only scaling up strategy's effectiveness, adoption, or health gain was reported will not be included.

Study design: Any study design that includes any type of empirical economic evaluation, as well as any modelling and methodological considerations will be included. We will include both full economic evaluation designs, such as cost-effectiveness analysis (CEA), cost-utility analysis (CUA) and cost-benefit analysis (CBA), and partial economic evaluation designs, such as cost minimization analysis (CMA), cost comparison/cost analysis, cost outcome descriptions, cost descriptions, and budget impact analysis. Additionally, included modelling studies can be based on a meta-analysis of data from randomised trials or using secondary data from literature and those based on observational studies or analysis of large administrative databases. Both published and unpublished grey literature will be included. We will exclude the following studies: reviews, systematic reviews, qualitative studies, clinical effectiveness studies, critical reviews, editorials, commentaries, abstracts, protocols, academic theses.

Settings: We will review studies independently of the settings, thus, including any healthcare setting (i.e., public health, primary care clinic, hospital, etc.) in both rural and urban areas. We will not restrict the

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inclusion criteria based on geography. Economic evaluations undertaken within any country context will be included.

Information sources

The information sources include a search of the following electronic bibliographic databases from their inception onwards: Medline, Web of Science, Embase, Cochrane Library Database, PEDE, EconLIT, INHATA. Additionally, since economic evaluation studies are often conducted for the government or by government agencies, we will systematically perform an internet search as this has been shown to regularly capture eligible studies not identified by other databases.[25] We will perform an extensive search strategy using free text, with no restrictions on date and year of publication. A search of web pages of international organizations, bilateral agencies, nongovernmental organizations (NGOs), and consultancy firms involved in the delivery, funding or evaluation of scaling up EBIs. Reports found to have a matching publication in the published literature will be excluded. We will search the following Internet search databases and data sources: Google, Google Scholar, INESSS (Institut national d'excellence en santé et en services sociaux), OpenGrey, Grey Literature Report, GreyNet, Canadian Evaluation Society, EuroScan, databases included in the "Grey Matters – A Practical Deep web Search Tool for Evidence based Medicine" (CADTH) Checklist, and region-specific databases (African Index Medicus, Eastern Mediterranean Literature (WHO), Index Medicus for South-East Asia Region, LILACS for Latin America). We will then conduct a webpage search of following organizations/agency/governmental websites: UNICEF, World Health Organization, GAVI Alliance, Program for Appropriate Technology in Health (PATH), Johns Hopkins School of Public Health, World Bank, Global Affairs Canada, UK Department for International Development, and United States Agency for International Development.

Search strategy

Our information specialist (NR) developed a Medline strategy with input from the project team. An iterative process of revision was conducted by the members of the research team. Comments will be integrated for a

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final version of the search strategy. This final version was approved by the team members. Once validated, the information specialist (NR) translated this search strategy for each electronic database mentioned above. The present protocol only includes the search strategy conducted in Medline on October, 14th 2020 (see supplementary file 2). A hand search will also be performed, and citations and bibliographies of included primary studies and relevant literature reviews will be reviewed for additional relevant articles.

The search will include a combination of the following two concepts: 1) scaling and 3) Economic Evaluation basic terms. No language restrictions will be applied. The search strategy in Ovid Medline is in the Supplementary Materials.

The following sources were used to find the search terms: 1) Previous reviews who used the concept of scaling up [7, 20] and the concept of economic evaluation [20, 21, 44]; 2) The knowledge of the experts of our multidisciplinary team in scaling up 3) The thesaurus of the consulted bibliographic databases. All words and expressions found were tested and evaluated by the information specialist before to be integrated or rejected in the search strategy. The search strategy was commented via an iterative process by the others members of the team for the production of the final version.

The concept Scaling was created for retrieved all the potential expressions for designed the idea of the spreading of an innovation. It is designed to retrieved very used expression like "scaling up", "scale up", "spread of technologies", but also many variations like "widespread adoption of the technology" or "rolling out the model of care". The concept of Economic Evaluation integrated all synonyms like "cost evaluation", "economic analysis" and "net benefit".

Study records

Data management

In this ongoing study, we exported all citations identified from the electronic databases into Endnote X9 (citation manager software). We used EndNote X9 to remove duplicates in addition to manual checking to

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identify unique citations for the study selection process. Unique records were then exported into Covidence (internet-based screening and data extraction tool).

Selection process

All stages of the selection process will be performed independently by two reviewers. One reviewer (FB) developed and tested (after team validation) together with the second reviewer a pilot screening form against the eligibility criteria on a 7.5% random sample of the retrieved citations (title and abstracts) to validate the process of inclusion of articles in the review (see the data extraction codebook form template in the supplementary file 3). This piloting stage ensured reviewers shared a common understanding of the eligibility criteria. At the title and abstract stage, the reviewers will independently screen the titles and abstracts with regard to the inclusion/exclusion criteria using Covidence. Studies not fulfilling the eligibility criteria will be excluded, and the full texts of the remaining studies will be retrieved for further assessment. Articles with abstracts that do not appear to meet the criteria for exclusion or are ambiguous, or that have a missing abstract, will be retained and reviewed in full. The full text of retained studies will be independently assessed for exclusion against inclusion/exclusion criteria by both reviewers. To resolve eligibility questions, we will contact the authors of the included studies to seek additional information. Discrepancies between reviewers will be solved through discussion, and – if needed – a consultation with a third reviewer. Any reasons for exclusion will be recorded in Covidence at the full text stage. The results of the identification, screening and inclusion process will be displayed using the PRISMA flowchart.[39]

Data collection process

A standardized data extraction template form will be piloted in duplicate by the reviewers. The extraction form will be informed by the study objectives, eligibility criteria and the JBI-ACTUARI tool.[37] This template form will allow to extract from each study information on the key characteristics, the results for the outcomes of interest, and the author conclusions.[38] The form will be tested on a 10% random sample of the included studies for data collection. This pilot test will help to identify extraction items that are missing

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from the template, or likely to be confusing or unnecessary. Authors' consensus will be required before the form can be modified if deemed appropriate. The investigators will use the finalized revised and agreed upon version of the data extraction form to extract data independently.

Data items

The data extracted will cover: firstly descriptive data about (i) the study general characteristics (e.g., title, short name, corresponding author name, funding source, conflict of interest), study type (published or grey literature), study population/participants, type of scaled up intervention and authors' description of intervention (including whether it was a standalone intervention or a combination of interventions), type of scaling up strategy (including scaling up level of implementation) and authors' description of strategy, its comparator(s) and outcomes; (ii) study methods including evaluation design type, analytic viewpoint(s), prices and currency used for costing, time period of analysis; sensitivity testing; source of effectiveness data, measures of resource use, cost and health effect/clinical and cost effectiveness; (iii) study context (geographical, healthcare and broader service delivery setting); secondly reported results for the resource use and/or cost and/or cost effectiveness measures; thirdly, when possible author conclusions about factors that promote and limit the cost-effectiveness of scaling up EBIs strategies.

Quality appraisal

There is still no consensus among health economic experts on which guidelines to follow when conducting systematic reviews of economic evaluations.[45-48] We will be using Drummond and Jefferson checklist, also known as the British medical journal (BMJ) checklist, as it was designed for full economic evaluations but also applicable to partial economic evaluations, report and commentaries on economic evaluations, thus aligned to our broad inclusion criteria.[49] The BMJ tool is a Yes/No, thirty-five items checklist organized in three sections: study design, data collection, and analysis and interpretation of results.[49] If items are not applicable to a specific study, a "not appropriate" (NA) response can be stated. Critical appraisal will be

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undertaken independently by two individuals. If any disagreements arise, they will be discussed between the two reviewers and if need be resolved by team consensus or by a third reviewer.

Data synthesis

We will use descriptive structured narratives, statistics, and tables to identify and summarize the key features of the included economic evaluations of scaling-up strategies and the elements considered in such evaluations. Narrative synthesis will be used to summarize the methods, highlighting important characteristics of the studies when relevant, focusing on differences/similarities and methodological weaknesses, and where possible identifying the main drivers of cost-effectiveness outcomes. In particular, the synthesis will focus on:

- The assumed key theoretical trade-offs (between levels and types of resources, and levels and types of outcome) of scaling up strategies used in the included economic evaluations.
- The level and configuration of scaling up resources examined in the economic evaluations, how they are related to the levels and types of outcomes observed, and the contextual/environmental factors accounted for in these relationships.
- The conclusions regarding the relationship between the cost-effectiveness of the scaling up strategy under examination and the economic evaluation approach.
- Strengths and weaknesses of each approach for evaluating scaling up strategies of EBIs.

We expect to include a plurality of economic evaluation studies assessing scaling up strategies of EBIs with diverse interventions, populations, and settings, thus we anticipate that there will be heterogeneity making difficult to perform a meta-analysis with interpretable results. We will explore this heterogeneity by narratively synthesizing the differences, and if possible, the similarities in settings, participants, intervention, comparison and outcomes characteristics across studies. For example, we will perform the data synthesis of economic evaluation methods according to the economic evaluation parameters reported.

Patient and Public Involvement

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Patients and the public were not involved in the design of this study.

DISCUSSION

The identification and description of the methods and issues related to the economic evaluations for the scaling up strategies of EBIs in health will help understand what constitutes the trade-offs of scaling up evidence-based interventions to allocate resources efficiently. It will contribute to both health economic evaluation research in scaling science and its implementation in policy and practice. Large-scale health intervention implementation warrants governmental investment, this will also require demonstrable benefits for the patients, providers, and society at large. As our world is currently hitting rock bottom by an unseen pandemic – i.e., Covid-19 – healthcare systems are in more need than ever to understand how to best reduce waste [50] and increase the roll out of what has more benefits than harms at the lowest cost. If deliberate efforts are not taken to efficiently allocate resources on a wide scale, healthcare systems will collapse.

To the best of our knowledge, this will be the first review that will systematically outline and summarize different economic evaluation approaches used in scaling up strategies of EBIs in health. The science of scale is young and has been too often either completely undermined or clustered with that of sustainability.[51] This study will offer a valuable picture of the advancements and gaps in the application of economic evaluation methods in the scaling science. Earlier reviews of economic evaluations considering scaling up strategies were narrower and focused only on scaling up strategies of specific health interventions. As such, we believe that the findings of this study will point to identify valid recommendations for action for future research and decision-makers. First, this study can help guide future research aimed at defining costing tools and models that can be easily used in scaling up frameworks and plans. It will contribute to define the nature and selection of costs that are integral to the successful roll out of EBIs on large scale, as well as the benefits and disadvantages of each economic methodological approaches aimed at evaluating strategies identified in the literature. Second, as scaling science is becoming an increasingly relevant area for research, policy, and practice, clarifying how underlying methodological assumptions are based on evidence and on the multi-factorial complexity of real-world scaling strategies will advance the quantity and quality of the

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information extractable from the evidence to inform both research and practice.[8] We believe this review will then offer opportunities for improvement in the quality, production, reporting, and application in practice of health economic evaluative methods to scaling up strategies.

Second, we hope that this work will support the use of economic evaluations in policies that aim to successfully implement EBIs on a large scale. While health economic evaluations are a well-established component of health technology assessments, their use in implementation science, and in particular scaling science, remains limited.[15 32] Yet, unless there are sufficient resources, not all possible scaling up strategies can be implemented. Health decision-makers need to have a clear, evidence-based understanding of the financial implications of scaling up EBIs to make an informed choice to use resources efficiently. Without systematically examining and reporting cost and cost-effectiveness evidence the allocation of financial resources to scaling up strategies may be too high or too low. Economic evidence is then crucial for decision makers to design scaling up strategies that are affordable and that represent an efficient use of current available resources.

Ethics and dissemination

Our research project is a systematic review based on existing primary studies and methodological papers and as such it will not be necessary to request ethics approval. Additionally, we follow the Canadian Institute for Health Research (CIHR) *Ethics Guidance for Developing Partnerships with Patients and Researchers* to guide the active dissemination of our findings.[52] As per CIHR guidelines, no ethical approval is required when engaging patients and public for actively disseminating research findings.

We plan to use passive and active dissemination strategies to disseminate our findings. First, we will publish this study's protocol and later the results of this project in leading peer-reviewed journals in health implementation and services research. We will also share our findings at local, national, and international conferences addressing audiences interested in implementation science, scaling science, and health economics. Second, findings from this project will be relevant for health administrators, decision-makers,

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health professionals and patients. To reach these audiences, we will use our networks with health organizations and health research groups (such as the Quebec Strategy for Patient-Oriented Research (SPOR) Unit). We will tailor the dissemination message to fit each audience and select champions to disseminate our results. Finally, we will use different communication channels, such as newsletters, organization websites, and webinars, to reach all relevant audiences.

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Author contributions: FB, ML, HTVZ and FL conceptualized the idea and developed the design for the systematic review. They developed the research questions which were discussed with NR, CBU, JM, AG, ST, and OA and agreed upon by all authors. NR designed the search strategy which was reviewed by all authors. FB, CBU, JM, AG, ST and OA contributed to a preliminary process of article selection, which enabled further clarification of the research question and of eligibility criteria for the studies that would be included. Members of the executive committee (FB, ML, HTVZ, AG, NR, and FR) contributed to the conception and design. FB drafted the initial version of the protocol which was critically revised by ML, HTVZ and FL. A revised version of the protocol was shared with co-authors who all provided a critical review of the protocol. All authors read and approved the final protocol.

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Competing interests statement: None to declare.

Abbreviations: EBIs: evidence-based interventions; LMICs: Low and Middle Income Countries; JBI: Joanna Briggs Institute; PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols; CINHAL: Cumulative Index to Nursing and Allied Health Literature; EMBASE: Excerpta Medica dataBASE; MEDLINE: Medical Literature Analysis and Retrieval System Online; PEDE: Paediatric Economic Database Evaluation; INHATA: International Network of Agencies for Health Technology Assessment; INESSS: Institut national d'excellence en santé et en services sociaux; CADTH: Canadian Agency for |Drugs and Technologies in Health; LILACS: Literatura Latino-Americana e do Caribe em Ciências da Saúde; PICOS: Population, Intervention, Comparison, Outcomes, Study design; ICER: incremental cost-effectiveness ratio; ICUR: incremental cost-utility ratio; QALY: quality-adjusted life year; DALY: disability-adjusted life year; CEA: cost-effectiveness analysis; CUA: cost-utility analysis; CBA: cost-benefit analysis; CMA: cost minimization analysis; ACTUARI: Analysis of Cost, Technology and Utilisation Assessment and Review Instrument.

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Economic evaluations of scaling up strategies of evidence-based health interventions: a systematic review protocol

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PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
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	☐	☐	N.a.
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	Open Access Framework. Registration number osf.io/fsq84
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	10
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	☐	☐	N.a.
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/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

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Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
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 (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	5-6
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	6-7
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	☒	☐	7, Supplementary file 2
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	7
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	7
Data collection process	11c	Describe planned method of extracting data from reports (e.g., 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 (e.g., 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	☐	☐	N.a.
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	8
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☐	☐	N.a.
	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 (e.g., I^2, Kendall's tau)	☐	☐	N.a.

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Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☐	N.a.
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	Descriptive structured narratives and descriptive statistics of key features of included economic evaluations 8-9
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., 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 (e.g., GRADE)	☐	☒	N.a.

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Table. 1 - Search strategy in Ovid MEDLINE

Medline-Ovid (2020-10-14)

Concepts	Search strategy keywords	Search
Scaling (Controlled Vocabulary)	"diffusion of innovation"/ or Organizational Innovation/	#1
Scaling (Free text)	("scal* up" or "scal* out").ab,kf,kw,ti.	#2
	(("scaling" or widespread or spread? or spreading or "rolling out" or "roll out" or "rolls out" or "rolled out" or upscaling or scalability or scalable) adj5 (innovation? or intervention? or technolog* or practice* or care or initiative* or program* or product? or therap* or service* or strateg* or change? or proces*)).ab,kf,kw,ti.	#3
	((bring* or brought or taking or take* or increas* or going or implement* or econom*) adj5 scal* adj5 (innovation? or intervention? or technolog* or practice* or care or initiative* or program* or product? or therap* or service* or strateg* or change? or proces*)).ab,kf,kw,ti.	#4
Scaling (Free text)	2 or 3 or 4	#5
Scaling	1 or 5	#6
Economic Evaluation (Controlled Vocabulary)	"costs and cost analysis"/ or cost-benefit analysis/ or Economics, Dental/ or exp Economics, Hospital/ or Economics, Medical/ or Economics, Nursing/ or Economics, Pharmaceutical/	#7
Economic Evaluation (Free text)	("cost analysis" or "cost-benefit*" or "cost comparison*" or (cost* adj2 description*) or "cost-effective*" or "cost estimat*" or "cost minimization" or "cost-utility" or "Economic analys*" or "Economic evaluation*" or "net benefit*" or overhead or (value adj3 money)).ab,kf,kw,ti.	#8
Economic Evaluation	7 or 8	#9
Scaling AND Economic Evaluation	6 and 9	#10
Scaling AND Economic Evaluation	Organizational Innovation/ec [Economics]	#11
Total Result	10 or 11	#12
Filter for abstract comment, editorial, protocol,	academic dissertation/ or clinical conference/ or clinical trial protocol/ or comment/ or editorial/ or meeting abstract/	#13

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Concepts	Search strategy keywords	Search
theses (Controlled Vocabulary)		
Filter for abstract comment, editorial, protocol, theses (Free text)	("clinical conference*" or comment* or congress* or "consensus development conference*" or editorial or "english abstract*" or lecture*).pt.	#14
	(Comment* or editorial or Protocol).ti.	#15
Filter for abstract comment, editorial, protocol, theses	13 or 14 or 15	#16
Without the filter for abstract comment, editorial, protocol, theses	12 not 16	#17
Filter for Review (Controlled Vocabulary)	META-ANALYSIS/	#18
Filter for Review (Free text)	("systematic review*" or "overview review*" or "literature review*" or "scoping review*" or meta-analy* or metaanaly* or meta-synthesis or metasynthesis or ((research or literature) adj3 synthesis)).ti.	#19
	(cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab.	#20
	("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn.	#21
	((review* or "Meta Analysis" or guideline* or "practice guideline*" or "systematic review*") not "Book review").pt.	#22
	19 or 20 or 21 or 22	#23
Filter for review	18 or 23	#24
Without the filter for review	17 not 24	#25

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Preliminary SCALECONOMICS CODEBOOK

General instructions for codebook:

- Add '**not applicable'**, '**not reported'** and '**unclear**' – for uncertain items that may promote review authors to contact study authors for clarification, especially on data items critical to reach conclusions.

Data extraction variable	Value type	Modality	Description of variable	Comments
Completed by	Text	Free text	Name of person extracting data	State the name of person who has filled out the initial data extraction sheet
What is the reference number of this article?	Numeric	Add reference ID number	Reference number of the record	It will be available in the initial data extraction sheet
General study characteristics				
First Author's last name	Text	Report: First author	It is the family name of the first author	It will be available in the initial data extraction sheet
Publication year	Text	Year	It is the year of paper's publication	It will be available in the initial data extraction sheet
Link to the publication	Text	Add hyperlink	It is the hyperlink for the paper's access	It will be available in the initial data extraction sheet
Sources of funding	Categorical (Drop Down)	Stated Not stated	The name of institute that funded the study was reported or not.	Check in the paper if the name of institute that funded the study was reported or not.
Competing interests	Categorical (Drop Down)	Stated Not stated	The competing interests were stated or not in the paper	Check in the paper if the competing interests were stated or not in the paper
Specify competing interests (if any)	Text	Free text	It is the description of competing interests	Please, report the description of competing interests if available or NOT REPORT if unavailable
Publication type (journal paper, HTA, or other)	Categorical (Drop Down)	Journal HTA report Other	It is a classification of the publication type	Duplicate publications of the same study need to be linked together.

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Data extraction variable	Value type	Modality	Description of variable	Comments
Publication type – Other: free-text	Text	Free text	It is a category other than Journal and HTA report.	Report type (if possible) and source
Does the economic evaluation refer to a published checklist/tool (e.g., CHEERS)?	Multiple choice	No	It is the published checklist was used or not for the study reporting	Please report the information if available or NOT REPORTED if unavailable
		Yes – BMJ		
		Yes – CHEERS		
		Yes – QHEC		
		Yes – CHEC		
		Yes – Phillips		
		Yes – Drummond Ten-Point		
		Yes – Modified Checklist (name)		
		Yes – Other (name)		
		Not reported		
		Unclear		
Other: Name and free-text description of published checklist/tool	Text	Free-text description	If checklist adapted from another checklist, please describe here which checklists they used and how.	Please report the information if available or NOT REPORTED if unavailable
Population characteristics				
Population used for effect/cost data	Multiple choice	Population delivering the intervention	The population of interest can be the population delivering the scaling up strategy (e.g., staff, health care workers, managers); the population of interest can also be the population receiving the intervention (e.g., patients, individuals)	Please, report UNCLEAR if it is not possible to say what population was studied.
		Population receiving the intervention		
		Both		
		Unclear		

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Data extraction variable	Value type	Modality	Description of variable	Comments
Population used for effect/cost data - Other	Text	Free-text description	Population benefiting from evidence-based practice	Please report the information if available or NOT REPORTED if unavailable
Population size, #	Integer	Number of population size	Number of individuals included in the study	Please report or calculate the information if available or NOT REPORTED if unavailable
Population description (free-text)	Text	Free-text description	Description of population from which study participants are drawn.	As reported by authors
Population sex	Numeric	Number of females Not reported	It is the number of females in the study sample	Please, report the number of females or NOT REPORTED if neither available nor calculable
Population age	Numeric	Number with one decimal	It is the mean of age for the study sample	Please, report the age mean if available or NOT REPORTED if neither available nor calculable
Ethnicity	Text	Free-text description	Ethnicity as a demographic factor	Describe as reported in text
%Ethnicity	Numeric	Number of Caucasians	It is the number of Caucasians in the study sample	Please, report the number of Caucasians or NOT REPORTED if neither available nor calculable
Clinical problem	Text	Free-text description	State the area(s) that the intervention targets (e.g., hypertension, oncology, preventive services). (Mark UNCLEAR if information is not available.)	Please report the information if available or NOT REPORTED if unavailable
Characteristics of participating providers: Profession	Text	Free-text description	For example, physicians, nurses, pharmacists, physiotherapists, dentists, psychologists, mixed, etc.	If applicable. If mixed, specify.
Characteristics of participating lay personnel: Profession	Text	Free-text description	For example, lay community workers	If applicable

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Data extraction variable	Value type	Modality	Description of variable	Comments
Characteristics of participating lay personnel: Level of training	Text	Free-text description	It is the description of the training level for the participating lay personnel	If applicable
Characteristics of participating lay personnel: Other	Text	Free-text description	Other characteristics of the lay personnel part of the scaling up intervention	If applicable
Intervention				
Scaling up strategy (free text)	Text	Free-text description	It is the strategy used to scale the evidence-based intervention during the study. A scaling up strategy in healthcare is the "deliberate efforts to increase the impact of successfully tested health interventions so as to benefit more people and to foster policy and program development on a lasting basis." In other words, scaling up strategies are systematic courses of action that aim to roll out successful local health interventions to regional, national, or international levels to reach broader populations and settings over time. When scaling up interventions, most organisations need to adapt. Manage organisational change through processes such as staff retraining, mentoring, leadership development and coaching.	Report the scaling up strategy as reported in text (if available).

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Data extraction variable	Value type	Modality	Description of variable	Comments
Vertical or horizontal scaling up strategy	Multiple choice (Drop down)	Vertical	A vertical approach involves the introduction of an intervention simultaneously across a whole system and results in institutional change through policy, regulation, financing or health systems change.	There are two main approaches to scaling up. These approaches are not mutually exclusive, and a combination of approaches can be used.
		Horizontal	A horizontal approach involves the introduction of an intervention across different sites or groups in a phased manner.	
		Combination	Vertical + Horizontal	
		Unclear		
Vertical or horizontal scaling up strategy: Unclear	Text	Free-text description	Unclear scaling up strategy	Describe the strategy and why unclear
Vertical or horizontal scaling up strategy: Other	Text	Free-text description	Describe other types of scaling up strategies	If applicable.
Level or scope of the scaling up strategy	Multiple choice (Drop down)	National	This item indicates how big the scope of the scaling up strategy.	From a dropdown menu in Excel pick one (or more) of these items based on what is reported in the study.
		Subnational (state/province/municipal)		
		Multiple countries		
		Multiple subnational within single country		
Scaling up of what type of health intervention	Text	As described in record	Health intervention that is being scaled up	Please report the information if available or NOT REPORTED if unavailable
Scaling up of what type of health intervention (free text)	Text	Free-text description	Health intervention that is being scaled up	Please report the information if available or NOT REPORTED if unavailable
Comparator				

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Data extraction variable	Value type	Modality	Description of variable	Comments
Comparator	Categorical (Drop Down)	Current practice (No scale up) Other scaling up strategy/ies	Type of comparator used in the economic evaluations.	Select one.
Comparator - Other	Text	Free-text description	Name & describe the comparator the other types of comparators/alternatives.	Please describe if other types of comparators are included in the study.
Comparator – Rationale for choice of the alternative	Text	Free-text description	The rationale for the choice of the alternative programmes or interventions for comparison should be given.	Please report as in text if applicable.
Settings				
Setting	Text	Free-text description	Healthcare setting (i.e., public health, primary care clinic, hospital, etc.) in both rural and urban areas	Describe the healthcare setting
Country (ies) where study took place	Text	Free-text description	Countries where the study took place	Name the country/ies
Study design				
Type of economic evaluation				
Cost-effectiveness analysis	Dichotomous	Yes/No	CEA is a type of full economic evaluation in which the results are expressed in terms of the incremental cost per measured unit of each outcome (i.e., measures of resource use are valued, usually in monetary terms, but outcomes are not). Comparisons are thus limited to services or treatment options that produce the same outcome,	Please report the information if applicable

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Data extraction variable	Value type	Modality	Description of variable	Comments
			which is measured strictly in one-dimensional, naturally occurring units. Interventions producing the same outcome are compared to assess the extent to which they may be judged favourably from an economic point of view. Cost-effectiveness analyses primarily address decisions relating to technical efficiency	
Cost-utility analysis	Dichotomous	Yes/No	CUA is a type of full economic evaluation in which the results are expressed in terms of the incremental cost per quality-adjusted life-year (QALY) (i.e., measures of resource use are valued in monetary terms and outcomes are valued in terms of QALYs –Quality-adjusted life-years) to allow comparisons of interventions within a given health system, in order to assess the extent to which they may be judged favourably from an economic point of view.	Please report the information if applicable
Cost-benefit analysis	Dichotomous	Yes/No	CBA is a type of full economic evaluation in which measures of both resource use and beneficial (and adverse) effects are valued in commensurate (often monetary) units, so that the costs and benefits of alternative interventions can be directly	Please report the information if applicable

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Data extraction variable	Value type	Modality	Description of variable	Comments
			compared to assess the extent to which interventions may be judged favourably from an economic point of view. Results may be expressed in terms of an incremental cost-benefit ratio or incremental net benefit.	
Cost-minimization	Dichotomous	Yes/No	It is sometimes argued that if the two or more alternatives under consideration achieve the given outcome to the same extent, a cost-minimization analysis (CMA) can be performed. However, it is not appropriate to view CMA as a form of full economic evaluation.	Please report the information if applicable
Cost comparison/cost analysis	Dichotomous	Yes/No	Approach that describes, measures and values resource use (costs) associated with alternative interventions.	Please report the information if applicable
Cost outcome descriptions	Dichotomous	Yes/No	Approach that describes, measures and values resource use (costs) and consequences (outcomes) associated with a single intervention, with no comparison between alternatives.	Please report the information if applicable
Cost descriptions	Dichotomous	Yes/No	Approach that describes, measures and values resource use (costs) associated with a	Please report the information if applicable

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Data extraction variable	Value type	Modality	Description of variable	Comments
			single intervention, with no comparison between alternatives.	
Budget impact analysis	Dichotomous	Yes/No	A BIA addresses the expected changes in the expenditure of a healthcare system after the adoption of a new intervention. A BIA can also be used for budget or resource planning. A BIA can be free standing or part of a comprehensive economic assessment along with a CEA.	Please report the information if applicable
Trial-based	Dichotomous	Yes/No	The use of clinical studies (such as rando ed trials) as vehicles for economic evaluation.	Please report the information if applicable
Model-based	Dichotomous	Yes/No	Economic evaluation using decision analytic models, where data from a number of different sources are brought together.	Please report the information if applicable
Methodological	Dichotomous	Yes/No	We define methodological papers as the presentation and critique of new approaches, changes to existing methods or the discussion of quantitative and data analytic approaches that are relevant to economic evaluation of scaling up strategies.	Overall, methodological papers can: • Outline and review a new analytical approach that has recently been, or has potential to be, applied • Provide a detailed description, using some empirical examples, of the application of a new technique/method (such as, but need not necessarily be, a quantitative technique) • Examine a particular method which might benefit from a methodological

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Data extraction variable	Value type	Modality	Description of variable	Comments
				re-think or a methodological re-think based on its application in a new area of research, trying to address gaps and limitations of the methodology/method itself.
Type of economic evaluation - Other	Text	Free-text description	Other (such a modified approaches).	Please describe.
If the study is model based, what is the model type:	Categorical (Drop Down)	Markov Decision Tree Discrete Event Simulation Microsimulation model Other	Detail any model used (e.g., Markov, Decision Tree, and Discrete Event Simulation).	Please report the information if available
If the study is model based, what is the model type: Other	Text	Free-text description	It is the description of the model type other than Markov, Decision Tree, and Discrete Event Simulation	Please report the information if applicable
Methods				
Perspective – What is the perspective of the analysis?	Multiple choice	Society Health-system Care provider Insurer Hospital Patient Other (describe) Not specified	State the viewpoint of the analysis.	You can select more than one (as reported in the study). If not specified, it can often be guessed when reading the study. Please report "not specified" the information was unavailable
Perspective - other	Text	Free-text description	It is the perspective description other than society, health system, care provider, insurer, hospital and patient	Please, report the information if available. If not present, mark UNCLEAR.

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Data extraction variable	Value type	Modality	Description of variable	Comments
Perspective – Justification	Text	Free-text description	A clear justification should be given for the form(s) of evaluation chosen in relation to the question(s) being addressed.	Please, report the information if available
Time horizon (years & months) - benefits	Integer	Number of years, number of months	State the time horizon for benefits.	Please indicated whether the number is in years/months. Write "Unclear" if not clear from the text.
Time horizon (years & months) - costs	Integer	Number of years, number of months	State the time horizon for costs	Please indicated whether the number is in years/months. Write "Unclear" if not clear from the text.
Costs				
Evidence-based health intervention costs	Text	Free-text description	Provide details about which costs are being reported (e.g., medication costs, transportation)	Add if included
Methods for identifying resource use – clinical (evidence-based intervention)	Text	Free-text description	Describe the methods used to identify resource use (e.g., questionnaire, survey, cost dairies, expert consultation, and formal consensus methods)	Add if included
Assumptions of the measurement of resources – clinical (evidence-based intervention)	Text	Free-text description	Describe all structural or other assumptions underpinning the decision-analytic model.	Describe, for instance, assumptions for the imputation method when incomplete measurement occurred
Scaling up strategy costs	Text	Free-text description	Provide details about which costs are being reported (medication costs, transportation, etc.)	Add if included – this should include the costs related to the implementation of the scaling up strategy
Methods for identifying resource use – scaling up	Text	Free-text description	Provide details of the methods used to identify resource use	

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Data extraction variable	Value type	Modality	Description of variable	Comments
Assumptions of the measurement of resources – scaling up	Text	Free-text description	Describe all structural or other assumptions underpinning the decision-analytic model.	Describe, for instance, assumptions for the imputation method when incomplete measurement occurred
Measurement of costs				
Methods used to calculate unit costs	Text	Free-text description	Describe the methods used to identify relevant unit costs (guidelines, own cost price calculations, and literature). Mark UNCLEAR if missing.	Add if included.
Cost estimation methods	Categorical (Drop Down)	Micro-costing Gross costing Hybrid Other (describe) Not specified	Methods used to estimate costs.	Add if included.
Cost estimation method - other	Text	Free-text description	It is the cost estimation method other than macro-costing, gross costing, hybrid.	Please, report the information if applicable
Valuing costs				
What is the currency?	Text	Free-text description	Currency used in analysis.	Please write the currency used for the analysis, and also whether there was any conversion (indicating the converted currency).
What is the year of pricing?	Integer	Number of pricing year	Year of pricing	Please, report the information if applicable
Health intervention effectiveness outcomes				
Clinical outcomes - health benefits in natural units	Numeric & Text	Free-text description	Specify number and type of natural units such as, for example, life years gained, disability days saved, points of blood pressure reduction, etc.	Add if applicable – Add in the way and measure presented in the study. If possible, when reporting the study outcomes, it is preferred to report the degree of uncertainty; therefore, in addition to reporting the mean (or median), a standard deviation (or range) should be reported.

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Data extraction variable	Value type	Modality	Description of variable	Comments
Clinical outcomes - health benefits in monetary values	Numeric & Text	Free-text description	Specify number of monetary values.	Add if applicable – Add in the way and measure presented in the study. If possible, when reporting the study outcomes, it is preferred to report the degree of uncertainty; therefore, in addition to reporting the mean (or median), a standard deviation (or range) should be reported.
Health utility values - health benefits in utility values	Numeric & text	Free-text description	Add values and utility measure, such as QALYs	If applicable
Patient-level outcomes (in natural units)	Numeric & Text	Free-text description	Add if included – Add in the way and measure presented in the study	If applicable
System-level outcomes (in natural units)	Numeric & Text	Free-text description	Add if included– Add in the way and measure presented in the study	If applicable
Health intervention effectiveness outcomes – Data sources				
Source of effectiveness data of evidence-based health intervention	Multiple choice (Drop Down)	Trials	It is the data source for the effectiveness of evidence-based health intervention	If applicable
		Observational studies		
		Published literature (e.g., systematic reviews)		
		Administrative data		
		Clinical databases		
		Medical records		
		Expert opinion		
		Observations		
		Other		
Source of effectiveness data of evidence-based health intervention – Other	Text	Free-text description	It is the data source other than the ones listed	If applicable
Year range of primary studies	Integer	Number of years	Year range	Add if applicable
Health intervention effectiveness outcomes - measurement				

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Data extraction variable	Value type	Modality	Description of variable	Comments
Methods of measurement of effects	Text	Free-text description	Specify source of effectiveness estimates (e.g., stated WTP, revealed WTP, and conjoint analysis).	If applicable
Methods of valuation of effects	Text	Free-text description	Specify methods of valuation of effects (e.g., indirect or direct measurement).	If applicable
Methods used for the synthesis of clinical effectiveness data - single experimental or nonexperimental study	Text	Free-text description	Describe fully the methods used for the synthesis of clinical effectiveness data	If the economic evaluation is based on a single experimental or non-experimental study with patient-level data → then report: information on methods of selection of the study population; methods of allocation of study subjects; whether intention-to-treat analysis was used; methods for handling missing data; the time horizon over which patients were followed up and assessed; and, where appropriate, methods for handling potential biases introduced from study design, for example, selection biases
Methods used for the synthesis of clinical effectiveness data - Synthesis-based economic evaluation	Text	Free-text description	Describe fully the methods used for the synthesis of clinical effectiveness data	If synthesis-based economic evaluation → Report a reference to the study, and information on the strategy adopted to search and select relevant evidence, as well as information related to potential bias arising from study selection and synthesis methods. In addition, it may require reporting of long-term extrapolation methods.

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Data extraction variable	Value type	Modality	Description of variable	Comments
Scaling strategy effectiveness outcomes				
Scaling up strategies' outcomes	Text	Free-text description	Scaling up strategies' implementation outcomes (see Milat, MacLean, Simons): coverage, acceptability adoption, appropriateness, costs feasibility, fidelity penetration, and sustainability	(**Not exhaustive, please be open to other types of outcomes present in the literature under review**) LIST of POTENTIAL SCLAING UP STRATEGY EFFECTIVENESS OUTCOMES: Acceptability, Adoption, Appropriateness, Feasibility, Fidelity, Penetration, Sustainability, Reach
Scaling up strategies' outcomes - Other	Text	Free-text description	It is the description of scaling up outcome other than the ones listed above	Please report the information if applicable
Scaling strategy effectiveness outcomes – Data sources				
Source of effectiveness data of scaling up strategy	Multiple choice (Drop Down)	Trials	It is the data source for the effectiveness of scaling up strategy	If applicable
		Observational studies		
		Published literature (e.g., systematic reviews)		
		Administrative data		
		Clinical databases		
		Medical records		
		Expert opinion		
		Observations		
		Other		
Source of effectiveness data of scaling up strategy - Other	Text	Free-text description	It is the data source other than the ones listed above.	Please report the information if applicable
Scaling strategy effectiveness outcomes - measurement				
Methods of measurement of effects	Text	Free-text description	Specify source of effectiveness estimates (*whether from one single study or a synthesis)*	Please, report the information if available OR NOT report if unavailable
Methods used for the synthesis of effectiveness data	Text	Free-text description	Specify methods for the synthesis of effectiveness estimates (*This*	Please, report the information if available OR NOT report if unavailable

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Data extraction variable	Value type	Modality	Description of variable	Comments
			one I am not sure how it would look like)	
Analysis				
Statistical methods used	Text	Free-text description	Describe all analytical 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 (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	The analytic strategy should be fully explained as part of the ''Methods'' section of the article
Modeling Methods – PLEASE NOTE: THIS SECTION APPLIES ONLY TO MODELING STUDIES				
Source of data incorporated into the model:	Multiple choice	Data collected alongside a trial	Sources of data used in the model	Please, select all that apply
		Population survey		
		Cohort study		
		Before and after study		
		Expert opinion		
		Other		
If from trial – identification of original study	Text	Free-text description	Study from which participants are drawn, please report	Please, report the information if applicable
If from trial – characteristics of participants in trial	Text	Free-text description	Report number, sex, and mean age of participants included in trial	Please, report the information if applicable
Source of data incorporated into the model - Assumptions made:	Dichotomous	Yes/No	Did the authors make assumptions about the sources of data	Please, report the information if applicable

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Data extraction variable	Value type	Modality	Description of variable	Comments
Source of data incorporated into the model - Assumptions made: If the answer is "Yes"	Text	Free-text description	If assumptions made please specify.	Please, report the information if applicable
Reasons for the specific model used	Text	Free-text description	Report reasons if described.	Please, report the information if applicable
Statistical assumptions	Text	Free-text description	Please specify statistical assumptions used in the model	Please, report the information if applicable
Statistical tests used	Text	Free-text description	Please specify what statistical tests were used in the model	For model-based economic evaluations, authors should describe and report how they estimated parameters, for example, how they transformed transition probabilities between events or health states into functions of age or disease severity.
Results				
Were findings reported as incremental costs?	Dichotomous	Yes/No	Incremental costs refer to the additional costs associated with an intervention in comparison to a specified comparator.	Please, report the information if applicable
Were findings reported as incremental effectiveness?	Dichotomous	Yes/No	Note that the results of such comparisons may be stated either in terms of incremental cost per unit of effect, or in terms of effects per unit of cost (life-years gained per dollar spent).	Please, report the information if applicable
Net costs reported	Numeric	Numeric-value	It is the value reported for the net costs	If added
Net benefits (outcomes) reported	Numeric	Numeric-value	It is the value reported for the net benefits	If added
Cost-benefit ratio	Numeric	Numeric-value	It is the value reported for the cost-benefits	If added
Incremental cost-effectiveness ratios (ICER, ICUR) reported	Numeric	Numeric-value	ICER. ICUR	If added

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Data extraction variable	Value type	Modality	Description of variable	Comments
Confidence intervals (e.g., 95 % CI) of incremental cost-effectiveness ratios (ICER, ICUR) reported	Numeric	Numeric-value	It is the confidence value of economic parameter reported	If added
Category or type of costs included in cost analysis and costs per category/type	Numeric & Text	Free-text description	Cost description of the type or category of cost; please specify (if available) whether the studies includes both (or only) direct and direct costs of the intervention.	Please, report the information if applicable
Results of cost-description studies	Numeric & Text	Free-text description	Description of costs per unit of analysis	Please, report the information if applicable
Results of cost-outcome descriptions	Numeric & Text	Free-text description	Description of costs and outcomes of one intervention (no alternative)	Please, report the information if applicable
Analyses of uncertainty				
Was analysis of uncertainty done?	Dichotomous	Yes/No	Sensitivity analysis is an exploration of the impact on the results of changing the value of one (or more) parameter(s) while keeping the values of all other parameters unchanged.	Please, report the information if applicable
Analyses of uncertainty (e.g., sensitivity analyses) - Type	Text	Free-text description	Describe the type of analyses of uncertainty (e.g., statistical comparison, bootstrapping, sensitivity analysis [one-way, multiway], threshold analysis, analysis of extremes, and best/worst case analysis) and probabilistic sensitivity analysis.	Please, report the information if applicable
Intervention parameters examined in uncertainty analysis	Text	Free-text description	List intervention parameters examined in uncertainty analysis	Please, report the information if applicable

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Data extraction variable	Value type	Modality	Description of variable	Comments
Outcome(s) of analyses of sensitivity analyses [Single study-based economic evaluation]	Text	Free-text description	Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	If applicable. Describe as reported.
Outcome(s) of analyses of sensitivity analyses [Model-based economic evaluation]	Text	Free-text description	Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	If applicable. Describe as reported.
Calibration				
Was a description of the data that the model was calibrated to provided?	Dichotomous	Yes/No	It is the description of the data that the model was calibrated to provide	Please, report the information if applicable
Were details of the data that the model was fit to provided?	Text	Free-text description	Details for the data that the model was fit	Please, report the information if applicable
Was the model calibrated to equilibrium or trends?	Dichotomous	Yes/No	It is to check if the model was calibrated or not	Please, report the information if applicable
What was the model calibration approach	Text	Free-text description	Target-fitting, minimize least squares, Bayesian, etc.	Please, report the information if applicable
What was the model calibrated to	Text	Free-text description	List the data types (disease prevalence in each group, etc.)	Please, report the information if applicable
What parameters were calibrated?	Text	Free-text description	List the parameters that were calibrated (uptake, etc.)	Please, report the information if applicable
Discounting				
Discount rate	Dichotomous	Yes/No	Was discounting performed?	Please, report the information if applicable
Discount rate for costs	Numeric	%	What was the discount rate for the cost(s)?	Please, report the information if applicable

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Data extraction variable	Value type	Modality	Description of variable	Comments
Discount rate for effects	Numeric	%	What was the discount rate for the effect(s)? (i.e., the rate used to account for different timing of costs and effects)	Please, report the information if applicable
Inflation rate	Dichotomous	Yes/No	Was adjustment for inflation performed if unit costs stemmed from different years?	Please, report the information if applicable
Data collection year	Integer	Year	Specify year.	Please, report the information if applicable
Limitations of methodology used for discounting	Text	Free-text description	Report limitations as described in text.	If authors report this.
Authors/ conclusion and interpretations				
Authors' conclusions	Text	Free-text description	As reported	Please, report the information if applicable
Authors' considerations of study limitations	Text	Free-text description	As reported	Please, report the information if applicable
Results compared with those of other economic evaluations	Text	Free-text description	As reported	Please, report the information if applicable

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Table 1.1 Measurement of costs and consequences in economic evaluation

Type of study	Measurement / valuation of costs in both alternatives	Identification of consequences	Measurement/ valuation of consequences
Cost analysis	Monetary units	None	None
Cost-effectiveness analysis	Monetary units	Single effect of interest, common to both alternatives, but achieved to different degrees	Natural units (e.g. life-years gained, disability days saved, points of blood pressure reduction, etc.)
Cost–utility analysis	Monetary units	Single or multiple effects, not necessarily common to both alternatives	Healthy years (typically measured as quality-adjusted life-years)
Cost–benefit analysis	Monetary units	Single or multiple effects, not necessarily common to both alternatives	Monetary units

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Some types of scaling up effectiveness outcomes (this is NOT an exhaustive list, and some items may not be relevant, but these should just work as a conceptual handle):

	Proctor	Milat
Acceptability	Acceptability= perception that an intervention (scaling up strategy) is acceptable, palatable and satisfactory	Milat ties it to reach → meaning the likely reach and acceptability of the intervention for the targeted population
Adoption	Adoption is defined as the intention, initial decision, or action to try or employ an innovation or evidence-based practice. Adoption also may be referred to as ''uptake.''	Adoption is the proportion of settings, practices or organisations that adopt an intervention.
Appropriateness	Appropriateness is the perceived fit, relevance, or compatibility of the innovation or evidence-based practice for a given practice setting, provider, or consumer; and/or perceived fit of the innovation to address a particular issue or problem. The construct ''appropriateness'' is deemed important for its potential to capture some ''pushback'' to implementation efforts, as is seen when providers feel a new program is a ''stretch'' from the mission of the health care setting, or is not consistent with providers' skill set, role, or job expectations.	Milat does not explain this in the context of scaling up but does mention it.
Feasibility	The extent to which a new treatment, or an innovation, can be successfully used or carried out within a given agency or setting	Mentioned by Milat but not explained.
Fidelity	Fidelity is defined as the degree to which an intervention was implemented as it was prescribed in the original protocol or as it was intended by the program developers.	Effects of interventions are likely to be smaller as they are scaled up; therefore, relatively large effect sizes should be demonstrated in the efficacy stage if an acceptable level of effect is to be maintained when interventions are scaled up.4 This reduction in effect is in part because of difficulties maintaining the dose and fidelity of the original intervention in real-world settings. It is rare for interventions to remain unchanged as they are scaled up, because of the need to adapt them to suit the local context and the organisational, financial and human resources available for scaling up.4,6,10 These adaptations may reduce effectiveness, but they can improve acceptability and efficiency, highlighting the importance of measuring intervention effectiveness throughout the scaling up process.
Penetration	Is defined as the integration of a practice within a service setting and its subsystems. (…) Penetration also can be calculated in terms of the	

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	number of providers who deliver a given service or treatment, divided by the total number of providers trained in or expected to deliver the service.	
Sustainability	is defined as the extent to which a newly implemented treatment is maintained or institutionalized within a service setting's ongoing, stable operations	
Reach		Reach refers to the level of individual participation of an intended target population in an intervention.

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