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Implementing a Package of Essential Non-communicable diseases intervention in low- and middle-income countries: A realist review protocol

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Abstract

Introduction: The burden of non-communicable diseases is increasing rapidly, particularly in Low- and Middle-Income Countries (LMIC), accounting for 85% of premature deaths in the region. LMICs have been facing an increasing trend of a double burden of disease (infectious diseases and NCDs) that has led to multiple challenges in prioritising strategies for NCD control amidst limited resources. Evidence indicates that measures such as the World Health Organization's Package of Essential Non-communicable diseases (PEN) interventions can prevent and control non-communicable diseases. However, because of the complexity of such health interventions, there is limited evidence that explains how the intervention works, for whom, and in what context. We aim to unpack the causal mechanisms explaining how, why, for whom and in what context PEN prevents and controls non-communicable diseases.

Methods and analysis: We propose a realist review to understand how, why, for whom, and under what circumstances PEN works or does not work. The review process includes five steps applied iteratively throughout the study: clarification of review scope, searching for evidence, appraising and extracting data, synthesising evidence and drawing conclusions, and disseminating the findings.

Data analysis: Programme theories will be developed using the realist logic for theory formulation – Retroductive Theorising. The Context-Mechanism-Outcome heuristic tool will be used to develop the programme theories. Portions of the reviewed documents describing constructs of context, mechanism and outcomes will be coded inductively and extracted. These extracted constructs will then be linked abductively to formulate Context-Mechanism-Outcome configurations.

Ethics and Dissemination: Formal ethical approval is not required for this review**.** The study findings will be disseminated through publications in peer-reviewed journals, conference presentations, and formal and informal reports. The programme theories generated in this review will be tested and refined in a realist evaluation.

Keywords

Low- and middle-income countries, non-communicable diseases, Package of essential non-communicable diseases intervention, Realist review, Retroductive Theorizing.

Strengths and Limitations of the study

- The realist review approach will provide explanatory evidence to understand the underlying causal mechanisms triggered in different contexts for effective prevention and control of non-communicable diseases in low- and middle-income countries.
- The review will incorporate a wide range of evidence, including academic and grey literature, to understand what works, for whom, and in what circumstances for the Package of Essential Non-communicable diseases interventions to prevent and control non-communicable diseases.
- The findings from this study are expected to provide contextually relevant information to improve the effectiveness of PEN programme implementation and inform policy decisions.
- The study findings will generate plausible explanations about the programme emerging from the literature and develop transferable theories that can inform implementation of the programme in different settings.

Introduction

The burden of non-communicable diseases (NCDs) is increasing, thus emerging as a significant public health issue globally. [1,2] The latest global estimates indicate that 41.1 million deaths occurred due to NCDs, corresponding to 73.4% of all deaths in 2017. Globally, recent patterns of the cause of mortality indicate epidemiological transition with a steady decline in the proportion of deaths due to Communicable, Maternal, Neonatal, and Nutritional (CMNN) causes, while deaths due to NCDs were on the rise. [2] Similarly, most of the NCD-related deaths worldwide were due to Cardiovascular Disease (CVD), cancer, Chronic Obstructive Pulmonary Disease (COPD) and diabetes. [3,4] Among these, 15 million deaths attributed to NCDs were among the productive age group of 30 to 69. More than two-thirds (85%) of premature deaths due to NCDs took place in Low- and Middle-Income Countries (LMICs). [3,4] LMICs are facing an increasing trend of a double burden of disease

(infectious diseases and NCDs) leading to a syndemic, causing multiple challenges in prioritising strategies for NCDs control amidst limited resources. [5,6]

Policy initiatives for prevention and control of non-communicable diseases

Research has shown that a Primary Health Care (PHC) approach as a promising, effective, and cost-effective approach to address NCDs. [7,8,9] Global commitments and prioritisation to address the NCDs issues were initiated by adopting the "Political declaration of the high-level meeting of the General Assembly on the prevention and control of NCDs" in 2011. [10] This initiative marked a turning point in policy initiatives at the national and global levels. [10] The Astana declaration restated the principles of the Alma Ata declaration and recognised the crucial role of the PHC approach in the prevention and control of NCDs and declared its contribution towards achieving Universal Health Coverage (UHC) and Sustainable Development Goals (SDG) 3. [11]

Package of Essential Non-Communicable (PEN) disease

Most of the individuals suffering from NCDs or at risk of developing NCDs need care for longer. [12, 13] In LMICs, where healthcare resources are limited, sustainable, efficient, community-based interventions and referral systems are required to effectively prevent and control NCDs. [14] Recognising the increasing burden of NCDs, especially in the context of LMICs, the World Health Organization (WHO) developed and recommended a Package of Essential Non-communicable (PEN) diseases interventions to prevent and control NCDs. PEN is a technologically operable, cost-effective intervention delivered through primary healthcare facilities targeted for resource-scarce settings. [15]

The success of any policy depends on its rollout approach and the roles and values of the actors in the organisation, influencing the implementation's effectiveness. [16] After the global initiative for the prevention and control of NCDs via the adoption of the political declaration of the high-level meeting of the General Assembly on the prevention and control of NCDs, many countries, especially LMICs, initiated NCDs policy initiatives. They adopted WHO PEN interventions for early screening, detection, prevention, control, and treatment of NCDs at the primary healthcare level. [17] PEN interventions have been implemented in varied settings across the globe, including Myanmar, Nepal, Bhutan, Korea in South Asia and Uzbekistan, Moldova in Central Asia. [14,18–22] However, evidence about the effectiveness of PEN programme implementation is inconclusive. [23] Hence, it is essential to understand how the PEN interventions work, the underlying mechanisms and the contextual

factors that influence the achievement or unsuccess of PEN goals. The realist approach offers the potential to explain the success or failure of complex interventions such as PEN interventions, which is crucial to achieve policy objectives and help unpack implementation challenges at the operational level. [24,25] Our protocol outlines a realist review proposed to formulate programme theories on implementing PEN interventions in LMICs. This review aims to explore how, why, for whom and in what context PEN intervention work or does not work for the prevention and control of NCDs.

Methods

Theory-informed research methods such as realist evaluation and synthesis are increasingly recognised as an appropriate approach to evaluate complex interventions (**Table 1**) so that researchers, policymakers, and practitioners can make sense of complex programmes. [26,27] Because of the complexity of social and health interventions, it has been argued that traditional systematic review is unsuitable for examining these programmes as its focus is to assess the effectiveness of an intervention. [28] Furthermore, systematic review methods assessing intervention effectiveness hold limited capacity to find the answer to how and why interventions are effective. [29] A realist review addresses this challenge and synthesises evidence about the intervention by exploring causal mechanisms that explain why the intervention works in some contexts while not in others. [30] Hence, we propose conducting a realist review of the PEN interventions underpinned by scientific realist and critical realist philosophies of science (**Table 1**).

Table 1. Key concepts

Category	Definition
Complex interventions	Interventions that are multi-faceted and consist of numerous interacting factors that can influence those providing and receiving the services leading to different outcomes. [35,36]
Context	The situations (e.g., individual, organisational, environmental factors) or the relational or dynamic features that influence or modify the mechanisms through which the programme works are likely to facilitate or hinder the programme at multiple levels of the system. [33,37,38]
Mechanism	Refers to causal entities that trigger or generate observable events in specific contexts. It is a combination of resources (e.g., components of an intervention) and responses (e.g. perceptions and attitudes of the participants) which will enable the researcher to understand how the intervention is perceived. [33,39]
Outcomes	Describes the effects of the PEN programme due to a combination of context and mechanism. [33]

Context-mechanism-outcome (CMO) configuration	CMO configurations represent causal explanations of how underlying mechanisms are triggered by contextual factors leading to specific outcomes. [33]
Programme theory	Theories that explain how the mechanisms introduced in previous context generate outcomes. [23,40]
Abduction	A process that begins with an incomplete set of observations that proceeds towards obtaining the most approximate explanation of those observations/events, driven by the researcher's imagination ("hunch-driven"), leading to theory generation. [41]
Retroduction	Generating inference on theories related to hidden mechanisms from explanations of available studies. [33,42]
Counterfactual thinking	Consideration of alternative or contradictory explanations of an interpretation generated from the evidence which is used to further test and refine programme theories. [23]

Pawson [31] mentions that contextual layers inform the implementation of a complex intervention. These layers can function at three different layers: macro-level (external situations that influence the function of the programme), meso-level (the structure and functioning of services), and micro-level (attitude and behaviour of stakeholders involved in the programme. Realist inquiry has been identified as a practical approach that provides a more comprehensive understanding of multi-faceted components within complex interventions. [32] Therefore, to obtain a thorough understanding of PEN interventions, programme theories (PT) will be developed and tested against the literature through a realist review. Qualitative interviews will follow this study to test further and refine the PTs in the future.

Our realist review approach is based on the methodological steps proposed by Pawson et al. [27], Realist and Meta-narrative Evidence Syntheses: Evolving Standards (RAMESES) guidelines[33,34], and recently published realist review protocols. [35–37] We will apply an analytical heuristic tool in Context-Mechanism-Outcome (CMO) configurations to formulate the programme theories of how and why PEN interventions do (not) work. The objective is achieved by clarifying the generative causal mechanisms that generate an outcome in a particular context and applying retroductive theorising (**Table 1**). [38,39]

The procedures employed in a realist review are iterative rather than linear and do not have a prescriptive method as in a traditional systematic review. [29] It is a complex and unpredictable process because the pre-defined criteria and specifications may change as the review proceeds. The authors

will describe what was planned in the initial protocol and what has changed, how and why during the study process. [33] The study will include five review steps elaborated in **Figure 1**. However, the review process will likely evolve as the review progresses.

Step 1: Clarify the scope of the study

This step involves the initial process of exploring through informal searches, discussing existing literature and establishing an understanding of the topic. To simplify the process, we will be using five intertwined processes in this step described by Hunter et al (**Figure 2**). [30]

Mapping the territory

An informal scoping of the literature around PEN interventions, in addition to stakeholder consultation, will be done to understand how the programme is intended to work, what features seem important, and the possible challenges encountered during its implementation. [31] The initial scoping exercise will be performed by AV using a database and a grey literature search.

Concept mining

The authors will identify and define key concepts during the process of familiarisation with the literature around PEN interventions. The concept mining involves exploring the literature on PEN and aligning it with the constructs of context, mechanism, and outcomes. This process will enable the authors to develop initial programme theories through the review of literature and supervisors and stakeholder consultation.

Stakeholders

Involving stakeholders throughout the review process is a crucial feature of realist review to ensure that the research focus and findings are relevant.[50] The supervisors and stakeholders with subject expertise, such as professional experts, service providers, or policymakers, will be consulted via online correspondence at various stages of this review to develop and refine programme theories, provide credibility checks, and provide advice about additional relevant data. [51]

Development of initial rough programme theories

The authors will develop initial rough programme theories (IRPTs) through consultation with the supervisory team, stakeholders, and literature review. Theory development will be elicited with the application of abductive thinking and retroductive theorising (see **table 1**), to unearth plausible explanations from the data. [38,39]

Articulate key theories to be explored

Pawson and Tilley [26] suggest using substantive theories and pre-existing theories established within a particular field, to help the researcher understand "why things happen the way they do". These theories can guide researchers to generate theories about how an intervention changes the reasoning and response of the service users. The literature will be read widely to identify substantive theories that can be used as a lens to understand how PEN interventions are thought to work in this phase.

Formalise hypotheses to be tested

After developing a set of programme theories, the authors will use these theories to create a hypothetical model of how PEN interventions are thought to work. Then, the IRPTs within this model will be tested by conducting a systematic search of empirical studies.

Step 2: Search for evidence

In this step, searching is guided by the study's objective, and iterative searching is applied according to the emerging data. [33] We will use the blended approach suggested by Booth et al. [52] in which we will search the keywords in three databases: PubMed, Scopus, and Google Scholar, which will be supplemented by complementary search techniques such as citation tracking, purposive sampling, snowballing, berry picking, cluster searching, and literature as per the recommendation of stakeholders.

The selection of studies in this review will be iterative and purposive. The author will purposively only extract and interpret specific data from the searched articles that the authors deem relevant for developing, refining, and refuting the initial programme theories. Initial screening of the studies' title, abstract and keywords will be conducted simultaneously by AV. The inclusion criteria used for screening are described in table 2. A 10% random sample will be checked by FCM, and disagreements, if any, will be discussed with PS and resolved by consensus. AV will review full texts with a 10% sample checked by FCM, ACKL, and SJ and again, disagreements, if any, will be determined via agreement. Because a realist review incorporates an iterative process, the authors will remain transparent about their methods by presenting how and why the literature search was conducted and whether papers were selected or excluded.

Table 2. Inclusion criteria

Language	English
Publication date	Studies published after September 16, 2011, because the Political declaration of the high-level meeting of the General Assembly on the prevention and control of NCDs was conducted in 2011 until December 30, 2022.
Study design	Any
Document Type	Any that can inform the review question if they are from peer-reviewed journals and relevant sources of grey literature, including relevant policy documents.
Setting	Primary health care of LMIC
Population	Health service providers directly or indirectly involved in the delivery of PEN intervention, officials involved in the regulation and implementation of PEN intervention

Step 3: Study appraisal and data extraction

A realist review process includes a series of researcher's judgements about the relevance and rigour of the data to answer the research question. A pragmatic approach will be employed to appraise the quality of the included data and evaluate relevance, richness, and rigour.

Relevance and richness

The RAMSES publication standards for realist syntheses defined relevance as data contributing to theory formation and/or refinement. [33] The paper's relevance will be decided in two ways: the evidence in the paper is relevant to the topic area, and the evidence is relevant for theory development, refinement, and testing. Screening of the relevant papers will be conducted similarly to other reviews based on the inclusion and exclusion criteria of the review.

Pawson et al. [53] mentioned that the relevance of the study in a realist review applies not only to a specific topic but also to the programme theory being tested. However, the paper's relevance changes as the theory evolve, and the papers that were non-relevant and excluded previously may become relevant in the iterative review process. To address this issue, Hunter et al. [30] recommends retaining the search results and excluding papers to revisit the resources. However, this may result in a large amount of data with not all having detailed information to support the theory. To organise the retained papers and review process, the authors will add a category of richness to the included papers in this review. The papers with a higher density of evidence regarding CMOs relevant to the study

scope and theory development will be categorised as high richness. Those that provide less evidence and deem less relevant will be classified as low richness. [54]

Rigour

The RAMSES publication standards for realist syntheses defined rigour as the methods used to generate the data being credible and trustworthy. The realist review requires the authors to consider how evidence is utilised in the literature rather than solely focusing on methodological approaches.[31] The theory generated in a realist review is developed from numerous arguments, analyses and interpretations derived from multiple sources, making it difficult to appraise the quality of all the data. The authors will assess rigour of the studies based on two components: trustworthiness of the evidence and coherence of the programme theory. The following components will be considered while considering the trustworthiness of the data: ensure that data obtained empirically have used some methods and are unlikely to be fabricated. If information about the methods used is uncertain, "treat them with scepticism; and try to find more than one source of data relevant to an aspect of programme theory".[51] Balancing traditional assessments of quality is important in a realist review as "*'nuggets' of wisdom can be found in methodologically weak studies, and realist review encourages the use of non-academic sources*".[55] While assessing the rigour at programme theory level, the authors will assess the generated theory better explains greater range of data (consilient), is simple, and aligns with credible existing substantive theories, which can further assist in formulation of a more comprehensive theory.[56,57]

Step 4: Synthesis of evidence and conclusions

The research team will record judgements about each study in the data extraction form. Searching for articles will continue until the researcher finds sufficient data ('theoretical saturation") to refine the programme theories and make them coherent and plausible. The full texts of selected documents will be imported into NVivo software (a qualitative data analysis tool) and analysed thematically based on the context, mechanisms, and outcome constructs.[58] The authors will record a core set of descriptors of each study, such as (author, title, year, country), type of data (primary study, study type, review, policy document), health setting, study population, intervention description and outcomes. The authors will also record, using memos, the data that generates, supports, or contradicts the initial programme theory and explain how and why the programme may have worked in specific conditions. The information about what was extracted and why will be reported in the

data extraction form so that the link between the research question and data is clarified, which will further add to the transparency of the review process.

The realist logic will be applied in this review to uncover the underlying mechanism (M), triggered in a specific context (C) leading to intended or unintended outcomes (O) from the literature, and articulate realist programme theory. Retroductive theorising (Table 1) will guide the data analysis. Induction and deduction will be applied during data extraction by coding the data against CMOs. Recurrent patterns of outcomes (demi regularities) and their association with mechanisms and contexts will be identified and organised into programme theories through the abduction process.[59] The data selection, extraction, and synthesis process are iterative and will be undertaken concurrently. The programme theories will be developed through a consultative process with the supervisory team and relevant stakeholders. If it is felt that the programme theories are not described sufficiently by the identified literature in the initial searches, supplementary searches of academic and grey literature will be performed.

Step 5: Dissemination

The study will follow RAMSES quality standards for a realist review. The study findings will be submitted for publication in a peer-reviewed journal and will be presented at academic conferences. The review findings will inform a realist evaluation, in which programme theories developed from the realist review will be tested and refined via realist interviews with stakeholders involved in implementing PEN interventions. The review findings will develop plausible explanations from the literature and transferable theories, also known as 'middle range theories', that can inform the implementation of similar programmes in different settings. The review findings will potentially be helpful for the policy, decision-makers, and other key stakeholders, including non-government organisations and personnel working in programmes to prevent and control NCDs.

Ethics and dissemination

Ethical approval is not required for a realist review because it involves review of secondary research along with peer feedback from relevant stakeholders. Ethical approval has been obtained from the University of Huddersfield, School of human and health sciences, School Research Ethics and Integrity Committee (SREIC) and Ethical Review Board of Nepal Health Research Council for qualitative field work with wide range of participants. The findings of the review will be disseminated via different traditional academic channels such as publications, national and international conferences, and formal and informal reports.

Patient and public involvement

This realist review involves consultation with stakeholders at different stages of the review process. The stakeholders who will be consulted in this review will be supervisors of the first author, researcher's working in health system and policy researchers related to NCDs, officials at regulatory level and service providers involved in implementation of PEN intervention. The stakeholders will be consulted via either face to face or informal online medium such as email, viber, skype, and phone call as per the convenience of the stakeholders. This process of consultation and obtaining feedback from different range of stakeholders will enable the authors to capture varied inputs on developed programme theories and review findings.

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Author's contributions

All the authors contributed to conceptualization of the review. AV designed and drafted the protocol manuscript. FCM provided methodological guidance. PS, ACKL, SJ and FCM critically reviewed and edited the manuscript. All the authors read and approved the final manuscript.

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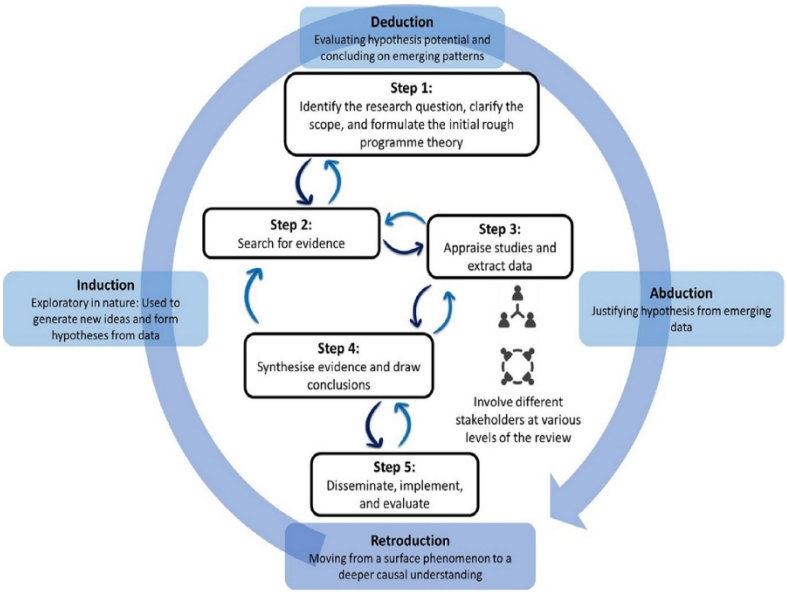

Figure 1: Proposed iterative process for searching articles. Adapted from Copper et al. 48,49 and Mukumbang et al. 49

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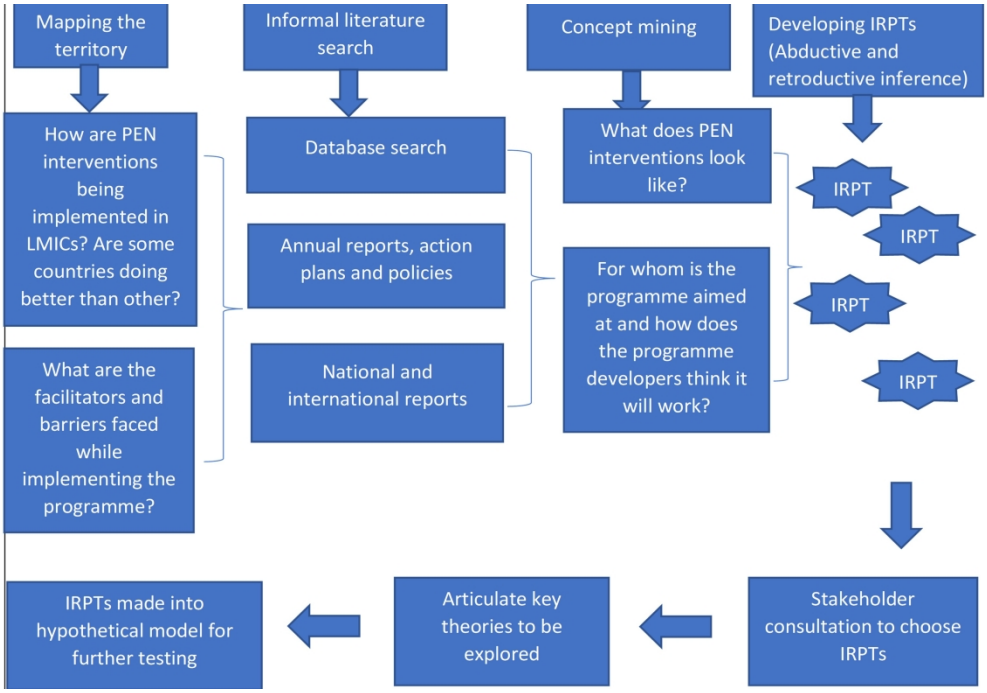

Figure 2: Mapping the research territory.

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Implementing a Package of Essential Non-communicable diseases interventions in low- and middle-income countries: A realist review protocol

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Implementing a Package of Essential Non-communicable diseases interventions in low- and middle-income countries: A realist review protocol

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Abstract

Introduction: The burden of non-communicable diseases (NCDs) is increasing rapidly, particularly in Low- and Middle-Income Countries (LMIC), accounting for 85% of premature deaths in the region. LMICs have been facing an increasing trend of a double burden of disease (infectious diseases and NCDs) that has led to multiple challenges in prioritising strategies for NCDs control amidst limited resources. Evidence indicates that measures such as the World Health Organization's Package of Essential Non-communicable diseases (PEN) interventions can prevent and control non-communicable diseases. However, because of the complexity of such health interventions, there is limited evidence that explains how the intervention works, for whom, and in what context. We aim to unpack the causal mechanisms explaining how, why, for whom and in what context PEN prevents and controls non-communicable diseases.

Methods and analysis: We propose a realist review to understand how, why, for whom, and under what circumstances PEN works or does not work. The review process includes five steps applied iteratively throughout the study: clarification of review scope, searching for evidence, appraising, and extracting data, synthesising evidence, and drawing conclusions, and disseminating the findings. Programme theories will be developed using the realist logic for theory formulation – Retroductive Theorising. The Context-Mechanism-Outcome heuristic tool will be used to develop the programme theories. Portions of the reviewed documents describing constructs of context, mechanism and outcomes will be coded inductively and extracted. These extracted constructs will then be linked abductively to formulate Context-Mechanism-Outcome configurations.

Ethics and Dissemination: Formal ethical approval is not required for this review**.** Study findings will be disseminated through publications in peer-reviewed journals, conference presentations, and formal and informal reports.

Keywords

Low- and middle-income countries, non-communicable diseases, package of essential non-communicable diseases intervention, realist review, retroductive theorizing.

Strengths and Limitations of the study

- The realist review approach will provide explanatory evidence to understand the underlying causal mechanisms triggered in different contexts for effective prevention and control of non-communicable diseases in low- and middle-income countries.
- The review will incorporate a wide range of evidence, including academic and grey literature, to understand what works, for whom, and in what circumstances for the Package of Essential Non-communicable diseases interventions to prevent and control non-communicable diseases.
- The development and refinement of programme theories will be guided by the advisory group members.
- The realist review findings cannot be generalized to all contexts, mechanisms, and outcomes relevant to prevention and control of non-communicable diseases; however, they may be transferrable to similar contexts.

Introduction

The burden of non-communicable diseases (NCDs) is increasing, thus emerging as a significant public health issue globally (1,2). The latest global estimates indicate that 41.1 million deaths occurred due to NCDs, corresponding to 73.4% of all deaths in 2017. Globally, recent patterns of the cause of mortality indicate epidemiological transition with a steady decline in the proportion of deaths due to communicable, maternal, neonatal, and nutritional causes, while deaths due to NCDs (specifically cardiovascular disease, cancer, chronic obstructive pulmonary disease and diabetes) were on the rise (2,3,4). More than two-thirds (85%) of premature deaths due to NCDs took place in low- and middle-income countries (LMICs) (3,4). LMICs are facing an increasing trend of a double burden of disease (infectious diseases and NCDs) leading to a syndemic, causing multiple challenges in prioritising strategies for NCDs control amidst limited resources due to poor political commitments, technical capacity and resource constraints, scarcity of NCDs area expertise, and

prioritization of other issues (5,6). The WHO NCD Country Capacity surveys (2019) demonstrated that only half of the 160 countries had developed national NCD guidelines, with half of the primary care facilities having only 6 essential technologies, and 32 countries having 6 or lesser essential medicines for NCDs management demonstrating inefficient programme implementation (7).

Policy initiatives for prevention and control of non-communicable diseases

Research has shown that a primary health care approach is a promising, effective, and cost-effective approach to address NCDs (8,9,10). Global commitments and prioritisation to address the NCDs issues were initiated by adopting the "Political declaration of the high-level meeting of the General Assembly on the prevention and control of NCDs" in 2011(11). This initiative marked a turning point in policy initiatives at the national and global levels (11). The Astana declaration restated the principles of the Alma Ata declaration and recognised the crucial role of the primary health care approach in the prevention and control of NCDs and declared its contribution towards achieving Universal Health Coverage and the Sustainable Development Goals 3 (12). A WHO-CHOICE (WHO- CHoosing Interventions that are Cost-Effective) analysis conducted by Bertram et al. emphasized the essentiality of implementing cost-effective and accessible interventions to reach universal health coverage. They evaluated the Package of Essential Non-communicable diseases (PEN) programme specifically for cardiovascular diseases, diabetes, chronic respiratory diseases, and cancer (13).

Package of Essential Non-Communicable (PEN) disease

Most of the individuals suffering from, or at risk of developing, NCDs need care for a longer period (14,15). In LMICs, where healthcare resources are limited, sustainable, efficient, community-based interventions and referral systems are required to effectively prevent and control NCDs (16). Bertram et al. highlighted the need to rapidly implement prevention and early detection programmes, which are more cost-effective than treatment programmes, and can mitigate future healthcare costs specifically in low resource countries (13). Recognising the increasing burden of NCDs, especially in the context of LMICs, the World Health Organization (WHO) developed and recommended the PEN programme to prevent and control NCDs. PEN is a technologically operable, cost-effective intervention delivered through primary healthcare facilities targeted for resource-scarce settings. The programme includes wide range of interventions implemented at primary health care facilities such as health education, early detection, and diagnosis of NCDs and its risk factors, using affordable technologies and medications for NCDs prevention and treatment, follow-up, and referral of the patients (17).

Studies demonstrated that policy implementation (including NCD policies) is a multifaceted process which is influenced by numerous factors such as the capacity and values of the service providers in the organisation, access to health care services, availability of free medicines, financial constraints, lack of clarity in process, and political factors (18,19,20). After the global initiative for the prevention and control of NCDs via the adoption of the political declaration of the high-level meeting of the General assembly on the prevention and control of NCDs, many countries, especially LMICs, initiated policy initiatives to prevent and control NCDs by adopting WHO PEN interventions for early screening, detection, prevention, control, and treatment of NCDs at the primary healthcare level (21).

PEN interventions have been implemented in varied settings across the globe, including Myanmar, Nepal, Bhutan, Korea, Uzbekistan, and Moldova (16,22-26). However, evidence about the implementation and effectiveness of PEN interventions is inconclusive and in order to promote more effective and efficient strategies for NCDs control, it is important to understand what does or does not work in the PEN programme (27-29). Hence, it is essential to understand how the PEN interventions work, the underlying mechanisms and the contextual factors that influence the achievement or failure of PEN goals. The realist approach offers the potential to explain the success or failure of complex interventions such as PEN interventions, which is crucial to achieve policy objectives and help unpack and surmount implementation challenges at the operational level (30,31).

This review aims to explore how, why, for whom and in what context PEN interventions work or do not work for the prevention and control of NCDs in LMICs. The specific objectives are:

(i) To unearth possible mechanisms and context conditions that orchestrate the successful implementation of the PEN programme in LMICs.

(ii) To unpack the possible mechanisms and context conditions that contribute to poor implementation of the PEN programme in LMICs.

(iii) To synthesize initial programme theories from objective (i) and (ii) findings that can be tested in future studies.

Context of the review

The burden of NCDs is in increasing trend accounting for major proportion of premature mortality particularly in LMICs. PEN programme was one of the interventions recommended by WHO for early detection, diagnosis, treatment, and care of NCDs. To address NCD issues, the number of countries implementing WHO recommended NCD policies were increasing in number (32,33).

However, studies have demonstrated slower rate of improvement of the NCDs in many countries in South Asia and sub-Saharan Africa (33). Similarly, Tripathy & Mishra highlighted that critical gaps and insufficient preparedness of health facilities to implementation of PEN programme was found in LMICs (27). Furthermore, there is limited evidence about the programme delivery and ways through which these programmes can be scaled up to meet the patient's needs particularly in low resource setting (34,35). This realist review aims to address this gap by unravelling the underlying mechanisms and contexts in which the PEN programme work or does not work.

The study findings can shed light on ways to address implementation challenges at the operational level and improve the efficiency of service delivery resulting in improvement of the health outcomes. There are numerous primary studies and systematic reviews around interventions for prevention and control of NCDs. Nevertheless, we are not aware of any realist reviews about implementation of PEN interventions in the context of LMICs that particularly intends to explore how, for whom, why and in what context PEN programme is being implemented to prevent and control NCDs. Thus, we consider that the findings from this review can complement the current or continuing works related to implementation of PEN programme for prevention and control of NCDs. The national and international policymakers can consider the review findings and recommendations in similar settings and increase their commitments to improve the implementation of PEN programme.

Methods

Theory-informed research methods such as realist evaluation and synthesis are increasingly recognised as an appropriate approach to evaluate complex interventions so that researchers, policymakers, and practitioners can make sense of complex programmes (**Table 1**) (36,37). Because of the complexity of social and health interventions, it has been argued that traditional systematic review is unsuitable for examining these programmes as its focus is to assess the effectiveness of an intervention (38). Furthermore, systematic review methods assessing intervention effectiveness hold limited capacity to find the answer to how and why interventions are effective (39). A realist review addresses this challenge and synthesises evidence about the intervention by exploring causal mechanisms that explain why the intervention works in some contexts while not in others (40). Hence, we propose conducting a realist review of the PEN interventions underpinned by scientific realist and critical realist philosophies of science (**Table 1**).

Table 1: Key concepts

Category	Definition

Complex interventions	Interventions that are multi-faceted and consist of numerous interacting factors that can influence those providing and receiving the services leading to different outcomes (41,42).
Context	The situations (e.g., individual, organisational, environmental factors) or the relational or dynamic features that influence or modify the mechanisms through which the programme works are likely to facilitate or hinder the programme at multiple levels of the system (43-45).
Mechanism	Refers to causal entities that trigger or generate observable events in specific contexts. It is a combination of resources (e.g., components of an intervention) and responses (e.g. perceptions and attitudes of the participants) which will enable the researcher to understand how the intervention is perceived (43,46).
Outcomes	Describes the effects of the PEN programme due to a combination of context and mechanism (43).
Context-mechanism-outcome (CMO) configuration	CMO configurations represent causal explanations of how underlying mechanisms are triggered by contextual factors leading to specific outcomes (43).
Programme theory	Theories that explain how the mechanisms introduced in pre-existing conditions generate outcomes (33,47).
Abduction	A process that begins with an incomplete set of observations that proceeds towards obtaining the most approximate explanation of those observations/events, driven by the researcher's imagination ("hunch-driven"), leading to theory generation (48).
Retroduction	Generating inference on theories related to hidden mechanisms from descriptions of existing studies (43,49).
Counterfactual thinking	Consideration of alternative or contradictory explanations of an interpretation generated from the evidence which is used to further test and refine programme theories (37).

Pawson (50) mentions that contextual layers inform the implementation of a complex intervention. These layers can function at three different levels: macro-level (external situations that influence the function of the programme), meso-level (the structure and functioning of services), and micro-level (attitude and behaviour of stakeholders involved in the programme). Realist inquiry has been identified as a practical approach that provides a more comprehensive understanding of multi-faceted components within complex interventions (51). Therefore, to obtain a thorough understanding of PEN interventions, programme theories will be developed and tested against the literature through a realist review.

Our realist review approach is based on the methodological steps proposed by Pawson et al., (37) Realist and Meta-narrative Evidence Syntheses: Evolving Standards (RAMESES) guidelines (52,53), recently published guidance on applying and reporting relevance, richness and rigour in realist evidence appraisals, and recently published realist review protocols (54-57). We will apply an analytical heuristic tool in Context-Mechanism-Outcome (CMO) configurations to formulate the programme theories of how and why PEN interventions do/do not work. The objective is achieved by clarifying the generative causal mechanisms that generate an outcome in a particular context by applying retroductive theorising (**Table 1**) (43,58).

The procedures employed in a realist review are iterative rather than linear and do not have a prescriptive method as in a traditional systematic review (39). It is a complex and unpredictable process because the pre-defined criteria and specifications may change as the review proceeds. The authors will describe what was planned in the initial protocol and what has changed, how and why during the study process (52). The study will include five review steps elaborated in Figure 1 which was adopted from studies conducted by Cooper et al. and Mukumbang et al. (59,60). However, the review process will likely evolve as the review progresses.

Step 1: Clarify the scope of the study

This step involves the initial process of exploring through informal searches, discussing existing literature and establishing an understanding of the topic. To simplify the process, we will be using five intertwined processes in this step described by Hunter et al (Figure 2) (40).

Mapping the territory

An informal scoping of the literature around PEN interventions, in addition to stakeholder consultation, will be done to understand how the programme is intended to work, what features seem important, and the possible challenges encountered during its implementation (50). The initial scoping exercise will be performed by the author (AV) using three databases (PubMed, Scopus and Google scholar) and a combination of search terms such as “Package of Essential Non-communicable diseases", PEN, “WHO PEN”, “essential NCD package”, “NCD prevention and control package”, prevention, control, “non-communicable diseases”, NCDs, “chronic diseases”, “lifestyle diseases”, cardiovascular, heart, cancer, respiratory, diabetes, hypertension, "low-income country”, "middle-income country”, LMIC, and "low and middle income countries", “developing countries”, “resource limited settings” (Supplementary file 1) and a grey literature search. Grey literature will be searched for official publications of UN agencies

(for example WHO) who lead on the global prevention and control of NCDs, in WHO IRIS (institutional repository of WHO for information sharing).

Concept mining

The authors will identify and define key concepts during the process of familiarisation with the literature around PEN interventions. The concept mining involves exploring the literature on PEN and aligning it with the constructs of context, mechanism, and outcomes. This process will enable the authors to develop initial programme theories through the review of literature and supervisors and stakeholder consultation.

Stakeholders

Involving stakeholders throughout the review process is a crucial feature of realist review to ensure that the research focus and findings are relevant (61). The supervisors and stakeholders with subject expertise, such as stakeholders with expertise in this area, officials of civil society organizations working in this area and service providers will be consulted via online correspondence at various stages of this review to develop and refine programme theories, provide credibility checks, and provide advice about additional relevant data (62).

Develop initial rough programme theories

The authors will develop initial rough programme theories (IRPTs) through consultation with the supervisory team, stakeholders, and literature review. Theory development will be elicited with the application of abductive thinking and retroductive theorising (see **table 1**), to unearth plausible explanations from the data (43,58).

Articulate key theories to be explored

Pawson and Tilley (36) suggest using substantive theories and pre-existing theories established within a particular field, to help the researcher understand "why things happen the way they do". These theories can guide researchers to generate theories about how an intervention changes the reasoning and response of the service users. The literature will be read widely to identify substantive theories that can be used as a lens to understand how PEN interventions are thought to work in this phase.

Formalise hypotheses to be tested

After developing a set of programme theories, the authors will use these theories to create a hypothetical model of how PEN interventions are thought to work. Then, the IRPTs within this model will be tested by conducting a systematic search of empirical studies.

Step 2: Search for evidence

In this step, searching will be guided by the study's objective, inclusion criteria (table 2) and iterative searching is applied according to the emerging data (52).We will use the blended approach suggested by Booth et al. (63) in which we will revise and use combination of search terms used initially in Step 1 (Supplementary file 1) in three databases: PubMed, Scopus, and Google Scholar targeting the generated programme theories , which will be supplemented by complementary search techniques such as citation tracking, purposive sampling, snowballing, berry picking, cluster searching, and literature as per the recommendation of stakeholders. As the review progresses, iterations of searches will be conducted based on the emerging programme theories. These activities will be reported transparently in the review.

Table 2: Inclusion criteria

Language	English
Publication date	Studies published after September 16, 2011, because the Political declaration of the high-level meeting of the General Assembly on the prevention and control of NCDs was conducted in 2011 until December 30, 2022.
Study design	Any
Document Type	Any that can inform the review question if they are from peer-reviewed journals and relevant sources of grey literature, including relevant policy documents.
Setting	Primary health care of LMICs as defined by the World Bank for year 2021-2022 (64).
Population	Health service providers directly or indirectly involved in the delivery of PEN intervention, officials involved in the regulation and implementation of PEN intervention

The selection of studies in this review will be iterative and purposive. The author will purposively only extract and interpret specific data from the searched articles that the authors deem relevant for developing, refining, and refuting the initial programme theories. Initial screening of the study title, abstract and keywords will be conducted simultaneously by the author (AV). The inclusion criteria used for screening are described in table 2. A 10% random sample will be checked by the author (FCM), and disagreements, if any, will be discussed with the author (PS) and resolved by consensus. The author (AV) will review full texts with a 10% sample checked by the authors (FCM, ACKL, and SJ) and again, disagreements, if any, will be resolved via agreement. Because a realist review incorporates an iterative process, the authors will remain transparent about their methods by presenting how and why the literature search was conducted and whether papers were selected or excluded.

Step 3: Study appraisal and data extraction

A realist review process includes a series of researcher's judgements about the relevance and rigour of the data to answer the research question. A pragmatic approach will be employed to appraise the quality of the included data and evaluate relevance, richness, and rigour (57).

Relevance

The RAMSES publication standards for realist syntheses defined relevance as data contributing to theory formation and/or refinement (52). The paper's relevance will be decided in two ways: the evidence in the paper is relevant to the topic area, and the evidence is relevant for theory development, refinement, and testing. Screening of the relevant papers will be conducted similarly to other reviews based on the inclusion and exclusion criteria of the review.

Pawson et al. (65) mentioned that the relevance of the study in a realist review applies not only to a specific topic but also to the programme theory being tested. However, the paper's relevance changes as the theory evolve, and the papers that were non-relevant and excluded previously may become relevant in the iterative review process. To address this issue, Hunter et al. (40) recommends retaining the search results and excluding papers to revisit the resources. However, this may result in a large amount of data not all of which will have detailed information to support the theory.

Richness

To organise the retained papers and review process, the authors will add a category of richness to the included papers in this review. Richness speaks to a paper's density of evidence regarding CMOs that are relevant to our study objectives, where ‘thick’ articles will be considered as those that offer more detail on CMOs relevant to PEN implementation and ‘thin’ articles provide less. The papers with a higher density of evidence regarding CMOs relevant to the study scope and theory development will be categorised as high richness. Those that provide less evidence and deem less relevant will be classified as low richness (66). We will assess relevance by scoring the articles in relation to the richness relative to the research questions as proposed by Waldron et al. (67). To score highly, an article should provide sufficient details in relation to how PEN was expected to work; documenting the process and explaining contextual factors that influenced PEN implementation and/or outcomes. We will rate the richness as follows:

0 = nothing of interest, not focused on design, implementation, or use,

1 = limited data of interest, likely to appear in other articles,

2 = limited data of interest, but quick to extract it and could add weight to findings,

3 = some good quality data,

4 = much valuable data.

Rigour

The RAMSES publication standards for realist syntheses defined rigour as the methods used to generate the data being credible and trustworthy. The realist review requires the authors to consider how evidence is utilised in the literature rather than solely focusing on methodological approaches (50). The theory generated in a realist review is developed from numerous arguments, analyses and interpretations derived from multiple sources, making it difficult to appraise the quality of all the data. The authors will assess rigour of the studies based on two components: trustworthiness of the evidence and coherence of the programme theory. The following components will be considered while considering the trustworthiness of the data: ensure that data obtained empirically have used appropriate methods that are unlikely to be fabricated and if information about the methods used is uncertain, they will be treated with scepticism; we will endeavour to find more than one source of data relevant to the generated programme theory (62). Balancing traditional assessments of quality is important in a realist review as "*'nuggets' of wisdom can be found in methodologically weak studies, and realist review encourages the use of non-academic sources*" (68). While assessing the rigour at programme theory level, the authors will assess if the generated theory better explains a greater range of data (consilient), is simple, and aligns with credible existing substantive theories, which can further assist in formulation of a more comprehensive theory (69,70). In case of grey literature, AACODS Checklist will be used to assess quality (71).

Step 4: Synthesis of evidence and conclusions

The research team will record judgements about each study in the data extraction form. Searching for articles will continue until the researcher finds sufficient data ('theoretical saturation") to refine the programme theories and make them coherent and plausible. The full texts of selected documents will be imported into NVivo software (a qualitative data analysis tool) and analysed thematically based on the context, mechanisms, and outcome constructs (72). The authors will record a core set of descriptors of each study, such as (author, title, year, country), type of data (primary study, study type, review, policy document), health setting, study population, intervention description and outcomes. The authors will also record, using memos, the data that generates, supports, or

contradicts the initial programme theory and explain how and why the programme may have worked in specific conditions. The information about what was extracted and why will be reported in the data extraction form so that the link between the research question and data is clarified, which will further add to the transparency of the review process.

Realist logic will be applied in this review to uncover the underlying mechanism (M), triggered in a specific context (C) leading to intended or unintended outcomes (O) from the literature, and articulate realist programme theory. Retroductive theorising will guide the data analysis (Table 1). Induction and deduction will be applied during data extraction by coding the data against CMOs. Recurrent patterns of outcomes (demi regularities) and their association with mechanisms and contexts will be identified and organised into programme theories through the abduction process (73). The data selection, extraction, and synthesis process are iterative and will be undertaken concurrently. The programme theories will be developed through a consultative process with the supervisory team and relevant stakeholders. If it is felt that the programme theories are not described sufficiently by the identified literature in the initial searches, supplementary searches of academic and grey literature will be performed.

Step 5: Dissemination

The study will follow RAMSES quality standards for a realist review. The study findings will be submitted for publication in a peer-reviewed journal and will be presented at academic conferences. The review findings will develop plausible explanations from the literature and transferable theories, also known as 'middle range theories', that illustrates the key contexts and underlying mechanisms of the PEN interventions delivered by the service providers at primary health care level to prevent and control NCDs. The strength of using realist method is that it may offer methodological advancement over the traditional methods of using published literature and provide clearer insights of the mechanisms that occurs in a particular context to produce outcomes of complex health interventions like PEN. The potential limitation of realist reviews is that the researchers must be cautious while applying the generated theories as they are only applicable in similar settings. The review findings will potentially be helpful for the policy and decision-makers, and other key stakeholders, including non-government organisations and practitioners to inform future work and co-design NCD targeted interventions.

Ethics and dissemination

Ethical approval is not required for a realist review because it involves review of secondary research along with peer feedback from relevant stakeholders. The findings of the review will be disseminated via different traditional academic channels such as publications, national and international conferences, and formal and informal reports.

Patient and public involvement

This realist review involves consultation with stakeholders at different stages of the review process. The stakeholders who are involved in PEN interventions such as service providers, stakeholders with expertise in this area, officials of civil society organizations working in this area will be approached to engage in the review as advisory group members. The stakeholders will be consulted either face to face or via informal online medium such as email, Viber, Skype, and phone call as per the convenience of the stakeholders. This process of consultation and obtaining feedback from a wide range of stakeholders will enable the authors to capture varied inputs on developed programme theories and review findings.

Figure 1: Proposed iterative process for searching articles (59,60)

Figure 2: Mapping the research territory

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Author's contributions

All the authors contributed to conceptualization of the review. AV designed and drafted the protocol manuscript. FCM provided methodological guidance. PS, ACKL, SJ and FCM critically reviewed and edited the manuscript. All the authors read and approved the final manuscript.

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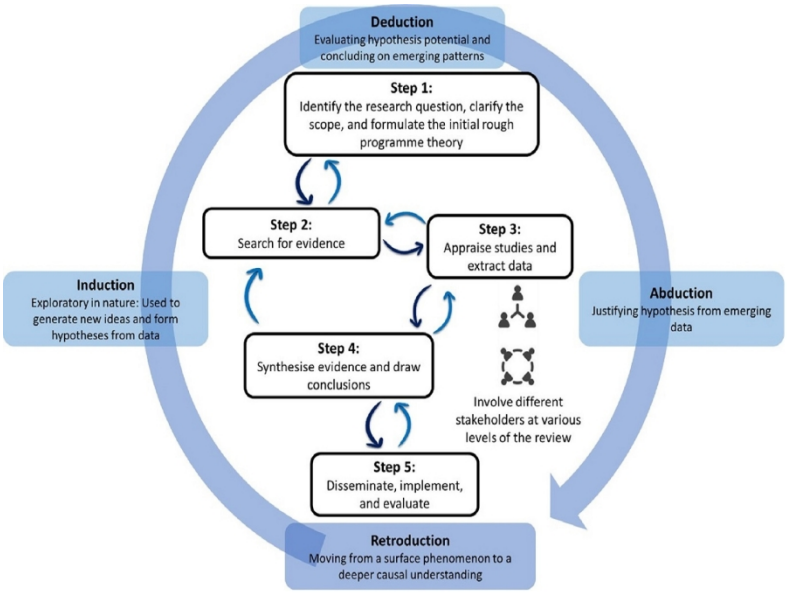

Figure 1: Proposed iterative process for searching articles. Adapted from Copper et al. 59,60 and Mukumbang et al. 60

173x130mm (300 x 300 DPI)

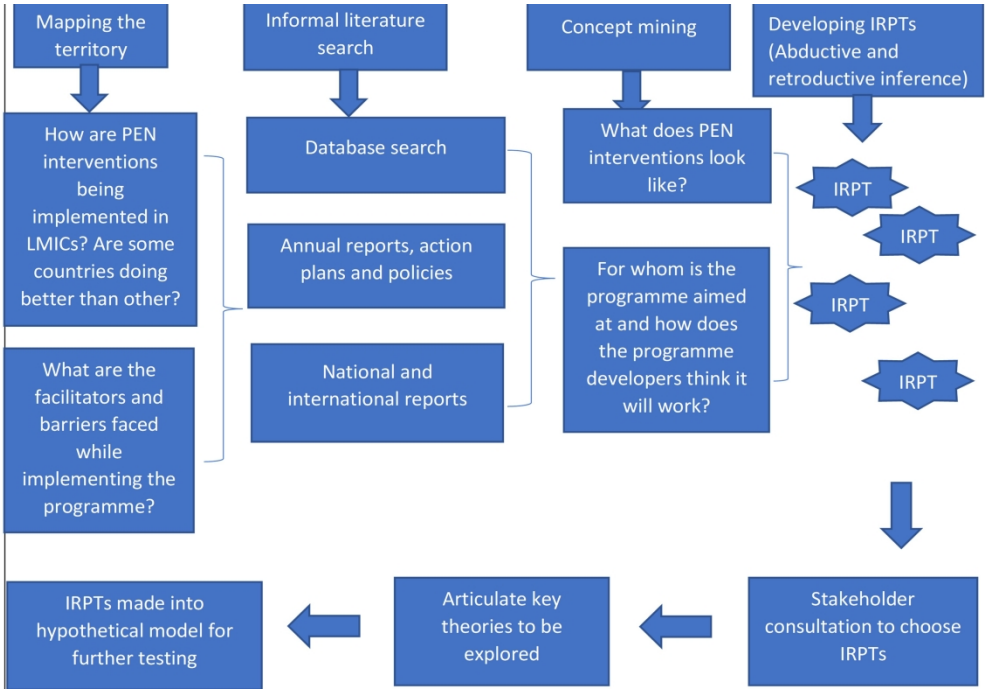

Figure 2: Mapping the research territory.

318x217mm (300 x 300 DPI)

Supplementary file 1: Initial searches by database

Implementing a Package of Essential Non-communicable diseases interventions in low- and middle-income countries: A realist review protocol

Authors: Anju Vaidya, Padam Simkhada, Andrew Chee Keng Lee, Susan Jones, Ferdinand C Mukumbang

PubMed: ("Package of Essential Non-communicable diseases" OR PEN OR "WHO PEN" OR prevention OR control) AND ("non-communicable diseases" OR cardiovascular OR cancer OR respiratory OR diabetes OR hypertension) AND ("low-income country" OR "middle-income country" OR LMIC OR "low and middle income countries")

Scopus: ({Package of Essential Non-communicable diseases} OR prevention OR control) AND ({non-communicable diseases} OR cardiovascular OR cancer OR respiratory OR diabetes OR hypertension) AND ({low-income country} OR {middle-income country } OR lmic OR **{low and middle income countries}**)

Google scholar: ("Package of essential non communicable diseases" OR prevention OR control) AND ("non communicable disease") AND ("low income country" OR "middle income country" OR LMIC OR "low and middle income countries")