Strengthening health systems through the use of process evaluations of complex interventions

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A thesis submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

for the Sydney School of Public Health, Sydney Medical School

The University of Sydney

June 2018

DECLARATION

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

Date: 30/6/2018

AUTHORS' CONTRIBUTIONS

This work presented in the thesis was carried out under the supervision of Professor Stephen Jan, Professor David Peiris and Associate Professor Maree Hackett. The overarching concept for the thesis of strengthening health systems through the use of process evaluations was conceived by the author, Stephen Jan and David Peiris. Under their and Maree Hackett's guidance, I refined the research questions and developed the methods included in this thesis. This work comprises of projects from three collaborations (Kanyini Vascular Collaboration, ATTEND Collaborative Group, and The Australian Prevention Partnership Centre), and the contributions of all co-authors in this work are described at the start of each chapter and certified by Stephen Jan in Appendix 1.

This thesis comprises nine manuscripts, of which seven are published, one is accepted for publication, and one is under review. Stephen Jan is a co-author on eight of the manuscripts David Peiris is a co-author on five of the manuscripts and Maree Hackett on four of the manuscripts. The chief investigators of the collaborations (including my three supervisors) envisaged the need for process evaluations alongside the randomised controlled trials; and Stephen Jan and I jointly envisaged the ideas for most of the studies with input from the co-authors as specified in the relevant chapters. For most of the manuscripts (except for those in Chapter 3), I was involved in the data collection, analysis and synthesis. I prepared the first draft of eight manuscripts, and am the corresponding author. For a manuscript in Chapter 4, the findings from the process evaluation that I led was a key part of the manuscript.

ETHICAL CLEARANCE

A Human Research Ethics Committee in the relevant jurisdictions has approved all the empirical research included in this thesis.

- Chapter 3 is based on the Kanyini Guidelines Adherence with the Polypill (GAP) pragmatic randomised controlled trial. The trial and its process evaluation was approved by human research ethics committees in all relevant jurisdictions.
- Chapter 4 is based on the Family Led Rehabilitation randomised controlled trial in India. The trial and its process evaluation as approved by the human research ethics committees in University of Sydney, and the relevant ethics committees in India.
- Chapter 5 is a qualitative study that was approved by the human research ethics committee in University of Sydney.
- Ethical approval was not required for the systematic review in Chapter 2.

ACKNOWLEDGEMENTS

The support of my family, friends and academics at the George Institute for Global Health have made this work possible. This work was financially supported initially through an UPA scholarship through the University of Sydney and subsequently though a National Health and Medical Research Council Postgraduate scholarship, with some co-funding by the George Institute for Global Health. I am thankful to these organisations for their investment in this research and in my work.

I am grateful for the ongoing support and guidance from my supervisors Stephen Jan, Maree Hackett and David Peiris. I am particularly thankful to Stephen Jan for the many opportunities he has provided in this journey to collaborate on international projects, and for his health systems approach towards these trials from the onset. Thanks to Maree Hackett for her mentorship especially during those difficult times when I was overwhelmed, and for her clarity in my times of doubt. Thanks to David Peiris whose insights are always spot on and for being a constant inspiration.

I would also like to acknowledge the co-authors on all the papers, and am grateful to have been able to learn from such a range of international experts in their fields through this PhD. I especially acknowledge Richard Lindley for embracing me into the ATTEND Collaborative Group to conduct the process evaluation, and for his continual guidance, encouragement and amazing opportunities to be in the field. Thanks to the trial management teams of Kanyini GAP and ATTEND, in accomplishing the mammoth task of practice-based trials. Thanks also

to my colleagues at the George, in particular the health economics and process evaluation team members who have provided advice and encouragement throughout this process.

Special thanks goes to Luciana Massi, Alim Mohammed and Janani Muhunthan for being the 'buddy' in doing the in-depth analysis of the qualitative interviews with me- allowing me to voice my inner thoughts and interpretation of interviews in a safe and constructive environment. Thanks to all the patients, health providers and policy makers for sharing their stories and insights.

Finally, to my husband John, and children Chloe, Sean and Carl for their unwavering support, and cheering me on during the difficult times, Thank you so much.

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PUBLICATIONS ARISING FROM THIS THESIS

This thesis contains mostly published work. The University of Sydney's Academic Board approved submission of published work as thesis on 14 August 2002. Specific author contributions are specified at the beginning of each chapter and the signed author contribution statement is provided as Appendix 1.

Chapter	Status	Details
2	1 published, 1 submitted	**Liu H**, Muhunthan J, Hayek A, Hackett M, Laba TL, Peiris D et al. Examining the use of process evaluations of randomised controlled trials of complex interventions addressing chronic disease in primary health care-a systematic review protocol. Syst Rev. 2016;5(1):138. **Liu H,** Mohammed A, Muhunthan J, News M, Hayek A, Hackett M, Laba TL, Peiris D, Jan S. A systematic review of process evaluations of primary care interventions addressing chronic disease. Submitted to BMJ open in 2018, under review.
3	3 published	**Liu H,** Massi L, Laba TL, Peiris D, Usherwood T, Patel A, Cass A, Eades AM, Redfern J, Hayman N, Howard K, Brien JA, Jan S. Patients' and Providers' Perspectives of a Polypill Strategy to Improve Cardiovascular Prevention in Australian Primary Health Care: A Qualitative Study Set Within a Pragmatic Randomized, Controlled Trial. Circ Cardiovasc Qual Outcomes. 2015 **Liu H,** Laba T, Massi L, Jan S, Usherwood T, Patel A, Hayman N, Cass A, Eades A, Peiris D. Facilitators and barriers to implementation of a pragmatic clinical trial in Aboriginal health services. Medical Journal of Australia 01/2015 **Liu H,** Massi L, Eades AM, Howard K, Peiris D, Redfern J et al. Implementing Kanyini GAP, a pragmatic randomised controlled trial in Australia: findings from a qualitative study. Trials. 2015
4	2 published, 1 accepted	**Liu H,** Lindley R, Alim M, et al. Protocol for process evaluation of a randomized controlled trial of family-led rehabilitation post stroke (ATTEND) in India. BMJ Open 2016;6 **Liu H**, Lindley R, Mohammed A et al. Family-led rehabilitation in India (ATTEND)-findings from the Process Evaluation of a Randomised Controlled Trial. 2018, International Journal of Stroke. (accepted for publication 31st May 2018) Pandian JD, **Liu H**, Gandhi DB, Lindley RI. Clinical stroke research in resource limited settings: Tips and hints. International journal of stroke: official journal of the International Stroke Society. 2017 Jan 1:1747493017743798.
5	1 published	**Liu HM,** Muhunthan J, Ananthapavan J, Hawe P, Shiell A, Jan S. Exploring the use of economic evidence to inform investment in disease prevention- a qualitative study, ANZJPH 2018

OTHER OUTCOMES FROM THIS THESIS

PUBLICATIONS

Vugts M, **Liu H,** Boumans J, Boydell E. The need for Theory-based evaluation of care coordination initiatives: Considerations from the 2017 International Conference on Realist Research, Evaluation and Synthesis. International Journal of Care Coordination. 2018

Hossain S, Harvey L, **Liu H** et al. Protocol for process evaluation of the CIVIC randomised controlled trial: Community-based InterVentions to prevent serIous Complications following spinal cord injury in Bangladesh. BMJ open. (in press, accepted 25th June 2018)

The ATTEND Collaborative Group. (Writing Group: Lindley R….**Liu HM** et al) Family-led rehabilitation after stroke in India (ATTEND): a randomised controlled trial. Lancet. 2017. doi:10.1016/S0140-6736(17)31447-2.

Alim M, Lindley R, Felix C, Gandhi DB, Verma SJ, Tugnawat DK…**Liu H,** et al. Family-led rehabilitation after stroke in India: the ATTEND trial, study protocol for a randomized controlled trial. Trials. 2016

Davy C, Cass A, Brady J, DeVries J, Fewquandie B, Ingram S..**Liu H** et al. Facilitating engagement through strong relationships between primary healthcare and Aboriginal and Torres Strait Islander peoples. Australian and New Zealand journal of public health. 2016

Davy C, Bleasel J, **Liu H**, Tchan M, Ponniah S, Brown A. Effectiveness of chronic care models: opportunities for improving healthcare practice and health outcomes: a systematic review. BMC Health Serv Res. 2015 May 10;15(1):194.

Davy C, Bleasel J, **Liu H**, Tchan M, Ponniah S, Brown A. Factors influencing the implementation of chronic care models: A systematic literature review. BMC family practice. 2015

CONFERENCE PRESENTATIONS

2018 What will we do?"- Household expenditure post stroke in India, a case study from ATTEND trial, accepted for poster presentation. October 2018, Fifth Global Symposium on Health Systems Research. Liverpool, UK

2017 (1) The CVD polypill strategy for Aboriginal and Torres Strait Islanders- a post-trial evaluation. (oral presentation) (2) Family-led rehabilitation post stroke in India- process evaluation of a RCT (Oral poster) (3) Exploring use of evidence to inform investment in disease prevention (Oral Poster)- Nov 2017, 10th Health Services and Policy Research Conference, Gold Coast

Family-led rehabilitation post stroke in India- process evaluation of a RCT, Oral Presentation, Oct 2017, International Conference for Realist Research, Evaluation and Synthesis, Brisbane.

2016 Exploring use of evidence to inform investment in disease prevention, oral presentation, Nov 2016. 5th Annual NHMRC Symposium on Research Translation, Melbourne.

A qualitative study of how Australian decision makers use economic evidence to inform investment in disease prevention, poster presentation. Nov 2016. Fourth Global Symposium on Health Systems Research: Resilient and Responsive Health Systems for a Changing World. Vancouver, Canada

Preliminary findings from a process evaluation of a randomised controlled trial of family-led rehabilitation post stroke (ATTEND) in India, poster presentation. Oct 2016, 10th World Stroke Congress, Hyderabad, India

(1)A qualitative study of how Australian decision makers use economic evidence to inform investment in disease prevention. Oral presentation, (2) Examining the use of process evaluations of randomised controlled trials of complex interventions addressing chronic disease in primary health care- a systematic review protocol. Poster presentation. June 2016. Primary Health Care (PHC) Research Conference, Reform and innovation in PHC policy and practice. Canberra

2015 Do pragmatic trials result in research translation- a post-trial evaluation. Oral presentation. Nov 2015, 4th Annual NHMRC Symposium on Research Translation, Sydney

Do pragmatic trials result in research translation- a post-trial evaluation. Oral presentation. July 2015. Emerging Health Policy Research Conference 2015, Sydney

Facilitators and barriers to implementation of a pragmatic trial in Aboriginal health services. Abstract accepted for poster presentation at Primary Health Care (PHC) Research Conference, PHC Research Matters, 29-31st July 2015. Adelaide

2013 'Understanding adherence to a cardiovascular polypill strategy '- A process evaluation of a pragmatic clinical trial. Abstract accepted for poster presentation at the World Congress of Cardiology, Melbourne

Guidelines Adherence with the Polypill?'-a process evaluation of a pragmatic clinical trial**.** Abstract accepted for oral presentation at Health Services Research Association Australia and New Zealand: Health Services and Policy Research Conference, Wellington. 2-4 Dec 2013

Implementing a pragmatic randomized controlled trial in Australia, lessons learnt from Kanyini GAP. Oral session presentation at NHMRC Research Translation Conference Sydney

Preface

Reflexivity- How I came to this research topic

In qualitative research, the term reflexivity describes the importance of 'self- awareness, political/ cultural consciousness, and ownership of ones' perspective.' This is important as it is a hallmark of quality in qualitative research and provides credibility to the findings. This thesis compiles the findings of my work within multi-cultural collaborations on projects in Australia and in India. Thus, I preface this thesis to share with the reader my background and its relevance to this body of work.

"I have been interested in socio-determinants of health since high school due to several key experiences. These included volunteering at centres for abused children, medical student attachments at Aboriginal Community Controlled Health Services in Australia, attachments to different types of hospitals in China, and a HIV clinic in Uganda. From these experiences, I observed health inequity and inequalities in both low to middle income countries, and within developed countries. I have a passion in taking a holistic approach to health and addressing social as well as biomedical determinants to health.

I completed a MBBS in Sydney, and worked in the public hospital system before completing a Masters in International public health. My work at the George Institute for Global Health with the Kanyini Vascular Collaboration and partnering Aboriginal Community Controlled health services have further consolidated my belief that primary health care which is universal, community-led, efficient, affordable and of high quality plays a crucial role in improving health for all.

During this journey, however, I have been frustrated with the process of research and its impact on public health. There is so much time, money and effort that is poured into this area but from my observations, the impact is minimal or at least is seemingly slow to effect change. However, I still believe public health research is needed to provide much needed evidence-based interventions to improve health systems. Thus, I humbly embarked on this journey of study, with the aim in understanding how to develop and evaluate 'holistic' interventions which can be translated into meaningful patient-centred outcomes, and in doing so, help close the gap in health equity."

THESIS ABSTRACT

Background

Strengthening health systems to provide affordable, effective and accessible care in a life-course approach is necessary to address the growing global burden from non-communicable diseases (NCD). To address deficiencies in the health system, researchers have designed and trialled 'complex interventions' which are defined as interventions with multiple interacting components, and complexity in its implementation. Process evaluations alongside randomised controlled trials (RCT) of complex interventions are highly valuable. They explore implementation and different stakeholders' perspectives as to for whom, how and why a complex intervention has an impact.

Research aim and Methods

My research aim is to demonstrate that PEs are necessary to enable a deeper understanding of how interventions are implemented in a given setting through the analysis of local health system context and stakeholders' perspectives; and in doing so, help refine the intervention to address local needs, and inform future research priorities.

This was done through:

1) A systematic review which provides a synthesis and appraisal of the methods used in process evaluations of primary care interventions, and their main findings on implementation barriers and facilitators. (Chapter 2)
2) Two process evaluations of complex interventions that aim to improve access to affordable evidence-based care. First, is the process evaluation of a RCT of a secondary cardiovascular prevention strategy. The trial examines the efficacy of the

combined cardiovascular polypill in Australian primary health care to improve prescribing and patients' use of indicated therapy. (Chapter 3) Second, is the process evaluation of a RCT of a tertiary intervention, which is the training of family carers to provide basic rehabilitation for post-stroke patients in India. (Chapter 4) In these chapters, I highlight the relevance of the process evaluation findings for health system strengthening, and examine the facilitators and barriers to collaborative research.

3) A qualitative study where we explored Australian decision makers' perspectives of how evidence generated by researchers can be more relevant in informing their investment in NCD prevention. (Chapter 5)

Overall findings and implications from the thesis

Synthesising the findings and implications of individual studies (Chapters 2 to 5), there were three key crosscutting findings in the thesis.

First, we found that individual, organisation and policy level factors were critical to the sustainability and scale-up of complex interventions. For example, factors affecting patient adherence (such as patient-provider relationship), providers' perspective of the inflexibility of dosages, and policy changes (such as pharmaceutical benefits scheme) should be considered in the future implementation of the cardiovascular polypill. This implies that a 'top-down' (i.e. engaging policy makers) and 'ground-up' (i.e. engaging patients and their providers) approach is concurrently required to address NCDs across the breadth of relevant stakeholders (as depicted in Figure 1, reproduced from Chapter 5). Therefore, relevant stakeholders should be engaged early in the design of complex interventions so that: the intervention is clearly aligned with the needs of local stakeholders; that the roles and

responsibilities of key actors are better understood; and unanticipated consequences arising from context-specific barriers to implementation can be minimised.

Second, we identified the facilitators and barriers to the effective co-production of evidence such that the evidence generated fits the needs of the end-users (practitioners, patients and policy-makers). Facilitators to effective ongoing co-production include relationship building, values (such as equality and reciprocity), and locally driven research. For example, because of the successful completion of the ATTEND trial, a local stroke network in India was successfully funded to capitalise on their existing research network and infrastructure (e.g. staff, data collection).

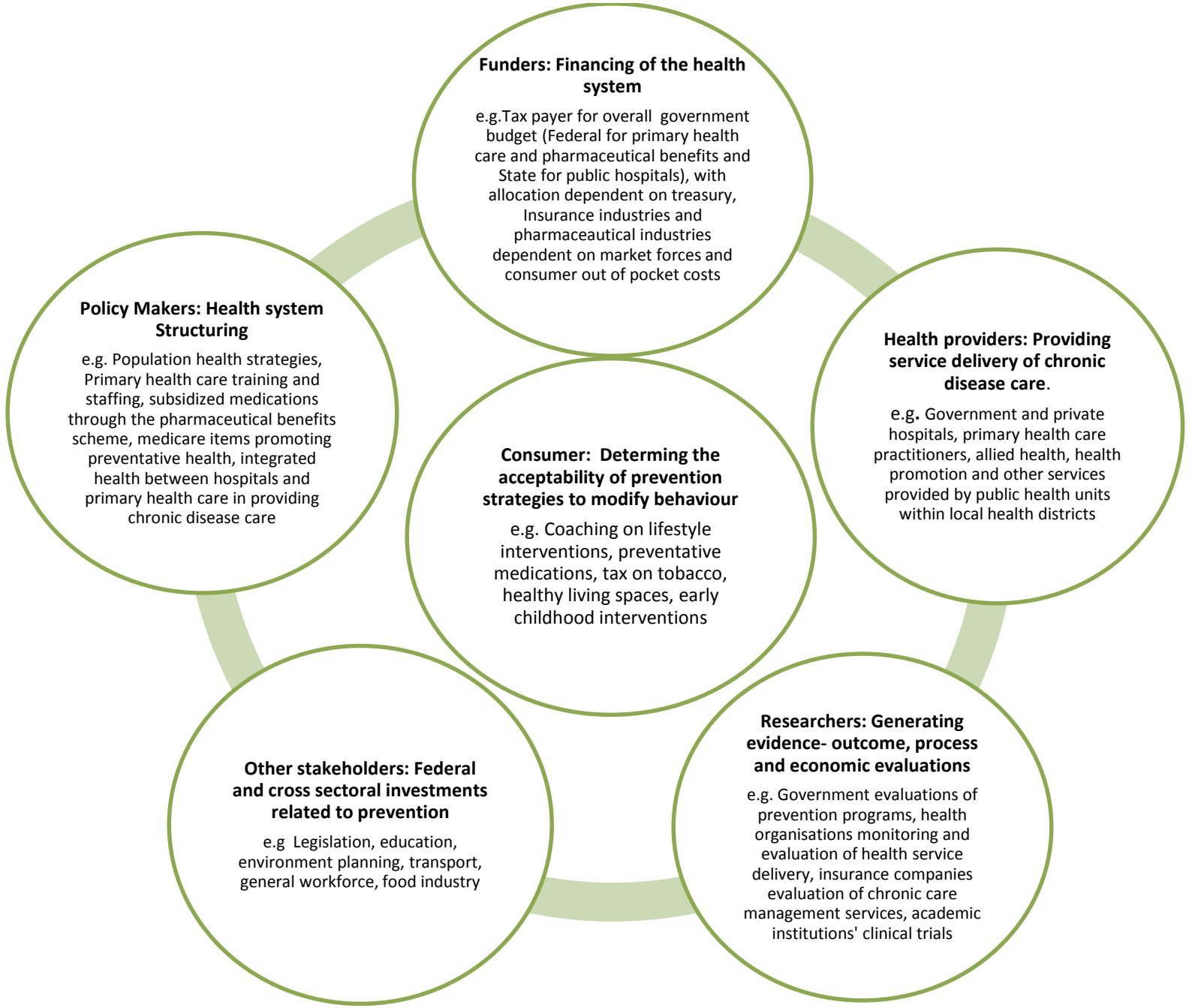
However, key barriers to co-production include challenges in reconciling stakeholders' diverse perspectives to align with the common research objective in a timely manner, and balancing competing service delivery and research activities. These findings imply that significant time for consultation and communication is required to build these critical relationships; and investment into capacity building and research infrastructure is essential.

Third, collectively this body of work demonstrates that process evaluations can be a *useful tool* for the effective co-production of evidence through two mechanisms. Process evaluations emphasises the importance of articulating the needs of end-users (patients, providers, practitioners, and policy-makers) within their local context; and doing so, further inform intervention design and implementation strategies needed for the sustainability and scaling up of locally relevant interventions. Moreover, a careful examination of contextual factors can help identify gaps in care and inform future research priorities. An example of a future research priority identified from the process evaluation of the ATTEND RCT is the

need to raise the public's awareness of stroke and the benefits of early presentation and rehabilitation.

Therefore, process evaluations can facilitate the effective co-production of evidence. This is possible through an iterative approach of understanding end users' ongoing needs, developing locally relevant interventions, implementation strategies, and identifying future gaps in care. This will provide critical evidence to stakeholders' question of '*is this intervention acceptable, effective, affordable and feasible (for me or) for this population*?' Making small but steady advances in strengthening health systems such that health care can be affordable, accessible and of high quality for all.

Figure 1: Contextual Map of Stakeholders in NCD prevention. The complexities of the provision of prevention strategies by various stakeholders, highlighting their roles and interlocking relationships which impact upon the consumer's behaviour change. (Reproduced here from Chapter 5)



CHAPTER 1: INTRODUCTION

Chapter Overview

Strengthening health systems to address the burden of non-communicable disease is challenging because the prevention of NCDs is inherently complex due to its distal and proximal determinants, and requires a life-course approach involving multiple sectors and stakeholders. Complex interventions as defined by their multiple interacting components (although additional dimensions of complexity include the difficulty in their implementation and the number of organisational levels they target), are used to target health system deficiencies. Process evaluations of complex interventions have been recommended to examine implementation and explore for whom, how and why an intervention has an impact.

This chapter presents an overview of the role of process evaluations in the field of health systems research. This chapter then sets out the research aim of the thesis with a description of the thesis structure and specific objectives related to each chapter. My research aim is to demonstrate that process evaluations can help us understand how interventions are implemented in given settings, through the analysis of local health systems and stakeholders' perspectives; and in doing so, help refine the intervention to address local needs, and inform future research priorities. The following chapters explore the methods and role of process evaluations of primary care interventions; contain case studies of process evaluations of secondary and tertiary interventions; and explore the use of evidence in informing investment in NCD prevention.

The Role of PEs in Health Systems Strengthening

Non-communicable diseases (NCDs) is rapidly rising in rank as a priority in lower and middle income countries (LMIC) undergoing epidemiological transition and already exert a huge burden in high income countries. (1) In 2016, it was estimated that 71% of deaths worldwide were due to NCDs. In 2018, there was a high level United Nations Meeting urging governments to reinforce their commitments to have a one-third reduction in the probability of dying from NCDs (between 30-70 years of age) by 2030. However, addressing the burden of NCDS is extremely challenging because the causes of NCDs are inherently complex, often involving an array of interacting social, environmental and individual life-style related risk factors. (2, 3) It involves taking a life-course approach requiring the effective integration of population health, primary and tertiary care, and other sectors (e.g. transport, food industry, and education), which adds another level of complexity.

The significant health and social impact of NCDs and the resultant inequity makes NCDs a priority for health systems research. The unpredictability and interconnectedness of human and ecological factors have been posited as a reason for the lack of global progress in addressing NCDs. (4) Some researchers have described that a way forward would be to embrace the 'complexity' through systems thinking and accept the complex and emergent changes inherent in the health system. (5) This would require the use of innovative interventions and evaluations to find sustainable solutions in the local dynamic context. (6) Increasingly, collaborative research using partnerships between health services and researchers to co-produce locally relevant evidence is desirable. This co-production approach presents a shift from the unidirectional traditional research pipeline of researchers generating evidence to be consumed by the end-users (patients, health practitioners, policy- makers). (7)

In order to strengthen the health system and address NCDs in an affordable, accessible and effective way, practitioners and researchers have designed and trialled complex interventions. These complex interventions are defined by their "multiple interacting components (although additional dimensions of complexity include the difficulty in their implementation and the number of organisational levels they target)." Evaluations of complex interventions include outcome/impact, process and economic evaluations. Impact evaluations determine effectiveness using comparison groups (i.e. in the absence of the intervention) and include study designs such as step-wedged and randomised controlled trials (RCTs). RCTs have been recommended as the gold standard in research designs to provide robust outcome evidence. (8) Therefore, in this thesis we decided to examine process evaluations of RCTs to determine whether and how evidence from RCTs can effectively and sustainably address NCDs.

Process evaluations alongside trials of complex interventions are important because they examine whether a complex intervention was implemented as intended, and address questions of for whom, how and why the intervention had an impact. (9) Process evaluation (PE) is defined by the UK Medical Research Council as a study which aims to '*understand the function of an intervention, by examining implementation, mechanisms of impact, and contextual factors*'. (9) Therefore, PEs can shed light on important contextual individual to policy level barriers that impact on the real-world implementation of an intervention. (10) For instance, the affordability of an intervention has an obvious influence on uptake of an intervention, but is also highly dependent on the level of subsidy available and the specific socio-economic circumstances of individuals. (11, 12) The quality of the interventions is dependent on the distribution and underlying training of the workforce, and on physical and

referral infrastructures. Access to services is impacted by factors such as patient awareness of need, long waiting times, and the availability of financial risk protection. (11) Therefore, PEs can improve our understanding of intervention mechanisms within local health system context through stakeholders' lived experiences. For example, in a PE, it may be useful to explore the impact of costs of care on end-users (patients, providers, policy makers). This is especially relevant for trials in low to middle-income countries (LMIC) and in populations who have complex needs. (13) This is because of the recognised decreased economic productivity resulting from NCDs and the burden on low-income households. (14) This forms a vicious cycle of financial catastrophe and family hardship, making future care (e.g. acute rehospitalisation or rehabilitation) less accessible and affordable. (13, 15, 16)

PE methodology is evolving. (9) Previously, they were used to examine the extent of implementation through the documentation and analysis of quantitative process indicators in a trial. Subsequently, PEs developed into qualitative research alongside trials to provide a deeper understanding of the disease condition, acceptability of an intervention and implementation issues. (8) These PEs were largely used to determine, in the wake of a negative trial result, whether the result was due to either implementation or intervention failure. However, there is growing recognition that using qualitative and quantitative data, and theoretical frameworks within PEs will help facilitate evidence to practice. (17, 18) Findings from such PEs can help inform stakeholders' question of 'Is this intervention acceptable, effective, affordable and feasible (for me or) for this population?' (19)

A recognised barrier in the translation of evidence into practice is the lack of stakeholder engagement with the results of the research.(20) As highlighted earlier, collaboration with and between stakeholders from the onset of the research through to dissemination may be a

solution. (21) However, collaborative research can be fraught with difficulties and exploring what enables or hinders effective stakeholder partnerships can be a useful component of a PE. Economic evaluations (such as cost-effectiveness studies, cost-benefit analysis) provide evidence of the cost effectiveness of a program versus the comparison. The underlying assumption by the research community is that the evidence from the impact, process and economic evaluations of complex interventions would inform decision makers in the investment for NCD prevention. To check this assumption and make progress towards NCD 2030, it would be useful to explore the use of economic evidence by stakeholders in informing investment in NCD prevention.

Research Aim and Structure of this Thesis

My research aim is to demonstrate that PEs are necessary to enable a deeper understanding of how interventions are implemented in a given setting through the analysis of local health system context and stakeholders' perspectives; and in doing so, help refine the intervention to address local needs, and inform future research priorities.

To achieve my research aim, the answers to the following questions are addressed in the subsequent chapters: *What are the methods and key findings of PEs of primary care interventions? Can I effectively conduct PEs of secondary and tertiary NCD intervention, and identify for whom, how and why these interventions have an impact on? And finally, how is evidence (outcome, process and economic) actually used by stakeholders in informing the investment for the prevention of NCDs*?

Chapter 2: The MRC PE framework is used to help synthesize the available evidence of published PEs of RCTs of complex primary care interventions. This is to identify key

implementation factors, the design features of PEs; and to highlight areas for improvement and development.

Chapters 3 and 4: In these chapters, PEs of complex interventions that aim to improve access to affordable, evidence-based care are presented. Chapter 3 contains the results of a PE of a randomised controlled trial (RCT) of a secondary cardiovascular prevention strategy, using the combined cardiovascular polypill, in Australian primary health care to improve prescribing and patient use of indicated therapy. Chapter 4 contains the protocol and results of a PE of a randomised controlled trial of a tertiary intervention, involving the training of family carers to provide basic rehabilitation for post stroke patients in India. The relevance of PE findings for health system strengthening are highlighted, and the facilitators and barriers to collaborative research are examined.

Chapter 5: Through a qualitative study, we explored the use of evidence in informing investment in NCD prevention by Australian decision makers, and provide recommendations on ways to bridge the research translation gap in the prevention of NCDs.

Chapter 6: The key findings from each chapter are consolidated providing a succinct summary of the thesis as a whole. Overall implications from the thesis for future research in this field are discussed.

This body of work was created as a useful resource for researchers, practitioners and policy makers regarding the use of PEs in informing the generalisability and sustainability of patient-centred complex interventions that are needed in health systems strengthening. While this thesis has a focus on addressing NCDs, there may be transferable insights to the evaluation of complex interventions in other fields.

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CHAPTER 2: SYSTEMATIC REVIEW EXAMINING THE USE OF PROCESS EVALUATIONS OF COMPLEX INTERVENTIONS ADDRESSING CHRONIC DISEASES IN PRIMARY HEALTH CARE

Chapter Overview

This chapter reports the protocol and the findings of a systematic review of process evaluations of complex interventions addressing chronic diseases in primary health care. The chapter consists of a published protocol and a submitted manuscript of its findings.

Process evaluations (PE) alongside randomized controlled trials of complex interventions are valuable because they examine implementation fidelity, and address questions of for whom, how and why the interventions had an impact. Recognising the rising global burden of chronic disease, and the pivotal role primary health care has in addressing it; we sought to identify key implementation factors, and methodology that could inform future research in this field. We used the UK Medical Research Council guidance for process evaluations as a guide, to provide a synthesis and appraisal of the methods used in PEs of primary care interventions, and their main findings on implementation barriers and facilitators.

Author Contributions: HL and SJ conceived the idea for the systematic review of process evaluations. DP, SJ and MH provided guidance to HL in the development of the protocol. AM, JM, and MN assisted HL in the selection of papers and data extraction. TL assisted with the adjudication of the papers. HL drafted the manuscripts and all authors contributed to the revisions of the manuscript and approved the final manuscripts.

Manuscript details:

(1) Liu H, Muhunthan J, Hayek A, Hackett M, Laba TL, Peiris D, Jan S. Examining the use of process evaluations of randomised controlled trials of complex interventions addressing chronic disease in primary health care-a systematic review protocol. Syst Rev. 2016 Aug 15;5(1):138.

(2) Liu H, Mohammed A, Muhunthan J, News M, Hayek A, Hackett M, Laba TL, Peiris D, Jan S. A systematic review of process evaluations of primary care interventions addressing chronic disease. Submitted to BMJ open in 2018, under review.

Liu et al. Systematic Reviews (2016) 5:138
DOI 10.1186/s13643-016-0314-5

Systematic Reviews

PROTOCOL Open Access

Examining the use of process evaluations of randomised controlled trials of complex interventions addressing chronic disease in primary health care—a systematic review protocol

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Abstract

Background: Randomised controlled trials (RCTs) of complex interventions in primary health care (PHC) are needed to provide evidence-based programmes to achieve the Declaration of Alma Ata goal of making PHC equitable, accessible and universal and to effectively address the rising burden from chronic disease. Process evaluations of these RCTs can provide insight into the causal mechanisms of complex interventions, the contextual factors, and inform as to whether an intervention is ineffective due to implementation failure or failure of the intervention itself. To build on this emerging body of work, we aim to consolidate the methodology and methods from process evaluations of complex interventions in PHC and their findings of facilitators and barriers to intervention implementation in this important area of health service delivery.

Methods: Systematic review of process evaluations of randomised controlled trials of complex interventions which address prevalent major chronic diseases in PHC settings. Published process evaluations of RCTs will be identified through database and clinical trial registry searches and contact with authors. Data from each study will be extracted by two reviewers using standardised forms. Data extracted include descriptive items about (1) the RCT, (2) about the process evaluations (such as methods, theories, risk of bias, analysis of process and outcome data, strengths and limitations) and (3) any stated barriers and facilitators to conducting complex interventions. A narrative synthesis of the findings will be presented.

Discussion: Process evaluation findings are valuable in determining whether a complex intervention should be scaled up or modified for other contexts. Publishing this protocol serves to encourage transparency in the reporting of our synthesis of current literature on how process evaluations have been conducted thus far and a deeper understanding of potential challenges and solutions to aid in the implementation of effective interventions in PHC beyond the research setting.

Systematic review registration: PROSPERO CRD42016035572

Keywords: Process evaluations, Primary health care, Complex interventions, Systematic review, Chronic disease, Qualitative

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Background

Why is this field of research important?

With a rapidly rising global burden of disease attributed to non-communicable diseases, access to high quality primary health care (PHC) is essential. Complex interventions, defined as '*interventions that comprise multiple interacting components, although additional dimensions of complexity include the difficulty of their implementation and the number of organisational levels they target*', are frequently deployed in an attempt to address health system deficiencies experienced by patients and providers [1]. Choosing a study design to assess effectiveness of complex interventions is not straightforward, and it is recommended to consider randomisation to prevent selection bias and provide robust evidence [2, 3]. Process evaluations, which are typically carried out in conjunction with randomised controlled trials of such interventions, can help explain for whom, how and why a complex intervention had a particular impact [4].

Such evaluations address the question 'Is this intervention acceptable, effective, affordable and feasible (for me or) for this population?' [5]. Process evaluations can enable patient-centred care by providing the opportunity for often over-looked patients' perspectives to be considered. As an example, while a pragmatic trial of a cardiovascular polypill in Australian PHC indicated the polypill was an effective, cost-effective strategy for improving patient adherence and the prescribing of indicated medications, our process evaluation interviews found that clinicians need to consider the polypill strategy alongside other evidence-based strategies. These strategies should cater to specific patient factors such as health literacy, sense of well-being, financial considerations, establishing ongoing respectful clinician and patient relationships and improving accessibility to health care [6].

Despite the generation of good quality evidence, this often does not translate into improved health outcomes [7]. A key barrier in the literature to research translation is cost at different levels, e.g. high outpatient costs for screening to the patient or cost of medications for the programme [8–10]. While health economic evaluations are increasingly being conducted as separate studies to provide evidence of cost-effectiveness to decision makers, there may be cost information that is relevant to the objectives of a process which needs to be investigated. For example, minimising indirect costs to patients is something that is important in understanding why an intervention may be more acceptable to patients compared to standard care. Conversely, for some, indirect costs associated with the intervention may discourage patients from seeking care. These are economic issues which we propose would be important to capture as part of process evaluations but are not strictly captured in health economic evaluations assessing the incremental cost-effectiveness of interventions. It would be pertinent as part of a process evaluation to incorporate relevant cost data from the onset, especially within PHC trials in low- and middle-income countries (LMIC) and in populations which have complex needs and limited funding to be allocated [9]. This would be important as part of a process evaluation, to unpack whether for whom and how an intervention can be implemented into routine practice after the trial is completed. These findings from process evaluations can then inform adoption of interventions into practice and thus the scalability and sustainability of interventions [11].

What is known about this field currently?

Process evaluation methodology is evolving [4]. Process evaluations were previously synonymous with qualitative research alongside trials and were conducted to provide a deeper understanding of the disease condition, implementation issues and mechanisms of the intervention [12]. However, there is a growing recognition that using qualitative and quantitative data (mixed methods) can help facilitate trial implementation and research translation [13–15]. For instance, stratifying quantitative outcome data by socio-economic status and triangulating it with qualitative interviews, multi-level modelling and embedded cost-analysis in a process evaluation may be useful in determining the relevance and feasibility of a proven effective complex intervention. Using mixed methods, a clearer picture of the intervention may emerge that could aid various stakeholders in their decision-making.

Although 'one size fits all' methods or methodologies are not available, various theories or frameworks to enhance implementation research have been used by researchers to assist in their process evaluations. In early 2015, guidance was published by the Medical Research Council (MRC) UK about the planning, conduct and reporting of process evaluations to aid researchers, policy makers and funders [11]. The article described the proposed functions of process evaluations of looking at feasibility and piloting, evaluation of effectiveness and implementation post-evaluation during the different stages of the development, evaluation and implementation of a complex intervention. These functions expanded upon the conventional definition of process evaluations being limited to during trial implementation and defined 'implementation' as '*the process through which interventions are delivered, and what is delivered in practice*'. For example, during the post-evaluation implementation stage, the authors recommend that the process evaluation serves to explore how there is '*routinisation of the intervention into new contexts, and long term implementation/maintenance*'. The authors suggest that this function of the process evaluation is needed as reviews have showed that post-trial, complex interventions are only partially maintained. Key recommendations regarding the planning,

design and conduct, analysis and reporting of process evaluations were also discussed in the MRC recommendations [4, 11]. For example, arguments for whether there should be a separation or integration of the process evaluation and outcome evaluation teams were presented. The need to integrate process and outcome data in the analysis and the timing of when process data should be analysed in relation to outcome data were discussed.

The appraisal of the quality of process evaluations has not been straightforward partly because of the variability in methods [11, 16, 17]. Grant et al. in a literature review found that the process evaluations were of poor and inconsistent quality and proposed seven criteria for the reporting of process evaluations including clearly labelling that it is a process evaluation [17]. Other suggestions include appraising the quality of the process evaluation based on the methods used. Given that most process evaluations will have a qualitative component, a set of criteria to examine the quality in the reporting of qualitative research will be relevant to most process evaluations [18, 19].

Dissemination and reporting of findings from process evaluations especially in academic publications can also be difficult due to a variety of reasons including feasibility due to limited resources for research projects, lag time till dissemination of result or publication bias as usually positive outcome trials will be reported but not necessary negative trials [11, 20]. This in turn could limit the likelihood of such relevant findings affecting policy and practice.

Why do this review?

The George Institute for Global Health has a current programme of research which focuses on addressing NCDs through cost-effective and equitable strategies in primary health care settings including LMIC, and with indigenous populations [21]. Our studies trial complex interventions such as capacity-building initiatives with local providers [22], use of innovative mobile technology [23], and cost-effective generic medications (e.g. polypill) within primary health care settings [24]. We have found that at times, despite acceptability and effectiveness of these strategies, there are significant challenges that impact upon their scale up. These barriers could be cultural, political or institutional factors [25], but an important reason for limited translation seems to lie in the lack of understanding of implementation issues within contextual factors for the different stakeholders (e.g. patient, provider, policy makers). For example, while a trial in India of a clinical decision support system on a mobile tablet improved initial diagnosis and antihypertensive management of trial patients, and was deemed acceptable by end-users, only 35% of patients attended the scheduled 1-month follow-up [23]. Interviews with stakeholders found that limited patient accessibility to medicines and doctors (for a variety of reasons including inadequate staffing, limited primary health care infrastructure) as the key barrier which needs to be overcome. This contrasts with other trials of electronic health tools (e.g. decision support, text messages) in Australia which tend towards generally more positive and sustained results as such presumably because system issues were less of a significant barrier given the universal and subsidised health care available [26–28]. Given the greater burden of early mortality from NCD in LMIC and disadvantaged populations [29], consolidating our findings in this proposed systematic review with an equity-focused lens to better understand how to strengthen PHC within relevant contextual policy and system issues would be useful. Indeed, systematic reviews of interventions in primary health care have concluded that in addition to clinical outcomes, rigorous evaluations of implementation outcomes (e.g. through process evaluations) are needed to ensure changes in practice [30, 31]. We hope that this systematic review will add to the process evaluation methodology and understanding of effective implementation strategies in different PHC settings [32, 33].

Objectives and key questions

To our knowledge, this is the first systematic review of process evaluations of randomised controlled trial (RCTs) in complex interventions in PHC. For complex interventions, the pre-specification of a theory for how an intervention is expected to work can be highly informative in identifying the mechanisms by which an intervention was hypothesised to have an impact and why it was found to be successful (or not). It provides a framework for assessing the behaviour of individual actors in the implementation of an intervention, potential breakdowns in the interactions between parties and puts into context these actions. Thus, findings from process evaluations from both positive and negative trials can shed light upon implementation facilitators and barriers, which would add to the collective lessons for researchers. Moreover, given that there are numerous theories and frameworks in this area, we thought it would be informative to describe the breadth of methods used and to make some recommendations on evaluation methods that should be incorporated into PEs of complex interventions. Thus, we aim to consolidate the methodology and methods from process evaluations of complex interventions in PHC and their findings of facilitators and barriers to intervention implementation in this important area of health service delivery.

These objectives will be achieved through addressing these questions: (a) Is there and what is the explicit theory behind the conducted process evaluations? (e.g. normalisation process theory, realist framework); (b) What are

the methods used in these process evaluations? (e.g. qualitative research through semi-structured interviews, surveys); (c) At what stage is the process evaluation done? (i.e. feasibility and piloting, evaluation of effectiveness, or post-evaluation implementation.); (d) If an aim is stated (i.e. in the evaluation of effectiveness stage), how are the results of the RCT integrated with the findings from the process evaluations?; (e) What are the strengths, limitations and potential solutions identified by the authors in conducting the process evaluations?; and (f) What are the barriers and facilitators to the implementation of complex interventions identified by the authors?

Methods/design

This systematic review will focus on process evaluations of RCTs of complex interventions addressing chronic disease in PHC. We have described our methods as per Preferred Reporting Items for Systematic Review and Meta-Analysis for protocol (PRISMA-P) recommendations, and this checklist is included as an Additional file 1 [34].

Eligibility criteria

Definitions as per PICO-D have been adapted for the purpose of this review [20, 35]:

Participants—participants include patients and health providers in the PHC setting addressing the prevalent chronic diseases as defined by the World Health Organisation—cardiovascular disease, chronic kidney disease, chronic respiratory disease, type 2 diabetes mellitus and depression. PHC as defined by the Alma-Ata declaration [36] as health services provided within the community setting by doctors, nurses and allied health with the goal to achieve better health for all through reforms in universal coverage, public policy, service delivery and leadership [37].

'Intervention'—complex interventions defined as those '*interventions that comprise multiple interacting components, although additional dimensions of complexity include the difficulty of their implementation and the number of organisational levels they target*' within PHC [4]. This includes a single-faceted intervention that requires multiple actors or pathways and thus makes the implementation complex. It is envisaged that the complex interventions for chronic diseases (if not explicitly defined as a complex intervention) will have elements of the Wagner chronic care model such as community support, case management, self-management, facilitated family support, organisational change, delivery system design, decision support for health care providers and clinical information systems [38].

Comparator—not applicable

'Outcomes'—(1) findings from the process evaluations of stated implementation barriers and facilitators to the complex intervention. (2) The stated strengths and limitations of the process evaluation methodology from the perspectives of the authors. Both findings will be useful for future conduct of complex interventions in PHC in the planning, conduct of process evaluations and in the consideration of intervention implementation and what barriers need to be overcome in different PHC settings.

Timing—years of search from 1998. This was chosen because a systematic review by Davies et al. shows that there was poor use of theory in implementation research until at least 1998 [39].

Design—process evaluations of randomised controlled trials of complex interventions in PHC. Process evaluation as defined by 'a study which aims to understand the functioning of an intervention, by examining implementation, mechanisms of impact, and contextual factors' [11]. As discussed by Grant et al., because process evaluations are not clearly labelled as such, qualitative research conducted alongside RCTs with similar aims will be included [17, 40].

Exclusion criteria—articles were excluded if they were not a journal article, not a report based on empirical research (e.g. protocol, editorial), not reported in English and reviews and not human research.

Search strategy

Information sources

Databases reporting academic publications (MEDLINE, SCOPUS, PsychInfo, CINAHL, EMBASE, Global Health.) In order to locate any process evaluations whose findings were not published or missed in the database searches, we will search major clinical trial registries for completed process evaluations (e.g. Cochrane Central Registry of Controlled Trials, EU registry, ANZTRN and clinical trial registry (USA)). Authors will be contacted in regard to the outcomes of the RCT and findings of their completed process evaluations.

A search strategy was developed and adapted for each database with the initial support of a medical research librarian. Search terms were based on the review objectives and early scoping searches (see Additional file 2: search strategy), key words: process evaluations (including programme evaluation, qualitative research), complex intervention (including chronic care model and its components of community support, case management, self-management, facilitated family support, organisational change, delivery system design, decision support for health care providers and clinical information systems), randomised controlled trials, PHC (including family practice, general practitioners) and chronic disease (including cardiovascular disease, chronic kidney disease, chronic respiratory disease, type 2 diabetes mellitus and depression).

Study records

Data management

After the searches, the shortlisted articles will be exported to Endnote. Data will be stored in a common file that is

password protected on the Institute's server that is accessible by the two reviewers. At each stage of the data selection process during the review (e.g. after consolidation of all articles prior to assessing eligibility based on title and abstract), back up files of the endnote database will be made in order to retrace any steps as needed in the review process, and for any third party adjudication.

Selection process

Two reviewers will screen all titles and abstracts identifying potential eligible studies based on inclusion and exclusion criteria, and duplicates are to be removed. This will be done independently to reduce the risk of bias. All eligible studies will be retrieved in full text and reviewed by the two reviewers using predesigned eligibility forms (see Additional file 3). Disagreements will be resolved by consensus of a third party in the review team.

Data collection process

Data from all included studies will be extracted by two reviewers using the eligibility and data extraction forms. The data extraction forms (see Additional file 4) were partly guided by the MRC recommendation for process evaluations and Grant et al.'s suggested minimal factors for reporting on process evaluations [4, 17]. The forms will be pilot tested by the two reviewers on the same three articles, iterative changes will be made when appropriate and the two reviewers will independently extract data from the rest of the included list of articles.

Data items

Variables to be extracted include data on the RCT and its process evaluation: (1) RCT—study design, setting (rural, urban, country), results (positive, negative or equivalent); (2) process evaluation—any published process evaluation protocol or evidence of pre-specified process evaluation in the main trial protocol, or stated aims of the process evaluation (e.g. examining recruitment, or explaining results), the process evaluation theory, justified methods of integrating trial and process outcomes, stage during which the process evaluation is done (feasibility and piloting, evaluation of effectiveness and post-evaluation implementation), methods of analysis and inclusion of costs incurred.

Outcomes and prioritisation

The outcomes of interest for our aims are (1) the stated strengths and limitations of the process evaluation methodology from the perspectives of the authors and (2) findings from the process evaluation of stated implementation barriers and facilitators of the complex intervention. Both findings will be useful for future conduct of complex interventions in PHC—in the planning, conduct of process evaluations and when considering the scaling up of an interventions and what barriers need to be overcome in a PHC setting depending on context [1]. For example, the community's need, the type of model or availability of PHC services will be different in developed settings as compared to LMIC.

Risk of bias in individual studies

For this review, we drew on the use of Tong et al.'s criteria for reporting of qualitative studies [19], on Grant et al.'s proposed framework of minimal requirements for the reporting of process evaluations of cluster randomised controlled trials [17] and on MRC recommendations for process evaluations of complex interventions [4]. Combining insights from these papers, a form of appraisal for risk of bias was derived (see Additional file 5). For the purposes of this review in examining the use of process evaluations alongside RCTs in PHC, studies were not excluded based on quality [20]. Instead, the quality of the studies is presented as a risk of bias graph (low, unclear and high risk) [41].

Data synthesis

This will involve the aggregation or synthesis of qualitative findings to generate a set of statements that represent that aggregation and categorisation of these findings on the basis of similarity in meaning and contexts. These categories will then be subjected to thematic synthesis in order to produce a single comprehensive set of synthesised findings that can be used as a basis for evidence-based practice. The synthesis of these qualitative data aims to satisfy the criteria established for the reporting of the synthesis of qualitative health research [18]. Abstracted quantitative data (e.g. number of positive trials) will be presented together with a descriptive narrative form including tables and figures to aid in data presentation where appropriate. We will examine how authors address potential bias through a narrative synthesis how well these are reported in the papers and strategies that may have been employed to mitigate this (e.g. triangulation of key findings). Depending on papers included, there may be subgroup analysis of further exploration of any differences of the barriers and facilitators to intervention implementation by context such as indigenous versus non-indigenous and of developed settings as compared to LMIC.

Discussion

There is a global call for PHC reform in the areas of service delivery, public policy and leadership to enable greater equity and improved health to different populations. To effect this change will require complex interventions involving multiple players (clinicians, community, allied health professionals, policy makers), disciplines (e.g. education, health) and what is successful in one context may not be suitable in another. Process evaluations

conducted alongside RCTs of complex health interventions are valuable in determining whether a complex intervention should be scaled up or modified for other contexts.

The conduct of process evaluations is still a dynamic area with no clear defined method, partly due to the spectrum of methods (e.g. observation, interviews and routine monitoring data). De Silva et al. in 2014 outlined the integration of the Theory of Change into the MRC framework for complex interventions, and one of its aims was to combine '*process and effectiveness indicators into a single analysis which can help untangle whether, how and why an intervention has an impact in a particular context, and whether it may be suitable for scale up or adaptation for new settings*' [42]. Moreover, in regard to future scale up of complex interventions, economic issues pertinent to stakeholders (e.g. patients and providers) would be crucial to policy makers and funders—while this has not been traditionally incorporated together with process evaluations, it would be helpful to see if it has been done [35, 43].

Process evaluations of complex interventions have been increasing in recent years and seem to be variable in objectives, methodology and quality. The MRC guidance in the conduct of process evaluations and in the interpretation of the RCT outcomes may be helpful for researchers to aid in the implementation of effective interventions beyond the research setting. This protocol outlines our methods and design in our efforts to systematically consolidate the collective experience of researchers in this field in conducting, analysing and reporting process evaluations by assembling the findings within the MRC's process evaluation recommendations and to understand previous challenges and potential solutions in the implementation of evidence-based complex interventions in PHC according to context.

Additional files

Additional file 1: PRISMA-P checklist. (DOC 82 kb)

Additional file 2: Example of search strategy. (PDF 314 kb)

Additional file 3: Eligibility forms. (DOCX 14 kb)

Additional file 4: Data extraction form comprising of four tables. (DOC 34 kb)

Additional file 5: Form of appraisal for risk of bias. (DOC 33 kb)

Abbreviations
LMIC, low- and middle-income countries; MRC, Medical Research Council UK; PHC, primary health care; RCT, randomised controlled trial

Acknowledgements
Not applicable.

Funding
This systematic review forms part of HL's PhD thesis and is not externally funded or commissioned.

Availability of data and materials
Not applicable.

Authors' contributions
HL conceived the study, conducted the scoping searches, designed and piloted the forms and drafted the manuscript; she manages the overall study and will be involved in the study selection, data extraction, synthesis and analysis. JM assisted in the scoping searches, piloted the data and quality appraisal forms, contributed to the drafts of the manuscript and is involved in the study selection. MH provided guidance to HL in the overall design of the study, assisted in refining the data extraction forms and drafted the manuscript. AH helped revise the manuscript and will contribute to the study selection, data extraction and synthesis. TL contributed to the early drafts of the manuscript, revised the manuscript and will contribute to the study selection. DP contributed to the early drafts of the manuscript and revised the manuscript. SJ conceived the study, provided oversight to HL and drafted the manuscript. All authors read and approved the manuscript.

Authors' information
HL had been funded by a University of Sydney Postgraduate scholarship and is currently funded by a National Health and Medical Research Council (NHMRC) scholarship. JM is a recipient of a PhD scholarship from The Australian Prevention Partnership Centre. MH is a recipient of a National Heart Foundation Future Leader Fellowship, Level 2 (100034, 2014–2017). SJ is the recipient of an NHMRC Senior Research Fellowship. TL is the recipient of a NHMRC fellowship. DP is the recipient of a Harkness Fellowship.

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Not applicable.

Received: 29 April 2016 Accepted: 3 August 2016
Published online: 15 August 2016

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A systematic review of process evaluations of primary care interventions addressing chronic disease

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Word Count: abstract- 257/ 300, main text 4503/4000.

2 Figures, 2 Tables, 1 Box

5 Supplementary files : 4 tables, PRISMA checklist

ABSTRACT

Objective: Process evaluations (PE) alongside randomized controlled trials of complex interventions are valuable because they examine implementation fidelity, and address questions of for whom, how and why the interventions had an impact. We used the UK Medical Research Council guidance for PE as a guide to provide a synthesis and appraisal of the methods used in PEs of primary care interventions, and their main findings on implementation barriers and facilitators.

Design: Systematic review

Setting: Primary health care

Participants: Patients with non-communicable diseases, and their health providers

Findings: 69 studies were included. There was an overall lack of consistency in how PEs were conducted and reported. The main weakness is that only 30 studies were underpinned by a clear intervention theory often facilitated by the use of existing theoretical frameworks. The main strengths were robust sampling strategies, and the triangulation of qualitative and quantitative data to understand intervention's mechanisms. Findings were synthesized into 3 key themes: 1) a fundamental mismatch between what the intervention was designed to achieve and local needs, 2) the required roles and responsibilities of key actors were often not clearly understood and; 3) the health system context – factors such as governance, financing structures and workforce- if unanticipated could adversely impact implementation.

Conclusion: Greater consistency is needed in the reporting, and the methods of PEs. In particular, greater use of theoretical frameworks to inform intervention theory. More emphasis on formative research in designing interventions is needed to align the intervention with the needs of local stakeholders; and to minimise unanticipated consequences due to context-specific barriers.

Registration with PROSPERO Registry: registration number is CRD42016035572

Keywords: process evaluations, primary health care, complex interventions, systematic review, chronic disease, non-communicable disease, qualitative

Strengths and Limitations of the study

- A study limitation is appraising the studies using a tool which we developed based on the UK Medical Research Council's guidance on process evaluations, which has not been tested elsewhere.

- A strength of this review is having a multidisciplinary team of authors with vast experience in clinical trials and process evaluations to enable a reflexive thematic synthesis and interpretation of the papers.

INTRODUCTION

An accessible, effective and affordable primary health care (PHC) system is needed to equitably reduce the rising non-communicable disease burden. (1-3) Complex interventions comprising of "multiple interacting components (although additional dimensions of complexity include the difficulty in their implementation and the number of organisational levels they target)" are often used to reduce this burden. (4) Such interventions addressing chronic disease often require individual and organisational behaviour change within dynamic policy, local environment and health system contexts. (5) (6) Randomised controlled trials (RCTs) of complex primary care interventions have been conducted but there is often ambiguity as to what was actually implemented. (7-9) Process evaluations (PE) are conducted alongside trials examine if a complex intervention was implemented as intended, and to explore if, for whom, how and why the intervention had an impact. (4)

A process evaluation is defined by the United Kingdom Medical Research Council (MRC) as a study to '*understand the functioning of an intervention, by examining implementation, mechanisms of impact, and contextual factors'*. (4) The MRC process evaluation framework and guidance published in 2015 is based on the synthesis of influential frameworks and theories in public health research and informed by the authors' process evaluations. (4) Implementation concepts of reach, fidelity, and adoption were made explicit, as was the need for the intervention theory i.e. the hypothesis relating to how the complex intervention may interact with contextual factors to produce variation in outcomes (10, 11) Ideally the intervention theory would determine the process (qualitative and quantitative) data to be collected and analysed before the RCT outcomes are known. PE findings could potentially help explain variation in RCT outcome, refine the intervention theory and inform future research priorities. Recognising the need to facilitate implementation of evidence into practice and policy- the MRC guidance also expands on the importance for process evaluations to be conducted across all stages of research i.e. feasibility/piloting, evaluation of effectiveness, and post-evaluation stages. While the guidance was well-received, outstanding questions remain in this developing field. For example, what is the role of other theories and frameworks for process evaluations? What methods can be used and how?(12-14) Synthesising the collective 'experience' described in published process evaluations may answer some of these questions.

This review has two primary objectives. First, to review the methods used in published process evaluations and their alignment with the MRC guidance, and second to identify the key implementation barriers and facilitators reported in these process evaluations.

METHODS

The systematic review protocol has been prespecified, and described in detail elsewhere. (15) A summary is presented here according the PRISMA guidelines.(16)

Eligibility Criteria for the randomised controlled trials with the included process evaluation

Population: Patients with non-communicable diseases(Diabetes, Depression, Cardiovascular Disease, Chronic Obstructive Pulmonary Disease, Chronic Kidney Disease, Type 2 Diabetes Mellitus), and their primary care providers. (5)

Intervention: complex interventions which comprise "*multiple interacting components although additional dimensions of complexity include the difficulty of their implementation and the number of organisational levels they targe*t" within PHC.(4)

Comparator: the control condition may include treatment as usual, active control or placebo control.

Outcomes for this systematic review: (1) Strengths and limitations of each process evaluation using the MRC guidance as a reference point. (2) Identification of implementation barriers and facilitators for the complex interventions.

Timing: published data from 1998.

Design: process evaluation of the included randomised controlled trials (RCTs) as defined by the MRC as 'a study which aims to understand the functioning of an intervention, by examining implementation, mechanisms of impact, and contextual factors'. (4) Given that process evaluations are often not explicitly labelled as such (11), we included studies with comparable aims.

Exclusion criteria: not a journal article, not a report based on empirical research, not reported in English, reviews and not human research.

Search strategy and data extraction: Standard systematic review methods were followed for searching (1998 till June 2018), screening and extracting data from eligible studies. (15) Two reviewers (HL, AM) conducted most of the data extraction, with a third reviewer (MN) assisting in data extraction with some papers and as part of quality assurance, checked on the data extraction for a 10% sample of the identified papers. Given that a key aim of this study was about process evaluation methodology- we deviated from the published systematic review protocol, by including our interpretation in addition to the study's strengths and limitations posited by the authors of those papers.

Data analysis and synthesis

Descriptive items (e.g. number of positive RCTs) were tallied and synthesised into 3 tables. (1) Overall characteristics: presenting the studies grouped into different diseases and ordered by year of publication. (Appendix 1); (2) Methods table: grouping studies by the stages of the process evaluation (i.e. feasibility/ piloting, effectiveness, post-evaluation) (Appendix 2); (3) Quality assessment. (Appendix 3).

Extracted qualitative data were coded by HL, and grouped into categories of context, mechanisms and implementation. Inductive derivation of the key themes was done through constant comparison between the findings from the papers within each category and examining the relationships between them. Appendix 4 provides illustrative quotations. The methodological and implementation findings were triangulated using a modified MRC PE framework to examine how the process evaluations elicited the implementation findings.

FINDINGS

(1) Characteristics of included studies

We identified 69 studies. The PRISMA flowchart is presented in Figure 1. In summary, 66 studies were conducted in high income countries, 1 study in Zambia, 1 in Malaysia and 1 in India. Cardiovascular disease, diabetes mellitus, and depression were the conditions most often investigated, with only six studies on chronic obstructive pulmonary disease and one study on chronic kidney disease. Overall, the complex primary care interventions fit within the general categories of facilitating patient self-management (13 studies), organisational change to include collaborative care (15 studies), facilitating better case management using

clinical information systems (e.g. tele-health) (15 studies), and the use of decision support and guideline implementation (e.g. referral systems) (22 studies). In addition, 5 studies explored the challenges when conducting trials in primary care e.g. the recruitment of patients.

Only 22 studies were labelled clearly as process evaluations, though this was more common in recent years. Twenty studies were conducted at the feasibility stage with five labelled as PEs, 43 studies at the effectiveness stage with 17 labelled as PEs, and six studies at the post-evaluation stage with none labelled as process evaluations. In thirty-five studies the degree of separation between the process and outcome evaluation researchers was explicit. The cost considerations for the system and stakeholders was mentioned in 10 papers (see Table 1 for more detail). In Figure 2 the context of the studies and an overview of the main methodological and implementation findings are diagrammatically presented in a PE framework.

(2) Process evaluations' strengths and limitations

Description of Intervention theory- clear intervention description and clarification of causal assumptions

Thirty papers were assessed as having clear intervention descriptions and clarification of causal assumptions, and in sixteen it was unclear because despite clear intervention descriptions, the causal assumptions were not described explicitly. An example of a paper that explicitly describes intervention theory is Grant et al who uses the Template for Intervention Description and Replication (TIDieR) checklist to clearly describe the researchers' assumptions of the intervention's mechanism as compared to the stakeholders' perspectives. (17)

Use of existing theories and frameworks: A strength of 22 studies was the use of existing theoretical frameworks to inform their intervention development and/or evaluation. (See Table 2) Theories and frameworks used are grouped according to Nilsen's proposed categories.(18) This is depicted in Box 2, with illustrative examples from the identified studies. In essence, eleven studies used classic theory to inform the development of the intervention theory. In eight studies determinant, implementation theories and evaluation frameworks were used to assist in the synthesis and analysis of qualitative data. The

authors of two studies also used their findings and implementation theories to iteratively inform their implementation strategies. The evaluation frameworks were used by study authors to comprehensively evaluate and synthesise their process evaluation data. The MRC framework for complex interventions was used to inform the approach to intervention development in three studies.

The use of theoretical frameworks seems to enable an in-depth investigation of stakeholders' perspectives of the perceived mechanisms of the intervention; by in a sense, providing a checklist of actions and behaviours to be examined.(19-29) An illustrative example is the PE of a trial in improving primary care referrals of patients with diabetic retinopathy to specialists through the use of educational printed materials. (29) A behavioural theory was used to inform the design and use of a questionnaire to explore the mechanism of the intervention. It was found that the primary care providers' intention to refer patients was the same before and after the trial, and this may have explained their negative trial results. The authors highlighted that the use of existing behavioural theory enhanced the '*generalisability and replicability'* of their methods.

Interaction with contextual factors: In fourteen papers the interaction of the intervention and contextual factors were explicitly explored. As mentioned above, theoretical frameworks often facilitated a closer and systematic way to consider context. For example, authors examined if there was 'contextual integration' i.e. organisational changes necessary to integrate a collaborative model of care for depression into routine practice. (30) Otherwise, contextual factors (e.g. impact of the introduction of a new policy (31)) were reported retrospectively in some papers in a more ad hoc manner- as reported implementation facilitators and barriers, or discussed as possible influences on the outcomes.

Methods used

Most authors clearly justified the choice of their methods and clearly stated the studies' purpose. The methods could be categorised as: qualitative studies (e.g. interviews, focus group discussions, documentary analysis), quantitative (e.g. processes of care, baseline demographics, secondary outcomes) and studies which presented the synthesis of qualitative and quantitative data sources to indicate implementation, acceptability, fidelity

and reach. Most of the qualitative studies were of reasonable quality as assessed by the consolidated criteria of reporting of qualitative research (COREQ). (See Table 2 and Appendix 3 for more detail.)

A strength of some studies was the triangulation of quantitative indicators with the qualitative findings of the acceptability and implementation of the intervention to determine intervention fidelity (i.e. whether the intervention was delivered per protocol). (See Appendix 2 for more detail.) (32, 33) The data sources indicating intervention fidelity included routine administrative data, trial/study management logs (22) and trial secondary outcomes. (34-36) Innovative indicators of e-health interventions included recording process measures such as time logged on by participants. (37) Other methods to determine intervention fidelity across multiple sites was having independent expert assessors reviewing intervention delivery using standardised forms. Three studies investigated 'for whom' an intervention had an impact on with the use of logistical regression of baseline demographics to identify relationships of the participants' characteristics with the primary or secondary outcomes. (38)

Sampling limitations in the qualitative studies were described as potentially introducing bias in the findings about intervention acceptability/mechanisms. (19, 20, 24-26, 29, 39-42) For example, authors highlighted that respondents who having agreed to be interviewed may have a more favourable opinion of the intervention. (19, 39, 43-45) Maximum variation sampling (types of participants, socio-demographics, by 'negative' baseline of outcome characteristics'), comparing the characteristics of participants who did not partake in the interviews/surveys with the participants who did and triangulation with other data sources may increase the robustness of such findings. (20, 21, 23, 29, 39, 40, 46)

(3) Process evaluation findings under mechanisms, implementation and context

Does the intervention fit local needs?

Stakeholders were generally motivated to adopt/implement the complex intervention if it addressed the contextual gap in care i.e. intervention fit. For example, a nurse-led secondary prevention clinic was implemented effectively when the health providers perceived it as improving team work, care continuity and providing a 'safety net' for the patients. In contrast, at other sites, this intervention was poorly implemented by the health

care providers who viewed it as duplicating the existing model of care. (47) As another example, general practitioners reported that training them to manage acute and discrete episodes of depression, did not improve their management of depression. This was because this training did not upskill them for the chronic and relapsing nature of depression associated with personality and social problems increasingly seen in primary care. (42, 48) Similarly, patients' health literacy about their chronic disease (e.g. effectiveness of lifestyle modification for diabetes) was crucial as it affected engagement with the primary health care services, and their uptake of the intervention. (23, 26, 49-51)

Do key actors believe in and adopt their 'assigned' roles and responsibilities?

The extent to which key actors believed in and adopted their 'assigned' roles and responsibilities as part of implementing the complex intervention was a key theme under the heading 'Implementation.' (22, 27, 28, 43, 48, 52) For example, in a study which used tele-monitoring to improve management of COPD patients in the community- there were differing views of the role of the patient. Some health providers described concerns that tele-monitoring would reinforce the 'sick role' of the patient, and an over-reliance on technology and practitioner support; and as such were less willing to implement this model of care. On the other hand, some patients described that tele-monitoring was empowering as it provided knowledge and increased access to health practitioners who could provide reassurance in the management of the disease- and were keen to continue this model of care.(23)

Facilitators to improve key actors' uptake of the interventions included the provision of intense training over a transition period prior to the start of the trial, significant research support, and ongoing communication with the researchers to help identify key actor's concerns and tailor implementation strategies to address them. For example, implementation strategies to ensure adequate communication between nurse practitioners and general practitioners were essential in task-shifting models of care. This facilitated greater trust between nurse practitioners and doctors which was needed to effectively deliver collaborative services. (52) Such strategies were especially relevant for collaborative care interventions where new tasks were introduced within established hierarchical systems and interaction between different stakeholders was necessary for effective implementation.

Is the context of the intervention conducive?

Health system structures such as governance, health financing structures and workforce, were often mentioned as impacting on intervention implementation. Governance structures was pivotal to the successful adoption of the intervention (24, 34). For example, an intervention to enhance referrals to mental health services was implemented well at a site when it was perceived as 'service delivery' and directly supported by the mental health trust. In comparison, uptake of the intervention was limited when the intervention was not viewed as 'service delivery' and was considered 'primary research'. (34) Similarly, cultivating a strong partnership between researchers and clinicians through the formation of clinical advisory teams facilitated the intervention implementation in bureaucratic and geographically complex environments. (24) A limited workforce and equipment shortages, and inadequate funding structures were reported by several authors as barriers to the adoption of the intervention. For example, health providers stated that the lack of government reimbursement for allied health services reduced the acceptability of the tele-health model of care for ongoing monitoring of diabetes at home. (40) General practitioners reported that time constraints in their busy practices prevented them from using the skills they learnt through an educational intervention to better manage depression. (42) Likewise, macro level context such as medication being out of stock in rural Zambia, was a barrier to the better outcomes, in spite of an evidence-based intervention to improve clinical assessment and management. (33)

Importantly, an iterative collaborative approach was described as a facilitator of intervention fit. (19, 37, 45, 50, 51, 53, 54). For example, study authors described how early stakeholder involvement identified the key characteristics of the lay worker needed (i.e. female, with visibility in the community) for their intervention to improve mental health care in India. This preparatory phase in the development of their model of care led to a definitive RCT with positive outcomes. In their process evaluation of the RCT- they found that the provision of a lay worker was not relevant for the private primary care practitioners with established therapeutic relationships with their patients, but more so for the public health providers who were time poor. These findings would then inform future scale up of the intervention within the right context (i.e. public health system) for the intervention. (53, 55)

Discussion

Statement of principal findings

To our knowledge this is the first systematic appraisal using MRC guidance on process evaluations of primary care interventions. 66 of 69 studies were conducted in high-income countries; whilst cardiovascular disease, diabetes and depression were the most frequently studied conditions. There was an overall lack of consistency in the way PEs were conducted and reported. Indeed there was a lack of consistency in nomenclature with only 47 of the 69 studies identifying as 'process evaluations' although their purpose were essentially as such. Few studies (n=30) were underpinned by an intervention theory- description of hypothesised intervention mechanisms of action within local contextual factors. Most studies used robust sampling strategies and frequently triangulated qualitative and quantitative data to better understand the mechanisms of implementation. The MRC PE guidance with its focus on the interaction/configuration between context, implementation and mechanisms of intervention, provided a useful framework for the synthesis of the findings. The findings of these studies can be synthesised into a number of key messages: 1) that often there was a fundamental mismatch between what the intervention was designed to achieve and local needs, 2) that the roles and responsibilities of key actors required to implement the intervention were often not clearly understood and; 3) that health system context – factors such as governance, financing structures and workforce – were often critical to implementation and as a consequence there were a number of studies where the unanticipated influence of these adversely impacted on implementation.

Comparison to other literature and implications

A key finding is identifying the breadth of literature which fits the MRC definition of process evaluation. This highlights the growing scope in this field to potentially address the evidence to practice gap through greater understanding of the interactions between intervention mechanisms, context and implementation. (13, 56, 57) However, greater consistency is needed in the reporting of PEs – as this would facilitate evidence synthesis, prevent research duplication and enhance transferability of interventions to other settings. (58) We note that the consistency in reporting seems to have increased since the publication of the MRC guidance.

An important finding is that theoretical frameworks helped guide a more in-depth development of intervention theory, design and implementation. (13, 59) The MRC PE guidance suggests that PE can help to explain the outcomes variations, and by doing so help refine the intervention theory. (18) We note that given the growing focus on self–management for chronic diseases, that the theories around behavioural change (e.g. empowerment) were most commonly used. Secondly, the focus on organisational change and the adoption of guidelines in NCDs, meant that implementation theories such as Normalisation Process Theory (NPT) were particularly relevant. Thus, there should be more consistent use of theoretical frameworks, recognising that different frameworks will be applicable to different settings. In addition, the use of checklists such as the Template for Intervention Description and Replication (TIDieR), or the Standardised for Reporting Implementation (StaRI) will ensure consistency in the reporting of intervention theory and implementation, thus reducing research waste. (56, 60, 61)

We found that the intervention interaction with dynamic contextual factors was often inconsistently reported or reported retrospectively in an ad hoc manner. This gap has been similarly reported in the literature. (62)These findings emphasis MRC PE guidance's value in explicitly appraising context through "*examining factors that shape theories, and affect implementation, and act to 'sustain the status quo, or potentiate effects*." (4) However, this guidance is relatively broad and non-specific, and the question remains as to what should be explored a priori, and how best to report such findings. For example, the Context and Implementation of Complex Interventions (CICI) framework highlights seven domains of context ("*geographical, epidemiological, socio-cultural, socio-economic, ethical, legal and political context"*) that could be examined.(56) Similarly, STaRI checklist has context as an item in the methods (*i.e. "consider social, economic, policy, healthcare, organisational barriers and facilitators that might influence implementation elsewhere"*) and in the results ("*contextual changes (if any) which may have affected outcomes"*.)(60) These domains are comprehensive, and as a consequence if a study is to examine only a subset of these factors, it is better that it this is pre-specified in full acknowledgment of the evaluation as a whole. This should be consistently reported, and linked through a full report or reference to a protocol. (4) As a baseline, a standardised PHC template informed by the questions of "*Does the intervention fit local needs? Do the key actors believe in and adopt their 'assigned' roles*

and responsibilities? Is the health system context (looking specifically at health workforce, governance, health financing structures and availability of medications) conducive?" and relevant implementation theories (e.g. NPT) could be presented for testing in a systematic way. This could be done by primary health care researchers engaging with stakeholders at various time points, and iteratively added to. (63-65) Such an approach could potentially facilitate a greater shared understanding between stakeholders and greater consistently in the reporting of context. (62, 64, 66-68)

Most of these studies were conducted in high income countries with established PHC systems and universal health coverage (e.g. National Health Service in the UK). Therefore, some primary care interventions (e.g. improving referrals in collaborative care) may be of limited relevance to LMIC PHC systems given the different context especially with regards to health system structures. (69, 70) This reinforces the need for more formative research with local stakeholders when developing evidence-based interventions which addresses local needs, and minimises the unanticipated consequences of health system factors. (71, 72)

Strengths and limitations of this study

We were unable to conduct a subgroup analysis of implementation findings by country context (i.e. of high income countries as compared to lower middle income countries)as we identified studies conducted mainly in high income countries. Some studies conducted in LMIC initially identified in the search were excluded because they did not meet our criteria (not RCTs, not on NCDs) and as such, a review with different inclusion criteria may be better suited for this secondary objective. Another limitation, is that we appraised the studies using a tool which we developed based on the MRC guidance (4), which has not been tested elsewhere. This was challenging given the heterogeneous studies that were included. For example, we only assessed qualitative methods with COREQ, and did not appraise the quality of statistical methods such as modelling. A strength of this review is having a multidisciplinary team of authors with vast experience in clinical trials and process evaluations to enable a reflexive thematic synthesis and interpretation of the papers. (73)

Conclusion

Greater consistency is needed in the reporting of, and the methods used, in PEs. In particular there should be more consistent use of theoretical frameworks to inform intervention theory; and the triangulation of qualitative and quantitative data. Greater emphasis on formative research in designing primary care interventions is needed so that they are clearly aligned with the needs of local stakeholders, that the roles and responsibilities of key actors are better understood and that unanticipated consequences arising from context-specific barriers to implementation are minimised. We hope this review will inform future process evaluations and facilitate the sustainability of evidence-based interventions.

Declarations

Abbreviations:

MRC: Medical Research Council

PE: Process Evaluations

NPT: Normalisation Process Theory

NCD: Non-communicable diseases

LMIC: Low and middle income countries

PHC: Primary health care

RCT: Randomised Controlled Trials

TIDieR: Template for Intervention Description and Replication

COPD: Chronic Obstructive Pulmonary Disease

COREQ: consolidated criteria of reporting of qualitative research

STaRI: Standardised for Reporting Implementation

CICI: Context and Implementation of Complex Interventions

Original protocol: This has been published in an open access journal and is referenced in the manuscript.

Ethical Approval and Consent to participate : not applicable

Competing interests: The authors declare that they have no competing interests.

Authors' contributions: HL and SJ concieved the idea for a systematic review of process evaluations. DP, SJ and MH provided guidance to HL in the development of the protocol. AM, JM, and MN assisted with the selection of papers, data extraction and analysis. TL assisted with the adjudication of the papers. HL drafted the manuscript and all authors contributed to the revisions of the manuscript and approved the final manuscript.

Funding Statement: This systematic review forms part of HL's PhD thesis and is not externally funded or commissioned.

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Figures and Tables

Figure 1: PRISMA figure

Figure 2: MRC PE framework which provides an overview of the findings (legend: MRC PE framework that provides an overview of the findings across context, mechanisms, and outcomes (key areas of the process evaluation, in blue), and the intervention description and outcomes. This is done by showing the number of studies across these headings, and to triangulate the synthesised qualitative findings about the studies' strengths and limitations, and barriers and facilitators).

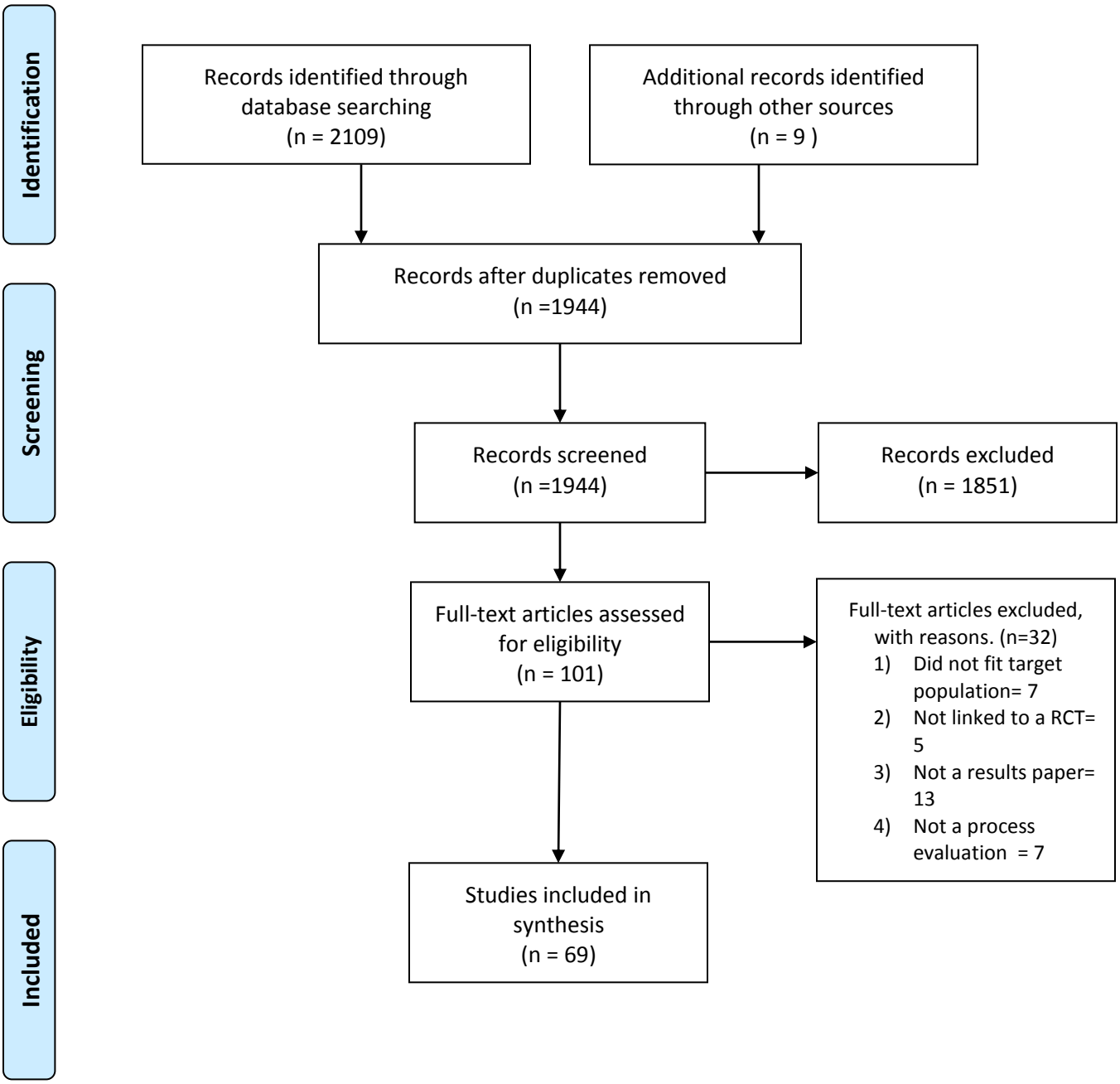
Table 1: Summary of the characteristics of the included studies

Table 2: Summary of the methodology used and quality assessment of the studies

Box 1: Illustrative examples of the use of Theories and Frameworks

APPENDIXES

1) Table 1- PICO table (organised into sections based on the types of NCDs, and within each section, studies are ordered by years)
2) Table 2- Methods table, organised into sections based on stage of process evaluation, and within each section, ordered by years)
3) Table 3- Quality of studies table as informed by the MRC recommendations and the COREQ
4) Table 4- Illustrative examples for the synthesised findings
5) PRISMA Statement



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For more information, visit www.prisma-statement.org.

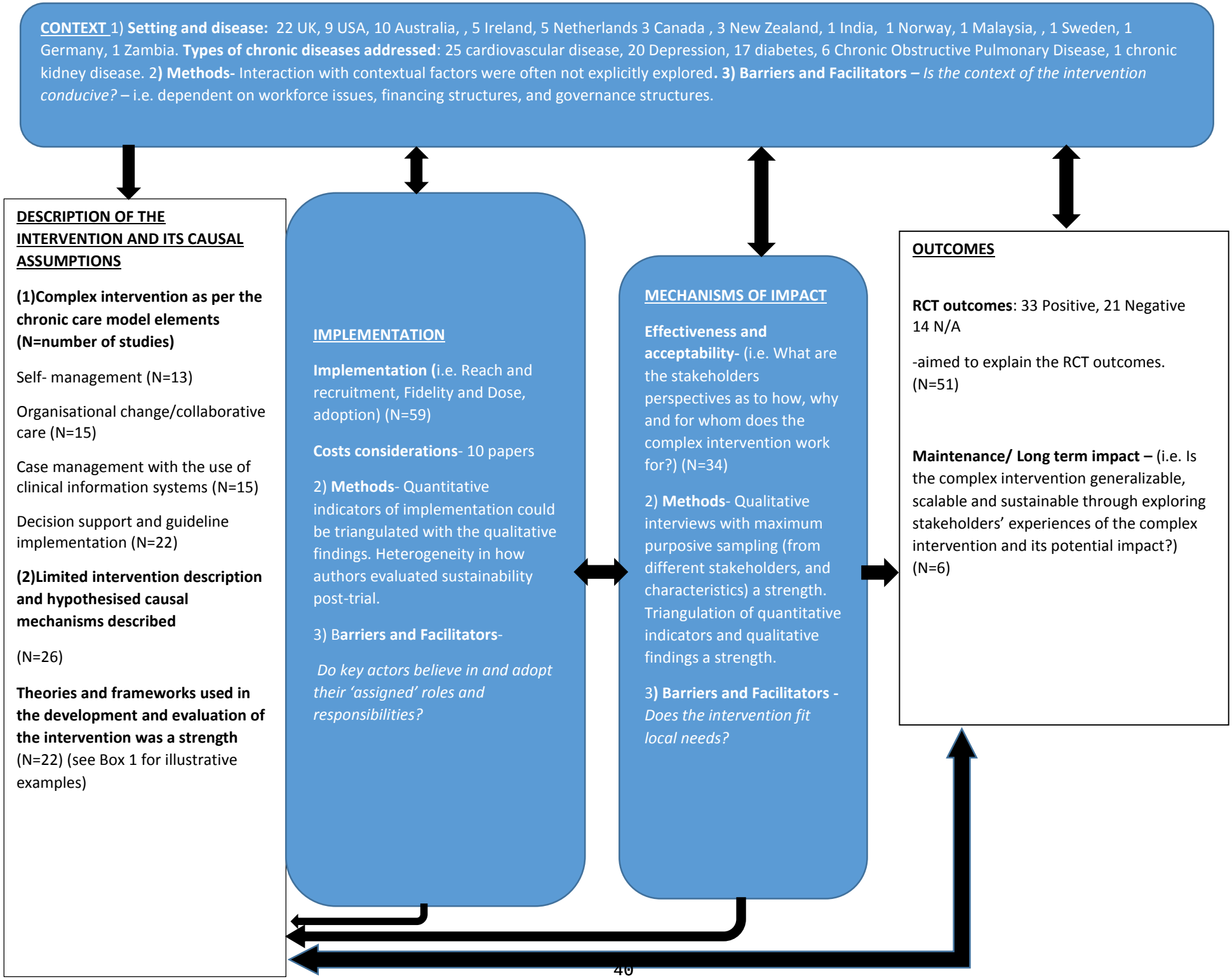
CONTEXT 1) Setting and disease: 22 UK, 9 USA, 10 Australia, , 5 Ireland, 5 Netherlands 3 Canada , 3 New Zealand, 1 India, 1 Norway, 1 Malaysia, , 1 Sweden, 1 Germany, 1 Zambia. Types of chronic diseases addressed: 25 cardiovascular disease, 20 Depression, 17 diabetes, 6 Chronic Obstructive Pulmonary Disease, 1 chronic kidney disease. 2) Methods- Interaction with contextual factors were often not explicitly explored. 3) Barriers and Facilitators – Is the context of the intervention conducive? – i.e. dependent on workforce issues, financing structures, and governance structures.
DESCRIPTION OF THE INTERVENTION AND ITS CAUSAL ASSUMPTIONS
(1)Complex intervention as per the chronic care model elements (N=number of studies)
Self- management (N=13)
Organisational change/collaborative care (N=15)
Case management with the use of clinical information systems (N=15)
Decision support and guideline implementation (N=22)
(2)Limited intervention description and hypothesised causal mechanisms described
(N=26)
Theories and frameworks used in the development and evaluation of the intervention was a strength (N=22) (see Box 1 for illustrative examples)
IMPLEMENTATION
Implementation (i.e. Reach and recruitment, Fidelity and Dose, adoption) (N=59)
Costs considerations- 10 papers
2) Methods- Quantitative indicators of implementation could be triangulated with the qualitative findings. Heterogeneity in how authors evaluated sustainability post-trial.
3) Barriers and Facilitators-
Do key actors believe in and adopt their 'assigned' roles and responsibilities?
MECHANISMS OF IMPACT
Effectiveness and acceptability- (i.e. What are the stakeholders perspectives as to how, why and for whom does the complex intervention work for?) (N=34)
2) Methods- Qualitative interviews with maximum purposive sampling (from different stakeholders, and characteristics) a strength. Triangulation of quantitative indicators and qualitative findings a strength.
3) Barriers and Facilitators - Does the intervention fit local needs?
OUTCOMES
RCT outcomes: 33 Positive, 21 Negative 14 N/A
-aimed to explain the RCT outcomes. (N=51)
Maintenance/ Long term impact – (i.e. Is the complex intervention generalizable, scalable and sustainable through exploring stakeholders' experiences of the complex intervention and its potential impact?) (N=6)

Table 1: Summary of the characteristics of the included studies

Disease Condition	interventions	Setting	RCT Outcomes	Cost Considerations (Y/N/NA)
20 studies on depression.	Interventions mostly around collaborative care through increasing expertise of different roles (e.g. lay worker, nurse for pro-active care, GP for PHC) (16 studies), times to implement practice guidelines (4 studies), and trialling specific interventions such as physical exercise and cognitive behaviour therapy. (2 studies).	9 UK, 7 USA, 1 Sweden, 1 Germany, 1 Australia 1 India.	11 positive RCTs, 5 Negative, 4 N/A	4/19 Y, 14 N, 2 N/A
17 studies on diabetes	The interventions included improving guideline-based referral and treatment (7 studies), patient self-management, community support (7 studies) and tele-health (3 studies).	3 Ireland, 3 UK, 1 Norway, 2 USA, 2 Canada (1 of the First Nations), 2 Australia, 1 New Zealand, 1 Malaysia	6 Positive, 10 Negative, 1 N/A	3/16 Y, 13/16 N, 1/16 N/A
25 studies on CVD.	10 studies were about improving the screening and management of CVD using best-practice guidelines. (e.g. educational materials to improve referral, or decision analysis). 10 studies were about organisational change with models of care that incorporated new roles such as a nurse-led clinic, or the use of a lay worker for angina management, and technology (e.g. tele-monitoring, point of care testing). 5 studies explored trial implementation such as recruitment of patients and providers, and were less about the intervention.	9 UK, 6 Australia, 3 Canada, 2 New Zealand, 2 Netherlands, 1 Ireland, 1 USA, 1 Zambia	15 Positive, 5 Negative, 5 N/A	3 Y, 15 N, 6 N/A
6 studies on COPD (2 including other chronic disease), and 1 addressing CKD.	4 studies were about improving self-management of patients through educational materials, or use of monitoring, with support from health providers. 2 studies were about stimulating physical activity through the use of technology. 1 study was about implementing management guidelines in CKD in primary health care.	3 Netherlands, 1 Ireland, 1 UK (Scotland), 1 USA, 1 Australia	2 Positive, 1 Negative, 4 N/A	0 Y, 5 N, 2 N/A.
Overall Synthesis of 69 studies in total. 20 Depression, 17 Diabetes, 25 CVD, 6 COPD and 1 CKD.	**Overall, the complex primary care interventions fit within the general categories of facilitating patient self-management (13 studies), organisational change to include collaborative care (16 studies), facilitating better case management using clinical information systems (e.g. tele-health) (15 studies), and the use of decision support and guideline implementation (e.g. referral systems) (22 studies). In addition, 5 studies were exploring the conduct of trials in primary health care e.g. the recruitment of patients.**	**22 UK, 10 Australia, 9 USA, 5 Ireland, 5 Netherlands, 3 Canada, 3 New Zealand, 1 Sweden, 1 Germany, 1 India, 1 Norway, 1 Malaysia, 1 Zambia In addition, 2 studies focused on First Nations peoples in Australia and in Canada. 3 studies were focused on the populations living in disadvantage.**	**33 Positive, 21 Negative 14 N/A**	**10 Y*, 47 N, 11 N/A**

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; CKD: Chronic Kidney Disease; CVD: Cardiovascular Disease; GP: General Practices; N: No; N/A: Not Applicable; RCT: Randomised Controlled Trial; UK: United Kingdom; USA: United States of America; Y: Yes.

* Of note two were full evaluation reports (outcome, process and economic evaluations) in the UK journal of Health Technological Assessments in addressing the question of whether an innovation with limited evidence base in a pragmatic setting (e.g. introducing cognitive behaviour therapy in schools) should be scaled up. Eight papers included descriptions of the how costs considerations such as financing incentives/ government subsidies impacted on intervention implementation.

Table 2: Summary of the methodology used and quality assessment of the studies

Stage of process evaluation	**Methodology & Methods**	**Analysis**	**Quality criteria**
Feasibility/ Piloting 20 Studies	9 studies used theories or frameworks. 18 used interviews. 3 used focus group discussions, 4 used questionnaires or surveys, 2 studies used routine monitoring data, field notes, minutes of meetings and observations.	Thematic analysis, constant comparative approach most commonly used, with some using framework analysis.	Planning: Team description: 11Y, 6N, 3 N/A Design and Conduct: Purpose: 20 Y Intervention description and causal assumptions clarified: 5 Y , 6 unclear, 9 N/A, 0 N Justify choice of timing and methods: 19Y, 1 N COREQ covered out of the 3 domains (17 applicable studies): 3 domains: 11 2 domains: 4 1 domain: 3 Reporting Clearly labelled as process evaluations: 5 Protocol/full report: 8
Evaluation of effectiveness 43 studies	12 studies used existing theories and frameworks. (6 Classic theories, 3 evaluation frameworks, 3 implementation theories) 2000-2004: 3 studies documented specific processes of care as part of the process evaluation, which were reported as part of the main trial. 4 studies investigated acceptability of an intervention using surveys/questionnaires. 2005 onwards- 12 studies used interviews alone to explore implementation and acceptability; 20 studies used interviews triangulated with other sources of data (e.g. chart audit). 2 studies used routine administrative data to indicate fidelity. 3 studies used questionnaires or surveys.	Descriptive statistics were used for the quantitative data. Thematic, constant comparison and framework analysis for the qualitative data. The studies that used mixed methods, used the quantitative data to indicate level of implementation, reach and the dose. This was used to triangulate the qualitative findings on implementation and intervention acceptability. The studies which used evaluation frameworks (e.g. REAIM) and implementation theories (e.g. NPT) used them for the analysis and presentation.	Planning: Team description: 21 Y, 21 N, 1 NA Design and Conduct: Purpose: 43 Intervention description and causal assumptions clarified: 25 Y, 8 Unclear, 5N/A, 5N Justify choice of timing and methods:40Y, 1 N, 2NA Report whether the process data are analysed blind to trial outcomes/ or post hoc: 29Y, 7N, 7N/A COREQ covered out of the 3 domains (30 applicable studies): 3 domains: 12 2 domains: 13 1 domain: 5 Reporting Clearly labelled as process evaluations: 17 (of note- 2 before 2008, 6 till 2015, and 9 after 2015) Protocol/full report: 21
Post evaluation 6 studies	1 study used existing theory. 2 studies used interviews, 2 used documentary analysis, and 1 used the administrative data and registry data	Descriptive statistics, subgroup analysis and thematic analysis.	Planning: Team description: 3 Y, 2 N, 1 NA Design and Conduct: Purpose: 6 Intervention description and causal assumptions clarified:0Y, 2 unclear, 2 N/A, 2 N Justify choice of timing and methods: 5Y, 1 N COREQ covered out of the 3 domains (3 applicable studies): 3 domains: 1 2 domains: 1 1 domain: 1 Reporting Clearly labelled: 0 Protocol/full report: 1

Classic Theories

Theory of Planned behaviour-. "*Using the theory of planned behaviour (TPB), we hypothesised that changes in thiazide prescribing would be reflected in changes in intention, consistent with changes in attitude and subjective norm, with no change to their perceived behavioural control (PBC), and tested this alongside the RCT*…A *strength of this study is its use of a well-tested theory of behaviour operationalized according to best recommended practice to investigate the underlying mechanisms of an implementation intervention.*" (Presseau) This theory informed their process evaluation to explore if their intervention of printed educational materials increased practitioners' intention to prescribe according to recommendations in the guidelines.

Self Determination theory - "*self-determination theory which proposes that real shifts in behaviour arise through heightened autonomy or personal ownership of behavioural success*." (Chalder) This theory informed their theoretical model underpinning their intervention to improve physical activity for the management of depression.

Grounded theory- *" This qualitative study was conducted with the objective of better understanding the PP intervention in the BETTER Trial described above, including the development of the PP role, perceived barriers, facilitators, benefits and disadvantages, and of exploring the feasibility and sustainability of this approach for CDPS."* (Manca) This study used grounded theory to better understand their intervention as implemented and to retrospectively describe their intervention theory.

Diffusions of Innovation-"*Key principles, which derive from diffusion of innovations theory, include working initially with practices and clinicians that not only have an interest in the innovation and view it as compatible with their needs, values, and resources, but also have the ability to try it with minimal investment and observe its impact*." (Dietrich) The theory was used to inform their practice change strategy for the sustainability of a chronic care model for depression proven effective in an RCT.

Determinant Frameworks

PARIHS as an implementation model-"*We used the Promoting Action on Research in Health Services (PARIHS) framework as an 'Implementation model' to assist clinical partners in adopting the health-coaching intervention. The PARIHS framework posits three interrelated elements that influence successful implementation of evidence-based practices: the (I) perceived strength of the 'evidence', (ii) 'context' of the environment and (iii) 'facilitation' support created for implementation of the intervention….Using a codebook developed a priori from sub elements of the PARIHS framework "* (Naik) This study used PARIHS to inform their participatory approach between research team and primary health care teams, and also used it in evaluation of the qualitative data in assessing the building of the partnership to test and implement a health-coaching intervention.

Implementation theories

NPT- Normalisation Process Theory -"*as part of mixed-methods process evaluation, semi-structured interviews were conducted by phone with 27 providers participating in the study. Interviews were audio-taped and transcribed. Thematic content analysis was used to identify themes. Themes were categorized according to the four domains of Normalization Process Theory (NPT)".* (Vest) The authors discuss how the findings are informing their ongoing implementation strategies e.g. clinical mentors for the general practitioners who described a discomfort in their lack of expertise in screening and managing early chronic kidney disease. (other papers include: Burridge ,Coupe, Gask, Hanley, Vest)

Evaluation frameworks

MRC- Medical Research Council's framework for complex interventions,-"*The MRC framework provided a useful structure through which to examine our theoretical hypothesis and analyse the feasibility evidence*." (Sturt)
"*Guided self-help intervention was developed following a modelling phase which involved a systematic review, meta synthesis and a consensus process…"* (Lovell) The authors used the MRC framework for intervention development. Similarly Byrne et al also used the MRC framework for intervention development of literature review, focus group discussion and modelling and then interviews to refine the intervention.

REAIM- "*The process evaluation followed the RE-AIM (Reach, Efficacy/effectiveness, Adoption, Implementation and Maintenance) framework. Data were collected on attendance and attrition for classroom-based CBT and attention control PSHE by programme facilitators. An independent observer attended 5% of classroom based CBT sessions to assess treatment fidelity. Feedback was gathered from teachers, young people and facilitators using questionnaires and qualitative interviews*." (Stallard) (other papers include: Stallard, Wozniak, Lakeverld)

Realist Evaluation-

"*All data assigned to codes relating to the polypill strategy in CVD management were analysed …and the Realist framework of context–mechanism–outcomes utilized to develop the themes*" (Liu) The framework was used to guide the analysis of the qualitative data.

CHAPTER 3: A PROCESS EVALUATION OF THE KANYINI GUIDELINES ADHERENCE WITH THE POLYPILL (GAP) TRIAL

Chapter Overview

This chapter reports the findings of a process evaluation of the Kanyini GAP randomised controlled trial in Australian primary health care testing the combined cardiovascular polypill in mainstream general practices and Aboriginal health services. The chapter consists of three manuscripts titled: 1) Patients' and Providers' Perspectives of a Polypill Strategy to Improve Cardiovascular Prevention in Australian Primary Health Care. 2) Facilitators and barriers to implementation of a pragmatic clinical trial in Aboriginal health services. 3) Implementing Kanyini GAP, a pragmatic randomised controlled trial in Australia: findings from a qualitative study.

In Chapter 2, greater use of theoretical frameworks and mixed methods was highlighted as important for PEs. This chapter presents the PE of a RCT using the combined cardiovascular polypill to improve provider prescribing and patient taking of indicated therapy. I chose to use Realist principles for this PE. During the analysis of the qualitative data, an inductive conceptual framework was developed. This framework highlighted the relationships and links between the main codes identified through line by line coding and in-depth discussion. The conceptual framework highlighted the patient journey and acceptability of the polypill, and provided possible explanations for the outcomes. These findings resonated with the key questions of 'for whom, how and why' in Realist evaluation. Therefore, the Context-Mechanisms-Outcomes configuration used in Realist Evaluation seemed to be a natural fit for the synthesis of the thematic findings.

The first manuscript provides an example of how such contextual factors can be analysed and reported, and the relevance in the use of mixed methods to help explain variation in trial outcomes. For example, using Realist principles to inform the thematic synthesis helped identify the relevance of the polypill strategy in the midst of the contextual patient level factors that affected adherence to medications. In addition, using the secondary trial outcomes (such as prescribing data) to triangulate the qualitative findings highlighted that the polypill strategy in its existing formulations was more suited for high risk primary prevention patients as less tailoring of medication was required.

The next two manuscripts describes the facilitators and barriers in the conduct of collaborative research with practitioners in real world settings through pragmatic trials. Given the importance of locally driven Indigenous research, there was one manuscript focusing on the collaboration with Aboriginal community controlled health sector, and another manuscript exploring pragmatic trial implementation with the primary health sector in general.

Authors' contributions: HL was one of two lead analysts of the qualitative data of the process evaluation of Kanyini Guidelines Adherence with the Polypill (GAP) trial. HL helped manage the study, led the data analysis, drafted and revised all the manuscripts and is responsible for the integrity of the work. LM managed the study, led the data collection, conducted the analysis, and helped revise the manuscripts. SJ designed the study, helped with the data collection, analysis, and writing and revising of the papers. TL assisted with the set-up of the study, data collection, and helped write and revise the papers. AE assisted with data collection, and helped write and revise the paper. AC, AP, DP, JR, KH and TU helped

design the process evaluation, refine the theoretical and methodological approach, and helped write and revise the papers. All authors read and approved the final manuscripts.

In addition, The Kanyini Guidelines Adherence with the Polypill (GAP) trial was a project of the Kanyini Vascular Collaboration (KVC). HL was the program manager of KVC, prior to the start of the PhD, and was responsible for community engagement, trial set up, including ethics application, and the site recruitment and training of principal investigators at the sites and trial staff (e.g. project managers, monitors, research nurses).

Publications details:

Liu H, Massi L, Laba TL, Peiris D, Usherwood T, Patel A, Cass A, Eades AM, Redfern J, Hayman N, Howard K, Brien JA, Jan S. Patients' and Providers' Perspectives of a Polypill Strategy to Improve Cardiovascular Prevention in Australian Primary Health Care: A Qualitative Study Set Within a Pragmatic Randomized, Controlled Trial. Circ Cardiovasc Qual Outcomes. 2015 May 5. pii: CIRCOUTCOMES.115.001483. [Epub ahead of print]
http://www.ncbi.nlm.nih.gov/pubmed/25944629

Liu H, Laba T, Massi L, Jan S, Usherwood T, Patel A, Hayman N, Cass A, Eades A, Peiris D. Facilitators and barriers to implementation of a pragmatic clinical trial in Aboriginal health services. Medical Journal of Australia 01/2015;
http://www.ncbi.nlm.nih.gov/pubmed/26126563

Liu H, Massi L, Eades AM, Howard K, Peiris D, Redfern J, Usherwood T, Cass A, Patel A, Jan S, Laba T. Implementing a pragmatic randomised controlled trial in Australia: lessons learnt from the Kanyini Guidelines Adherence with the Polypill study (Kanyini GAP) Trials, 2015.
http://www.ncbi.nlm.nih.gov/pubmed/26399503

Manuscripts:

Original Article

Patients' and Providers' Perspectives of a Polypill Strategy to Improve Cardiovascular Prevention in Australian Primary Health Care

A Qualitative Study Set Within a Pragmatic Randomized, Controlled Trial

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Background—This study explores health provider and patient attitudes toward the use of a cardiovascular polypill as a health service strategy to improve cardiovascular prevention.

Methods and Results—In-depth, semistructured interviews (n=94) were conducted with health providers and patients from Australian general practice, Aboriginal community-controlled and government-run Indigenous Health Services participating in a pragmatic randomized controlled trial evaluating a polypill-based strategy for high-risk primary and secondary cardiovascular disease prevention. Interview topics included polypill strategy acceptability, factors affecting adherence, and trial implementation. Transcribed interview data were analyzed thematically and interpretively. Polypill patients commented frequently on cost-savings, ease, and convenience of a daily-dosing pill. Most providers considered a polypill strategy to facilitate improved patient medication use. Indigenous Health Services providers and indigenous patients thought the strategy acceptable and beneficial for indigenous patients given the high disease burden. Providers noted the inflexibility of the fixed dose regimen, with dosages sometimes inappropriate for patients with complex management considerations. Future polypill formulations with varied strengths and classes of medications may overcome this barrier. Many providers suggested the polypill strategy, in its current formulations, might be more suited to high-risk primary prevention patients.

Conclusions—The polypill strategy was generally acceptable to patients and providers in cardiovascular prevention. Limitations to provider acceptability of this particular polypill were revealed and a perception it might be more suitable for high-risk primary prevention patients, though future combinations could facilitate its use in secondary prevention. Participants suggested a polypill-based strategy as particularly appropriate for lowering the high cardiovascular burden in indigenous populations.

Clinical Trial Registration—URL: https://www.anzctr.org.au. ANZCTRN 12608000583347. (***Circ Cardiovasc Qual Outcomes*. 2015;8:00-00. DOI: 10.1161/CIRCOUTCOMES.115.001483.**)

Key Words: adherence ■ qualitative research

Cardiovascular disease is a major cause of mortality and morbidity worldwide and is projected to be the leading cause of death in 2030.[1,2] A major part of the problem is large treatment gaps globally—for instance, audits of primary healthcare in Australia indicated that prescription of guidelines-recommended therapy is as low as 50%.[3,4] Nonadherence to the treatment is likely to further extend this treatment gap because it is estimated that ≤50% of patients in high-income countries do not adhere to prescribed cardiovascular disease (CVD) medications, with similar suboptimal adherence in low- and middle-income countries.[5,6] The reasons for nonadherence fit into well-recognized categories—health

Received February 26, 2015; accepted March 20, 2015.

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The Data Supplement is available at http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/CIRCOUTCOMES.115.001483/-/DC1.

Peer review comments are available at http://circoutcomes.ahajournals.org/lookup/suppl/doi:10.1161/CIRCOUTCOMES.115.001483/-/DC2.

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WHAT IS KNOWN

- Although effectiveness trials have shown a significant improvement in patient medication use with a specific polypill formulation (a combination of a statin, 2 blood pressure lowering agents, and antiplatelet agent) when compared with usual care for high-risk primary and secondary CVD prevention, patients' and providers' perspectives of this approach are unknown.

WHAT THE STUDY ADDS

- After conducting qualitative interviews with both providers and patients involved in a pragmatic clinical trial in Australia, we found general acceptability of the polypill-based strategy with patients reporting greater convenience and cost savings with the polypill.
- However, some prescribers highlighted limitations of this particular formulation in regards to dosage inflexibility and recommended that more doage combinations be made available.

system, condition, patient, therapy, and socioeconomic.[7,8] A review of strategies targeting CVD medication nonadherence in disadvantaged populations found that interventions directed at patients and providers simultaneously showed statistically significant improvements in relative adherence.[6] Cardiovascular polypills which are fixed-dose combinations of frequently indicated cardiovascular medications for high-risk primary prevention and secondary prevention have been trialled internationally to improve provider prescribing and patient medication use. Encouragingly, recent results from randomized controlled trials have shown effectiveness in improving adherence.[9–11]

However, whether this promising result is generalizable and can be successfully implemented in health services outside of trial settings depends partly on whether the polypill strategy will be well received by health providers and importantly to patients. This can be addressed by qualitative research conducted alongside trials exploring relevant stakeholders' perspectives.[12–14] The Realist framework has been successfully used in process evaluations as a theoretical basis for identifying potential causal mechanisms of how an intervention works for whom, under what contexts, and thus fosters uptake of research-based knowledge into practice.[15–19]

In this article, we present the qualitative findings of a process evaluation set within a multicenter pragmatic randomized, controlled trial (PRCT) of a cardiovascular-based polypill strategy in Australian primary care known as the Kanyini Guidelines Adherence with the Polypill (KGAP) trial.[1,9] Patients received a fixed-dose combination containing aspirin 75 mg, simvastatin 40 mg, lisinopril 10 mg, and either atenolol 50 mg or hydrochlorothiazide 12.5 mg in the polypill group. The usual care group continued cardiovascular preventive treatment, with separate medications and doses prescribed at their treating doctor's discretion.

This pragmatic trial was conducted in a variety of primary healthcare services across Australia in urban, rural, and remote settings, thereby maximizing potential generalizability[20] and sought to improve patient medication use and the prescribing of indicated therapy for high-risk primary and secondary CVD prevention patients. Significantly, in Australia where indigenous patients have a higher burden of CVD,[21] the trial was conducted in accessible and culturally safe indigenous health services (IHS).[22,23]

Primary outcomes were measured by self-reported medication use and changes in biological markers of changes in systolic blood pressure and total cholesterol. Results showed that "After a median of 18 months, the polypill-based strategy was associated with greater use of combination treatment (70% versus 47%; relative risk 1.49; 95% confidence interval [CI] 1.30–1.72; $P<0.0001$; number needed to treat=4.4 [3.3–6.6]) without differences in systolic blood pressure (−1.5 mm Hg [95% CI −4.0 to 1.0]; $P=0.24$) or total cholesterol (0.08 mmol/L [95% CI −0.06 to 0.22]; $P=0.26$). At study end, 17% and 67% of participants in polypill and usual care groups, respectively, were taking atorvastatin or rosuvastatin." (ANZCTRN 12608000583347)[10]

We aim to explore the relevance of the polypill strategy for health providers and patients as a health service strategy to improve prescribing of indicated therapy and improve patient medication use.[24] Understanding the mechanism of the polypill strategy from patients and providers perspectives will assist in translation of the polypill intervention to other contexts and so inform policy and practice in the area.

Methods

A predefined protocol for the overall process evaluation was used and had been published.[24] Our methods are presented across key areas for reporting in qualitative research.[25]

Research Team and Reflexivity

Study investigators involved in the design and implementation of KGAP developed the process evaluation protocol and interview guides. The interviews were conducted by a team of 7 researchers who varied in qualitative research experience and had diverse backgrounds (nursing, health economics, pharmacy, Indigenous health). Three were indigenous and 4 were nonindigenous researchers. Two of the interviewers were research coordinators and had existing relationships with several of the participants interviewed, but the other interviewers were not known to the participants before the interviews.

Study Design

Participants were recruited purposively based on maximum variation of specified variables, which could potentially affect participants' views of a polypill-based strategy and with trial implementation. A sampling matrix was used with the following characteristics: for patients, these were location, age, sex, ethnicity, primary versus secondary CVD, and self-reported adherence at baseline; and for providers, location and profession.[26] All health providers and patients were approached by a letter of invite detailing the study and purpose and a follow-up phone call by the project coordinator. All health providers approached agreed to participate, though 5 patients declined to be interviewed and 2 patients were unavailable. Written informed consent was obtained.

The interview guides covered the key domains about the polypill strategy in CVD management, patient satisfaction or problems with the polypill, issues regarding trial implementation, and

translation of the polypill into clinical practice. Interview guides were iteratively revised to explore themes and issues emerging from earlier interviews. Interview guides are available as Data Supplements.

Ninety-four semistructured interviews were conducted at the end of KGAP with 47 providers (25 general practitioners [GPs], 13 pharmacists, 6 Aboriginal Health Workers, and 3 Chronic Care Nurses) and 47 patients in New South Wales, Queensland, and Victoria. Twenty-two and 25 patients were in the polypill arm and usual care arm, respectively. Twenty-one and 26 patients were in the primary and secondary prevention arm, respectively. There were 28 nonindigenous patients and 19 indigenous patients. Participant characteristics are included in Table in the Data Supplement.

Most interviews (ranging from 30 minutes to an hour) were conducted face to face either at home or at the health service and audio-recorded. Two interstate participants were unavailable at a time that coincided with travel to their health services. It was not feasible to schedule an additional visit because of time, interviewer availability, and cost. Instead, these 2 interviews were conducted by phone and audio-recorded. To ensure consistency, one researcher (L. Massi) was involved in most of the interviews. She conducted 42 alone and another 40 with another researcher.[26] L. Massi was trained in qualitative research methods and coordinated the study. Preliminary thematic data analysis was conducted by L. Massi alongside the interviews and discussed with the research team. Thematic saturation was reached, and further interviews were conducted to ensure that we had gleaned perspectives from the different regions.

Analysis

Interviews were professionally transcribed and coded by 2 researchers (H. Liu and L. Massi) using NVivo 9 (QSR International, Melbourne, VIC) at the completion of the interviews. Using the constant comparative method,[14] these researchers coded the same 12 transcripts independently through 3 iterative stages and developed an initial coding framework encompassing both patients' and providers' perspectives, allowing triangulation of findings within each code. Insights gained by the KGAP research team about the local setting and empirical results of the PRCTs were used to aid interpretation.[27,28] The coding framework was refined with input from study investigators and interview team. This included 2 IHSs clinicians who were site principal investigators and provided respondent validation.[27] H. Liu and L. Massi coded the remaining interviews equally, drawing up memos for each interview to provide additional context for others analyzing the data and recoded the original 12 interviews. Minor, iterative changes to code definitions were made. An audit trail was kept. For this article, all data assigned to codes relating to the polypill strategy in CVD management were analyzed by H. Liu and the Realist framework of context–mechanism–outcomes utilized to develop the themes[15,16] (see Figure). Further description of the major codes and the coding framework are available as Data Supplements. The study was approved by 7 regional ethics committees.

Results

Three principle themes relating to the polypill as a health service strategy to improve CVD prevention in Australian primary care were derived (Table in the Data Supplement is available with additional quotes).

Overall Acceptability of the Polypill Strategy

Ease and Convenience

A key strength described by many patients and providers was that overall the polypill was liked and perceived as a beneficial strategy because of the ease and convenience of a single daily-dosing capsule. It was physically easier to take and to remember to take, which was highlighted by some providers and patients as especially important for the elderly and for those with stressful and competing life priorities. A few providers assumed that the polypill would increase adherence because long-term adherence to preventative medication was challenging for their patients. An indigenous patient described how the polypill reduced her psychological pill burden:

> *… taking so many individual tablets became stressful, it's like you knew what was happening like this organ and that organ is not working but with the polypill, because it's all in one and you're not having these different things laid out before your eyes. It was easy. (Patient 31, remote IHS)*

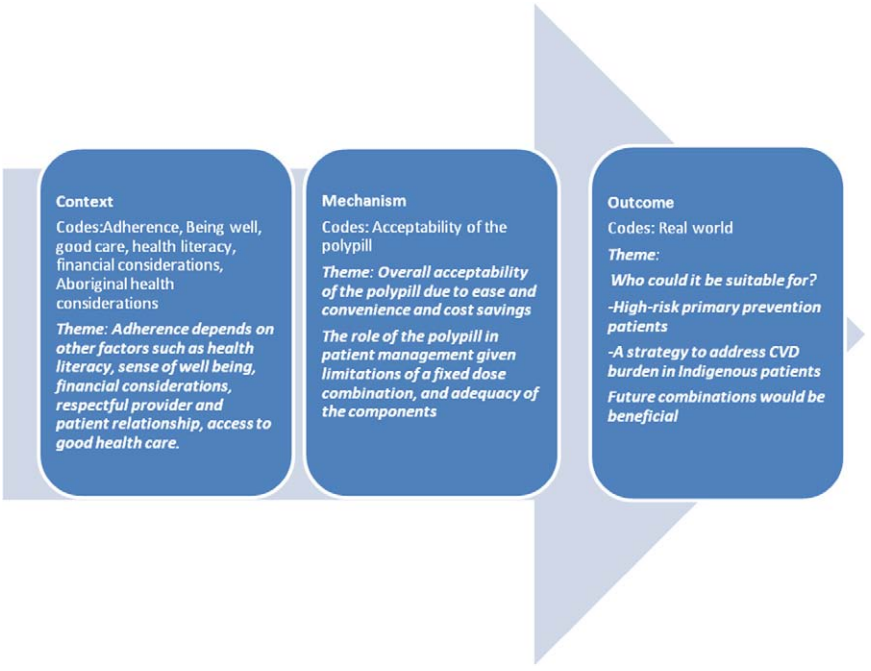

Figure. Codes and themes within the realist framework (context–mechanism–outcome). CVD indicates cardiovascular disease.

Cost Savings

The polypill strategy was a pragmatic trial, which aimed to mimic real-world cost impacts on participants. In the Australian context, where medications could be subsidized through the Pharmaceutical Benefits Scheme (PBS), nonconcession card holders would pay full copayments for prescriptions (≈$AUD30), whereas concession card holders would pay subsidized copayments of $AUD5.60 for each prescription. For these groups, there was a potential 4-fold cost advantage of the polypill. For indigenous participants who were eligible for complete medication subsidization through a government scheme newly introduced during the PRCT, there was no cost advantage of the polypill because treatment in both arms was subsequently free. Thus, depending on individual circumstance, the savings varied for the patients.

> *When I was working [all] my medications … used to cost me almost $320 a month at the full price. Individually some of them are very expensive; you might be paying $20 or $25 for each one. Now [on pension rates], it is $5.80 for the combined [polypill]. (Patient 17, rural GP clinic)*
>
> *[The cost of medications does not impact me because], I'm working, and I've got a good job. (Patient 38, regional GP clinic)*
>
> *Before I went on the polypill it was so hard. It's the affordability, and taking all these different tablets at different times, whereas now it's one tablet, and it's free, so you can't get it any better than that. (Indigenous patient 13, IHS)*

Most of the providers recognized that the polypill would help improve their patients' adherence to CVD medications because of ease, convenience, and cost-savings of the polypill. A GP described the advantages of the polypill for his patients and in starting medications:

> *Taking one pill instead of four is excellent and improves compliance with patients; there is a cost factor that is an advantage. There is a simplicity factor – it's easier to start someone early on, on a four-medication thing if they need it. If someone sort of never comes in and is poorly compliant and for months or years they've sort of had little warning signs that they really need something done but they don't really do it, the polypill does make it possible to fairly easily say, 'let's take this pill instead of this pill, it's just that this pill contains four medications.' (GP 27, urban IHS)*

The perceived advantages of the strategy as described by many of the providers may explain the difference in the prescription of antiplatelet, statin, and at least 2 blood pressure lowering agents which at baseline percentage was 50% and increased to 79% in the polypill arm and only 52% in the usual care arm.

Adherence Depends on Other Factors

However, despite many patients describing how and why the polypill could improve medication use, other factors were also described by the patients as being key to their adherence. Patients indicated that their adherence behavior was determined by intrinsic factors, such as establishing routine medication regimens, their sense of well-being, and their understanding of medications, aided by external factors, such as the perceived quality and accessibility of their healthcare, family, and community support, respectful patient–provider relationships, and financial assistance from the government. Examples of quotes illustrating these factors include:

> *Because the one [reason] that keeps my heart going, well, because I've got my little fellow now. I want to try and stay here long as I can for him. (Patient 22,regional GP clinic)*
>
> *I mean when you see the people that are dying around you … the same age as you and even younger, it's all to do with health that they died not taking medication. (Patient 4, urban IHS)*
>
> *Keep the medication affordable; cost of living is high enough now…especially for black people because for black people, diabetes, sugar and all those type of things, is something that has impacted on us since colonisation of this country and the introduction of processed foods. So we need to have medication available to us to keep us living a longer life than what we're currently living and if medication is the only way to keep us going then we need to be able to afford to have it. (Patient 10, urban IHS)*

Patients also described initiatives, such as having dose administration pack, removed the hassle of carrying many medications, and served as a reminder to take their medications.

Similarly, many providers perceived intrinsic and extrinsic factors affected their patients' medication use.

> *It's very hard, we've done motivational training [in regards to adherence] and the Division [of GP's] has tried all sorts of things to help these people and they're just not interested. They have lives often with so many complexities which they can't manage. (GP 36, regional GP clinic)*
>
> *Clearly the evidence around the world is that the primary care practitioner/patient relationship is the magic ingredient in the health system. There's continuity and there's trust. You get better outcomes and part of that is that people are more willing to commit to treatment plans. I think the General Practitioner's role is key in promoting adherence. (GP 1, rural GP clinic)*

Many providers indicated that the perceived potential impact of the polypill strategy in improving their patients' medication use depended on existing adherence behavior. For example, though pharmacist 42 (remote IHS-related pharmacy) talked about how if pill burden was a key barrier then the polypill would be ideal, another pharmacist described a limited impact of the polypill strategy if patients were already adherent and used dose administration devices:

> *People's compliance is pretty high. So whether they have good result or not, because they are using a [dose administration pack], they pop it anyway. So if they have four pills, all separate, or one pill in polypills, it's no difference. (Pharmacist 21, urban IHS-related pharmacy)*

Polypill Strategy in Patient Management

Limitations of a Fixed Dose Combination

Some providers described certain limitations of the polypill strategy in patient management. They commented on the inflexibility of a fixed dose combination and on the complexity in identifying which component of the polypill caused any reported side effect.

> *I think the Polypill is a good idea in principle but it also showed me how complicated it is to give somebody a pill with four components. One of the biggest parts of my work is dealing with adverse drug reactions and if you give a person one medication there's a pretty good chance they're going to get an adverse reaction. Now it may be a minor one, may not be, if you give them four, that's a lot more chances. And then teasing out which one is difficult. (GP 10, urban GP clinic)*

At some sites, providers described patients on the trial with complex medical problems that in hindsight were not sufficiently stable for the polypill.

> *I was surprised with some of the patients whom others had been happy to put on it because when we looked at the problems that some [patients] had, I thought, well I wouldn't have put that person in the trial, in the first place [because]) they were quite complicated and there will be potential risks of having some problems on the polypill. (GP 36, regional GP clinic)*

Some providers found that the polypill formulations used in the trial contained inadequate dosages for their patients, expressing an inclination to discontinue its use if additional medications were needed because the advantage of a one daily-dosing pill was lost.

Adequacy of the Polypill Components

The therapeutic efficacy of the generic components within the polypill was discussed by many of the providers. There were 2 perspectives: some GPs questioned whether these particular polypill formulations would represent best practice, given the perceived superiority of some of the newer on-patent medications available. Conversely, some providers preferred the use of off-patent medications contained in the polypill because of the cost-savings and the greater evidence-base of these older medications. A GP gave the following opinion of the on-patent medications compared with the older generics:

> *So much of the PBS is bound up with cardiovascular management. I have a personal belief that we spend far too much on the PBS. There are far too many medications that are not generic and we seem to want to have the most expensive and I personally don't believe in that. I think people are prepared to live their lives as they wish and [some] smoke and drink. We do our best and we assume that the medication is, a hundred per cent, is all the treatment, which it's not. So I don't believe they have to have Rolls Royce medications when they lead a beat up Hyundai Lifestyle. What they need is to actually take the medications regularly, understand what they're for... I'd much rather go with a lot more evidence-based cheaper medications and getting people to take them. (GP 39, remote IHS)*

Some GPs also expressed an uncertainty about the individual components. Several providers were uncertain about the use of aspirin for nondiabetic patients without established CVD. Some of the GPs and the patients' cardiologists preferred to prescribe the newer statins if possible. This was also reflected in the PRCT's data, which showed that at the end of the study, 17% and 67% of participants in polypill and usual care groups, respectively, were taking atorvastatin or rosuvastatin.

> *I think that there was one local cardiologist who wasn't at all supportive of the polypill …. And this particular cardiologist also tended to use the top end dose of statins when he'd seen a patient, so that had the potential to raise an issue for a patient who we would then have to prescribe polypill plus an additional statin to keep them on the same dose as the cardiologist… I'm not actually convinced that the patients all needed to be on that dose. (GP 25, urban IHS)*

These providers' perspectives about limitations of a fixed dose combination and questions regarding the adequacy of the polypill components offer possible explanations of why 28% of patients who were randomized to the polypill stopped it at some stage with around half of these discontinuations being because of prescribing and, thus apparently, were provider-initiated.

Future Combinations Would be Beneficial

Many providers and patients believed the above mentioned limitations could be overcome by having other polypills with different drug combinations. Some providers also stated a combination pill could be formulated for other diseases like diabetes mellitus, as in the following quote:

> *Once the general principle of a cardiac medication that's polyvalent is established then there ought to be some flexibility as to what components might be added, with the advantage of future research. (GP 23, urban IHS)*

Who Could it be Suitable for?

High-Risk Primary Prevention Patients

Many providers were of the belief that the polypill formulations used in the study were inappropriate for some secondary prevention patients because of the low and inflexible dosing. Rather, its niche was in high-risk primary prevention patients who were stable medically.

> *Using a generalised polypill with lower doses where you have a person who hasn't got the cardiovascular disease but has cardiovascular risk would be good just to help them from developing full-on cardiovascular disease. I think there's a role there - where there might be the one blood pressure tablet … because they might have had minor hypertension and putting a statin in there with aspirin just keeps everything functioning well and stops them getting established*

cardiovascular disease. Whether it's got a role in the patient who already has cardiovascular disease, I'm not sure because you can't alternate the doses the way you want. (Pharmacist 7, urban IHS)

This theme supports the trial finding of the polypill-based strategy, resulting in a proportionately greater improvement in combination treatment use among high-risk primary prevention patients, though this improvement was also significant in patients with established disease.

Strategy to Address CVD Burden in Indigenous Patients

Although the acceptability of the polypill strategy on improving adherence was reported by both patients and providers in IHSs and private clinics, a strong finding was that there could be particular advantages for indigenous patients. A GP thought the polypill could be an effective strategy to reduce the CVD burden in his community:

Being an Aboriginal doctor I see the burden of disease especially in cardiovascular health…. The youngest fellow we've had coming in here is 28 having a heart attack. So we see heart disease early and it's not uncommon for some of our patients to have heart attacks in their 30s, 40s and 50s. So I think we need some other strategy to help decrease that risk and that's where I've seen the place for the polypill and it'd be interesting to see what results come out of it. (GP 28, urban IHS)

A GP (Provider 43, remote IHS) described the usually lengthy process of starting medications in indigenous patients and how the polypill could be used to expedite this process. Moreover, by not having a pharmacist provide medications in a medication dose aid might mean increased ownership of health for his patients on the polypill. An indigenous patient thought the polypill would be a way to bridge the health literacy gap:

It would be a good thing … for a lot of our people … if they've got to take about half a dozen tablets or four tablets you know they might get confused. Some of our people you can't read much to know what tablets to take. They just take them... [They] don't know what they're taking it for. I reckon it's a good idea if they've got the polypill [which] is all in the one. (Indigenous patient 43, remote IHS)

Several GPs at some IHSs thought the polypill strategy complemented their services' chronic disease model of care, updated them on their CVD guidelines, and encouraged them to use the CVD absolute risk calculation in their patient management. Provider 20 (pharmacist, urban IHS) thought the polypill strategy worked synergistically with the GP's education of patients and the pharmacists' provision of the dose administration aid to improve patients' adherence.

It seemed that the polypill strategy could potentially be beneficial for the indigenous population, given the high disease burden and the complexities associated with taking multiple medications. It was viewed as an acceptable strategy by patients and providers for high-risk, medically stable patients. Many IHS providers thought the polypill strategy could be an effective component of CVD care that could be integrated into strategies that address other factors, such as accessible care, health promotion, and social determinants. Indeed, the PRCT subgroup analysis showed that there was a significant improvement in medication use among the indigenous patients randomized to the polypill strategy.

Discussion

The polypill strategy is relevant to patients' and providers' needs as an acceptable health service strategy to improve CVD prevention in Australian primary healthcare. Using the Realist framework, the effectiveness of the polypill strategy was dependent on whether the health provider felt that the polypill components were adequate for the management of individual patients' CVD, and would encourage patient's adherence because of its ease and convenience, and cost savings for the patient. However, the sustainability and impact of the polypill strategy in improving adherence depended on other patient factors, such as affordability of medications, level of health literacy, compatibility with existing adherence strategies, sense of well-being, patient–provider relationship, access to quality care, and disease stability and severity. The main limitation of the strategy was the inflexibility in dosing, but this was viewed as a shortcoming that could be addressed with introduction of a wider range of combinations. In its current formulations, many of the providers in this study deemed it to be particularly suited to high-risk primary prevention patients and some indigenous populations in Australia.

Our study confirms some findings of other qualitative studies which showed a growing acceptance of prescribing the polypill for primary and secondary prevention, provided there is evidence of effectiveness and cost benefits.[29–31] However, our study also highlighted overall patient acceptability of the polypill strategy and a key recommendation by providers to improve the flexibility of the polypill strategy in meeting the varied needs of patients by introducing more formulations. Using qualitative research alongside a PRCT enabled us to better appreciate the role of the polypill strategy in addressing inequity within contextual factors of Australian primary healthcare, such as high CVD burden within indigenous communities, existing costs of medications, and concurrent government policies for medication subsidies.

This study was limited in that it was an in-depth exploration of issues from a sample that was not necessarily representative of all participants and providers in the trial. Fewer interviews were done in remote sites, and staff who had left the service or participants who had withdrawn by the end of the study would not have been interviewed. Other limitations of our study include having 2 interviews done over the phone in comparison to face to face, varying level of experience of qualitative research among the study team and achieving only partial member checking during a presentation of preliminary findings to a subset of providers.

Though the KGAP trial showed that there was improved adherence in the polypill arm, patients' adherence in both arms of the study progressively declined over time, which is consistent with the literature.[32–34] Thus, the question remains as to how to best use the polypill strategy to improve sustained medication adherence. A method to characterize behavior

change interventions was proposed by Michie et al through the use of a behavior change wheel, which comprises a behavior system at the hub, encircled by 9 intervention functions aimed at addressing the deficits in capability, motivation, and opportunity and then by 7 policy categories to enable the interventions to occur.[35] Applying Michie's behavior change wheel to our results, it seems that the polypill strategy has the intervention functions of enablement and incentivization; to effect behavior change, but perhaps other intervention strategies and policies are needed for sustained change. Multifaceted approaches to improve adherence have been trialled internationally.[8,36,37] In Australian primary health care, a quality improvement intervention with pharmacists-led education to improve health literacy and electronic decision support for the prescribing of preventative medications has been shown to be effective.[36] Our study findings suggest that the polypill strategy could potentially be used successfully and synergistically with similar health service strategies to improve medication persistence in this setting.

The polypill strategy is increasingly being recognized as a part of a solution for improving global CVD prevention, with a growing body of evidence showing effectiveness in improving provider prescribing and patient adherence to indicated CVD medications.[10,11,38,39] The economic evaluation conducted with the KGAP trial[40] and a cost-effectiveness study of a multidrug regimen (similar to the polypill components) in a lower middle income setting[41] provide promising evidence that the polypill strategy could reduce the high global economic burden of CVD, given the availability of the inexpensive yet effective drugs. As more CVD medications come off patent, our findings imply a key challenge would be to have different polypill versions made available as an affordable and attractive health service strategy for both high-income and lower middle–income countries. However, barriers to the implementation of the polypill strategy include the manufacture of the polypill as a viable business for pharmaceutical companies, despite its huge public health potential and having supportive legislation and policy changes. As such, the amalgamation of evidence from international trials combined with further research in cost effectiveness and acceptability of the strategy in different contexts will determine the feasibility and policy significance of the polypill strategy in improving CVD prevention worldwide.

Acknowledgments

We thank Deborah Blair, Barry Fewquandie, and Chris Lawrence for assisting in the interviews. We also acknowledge staff and patients from participating general practices and IHSs who gave generously of their time in providing us their perspectives. An extensive team designed and implemented the KGAP trial (as listed in the main trial KGAP paper).

Sources of Funding

The study was funded by the National Health and Medical Research Council (NHMRC) of Australia (App: 1004623). A. Cass and A. Patel are funded by Senior Research Fellowships from the NHMRC. S. Jan is funded by an NHMRC Career Development Award. T. Laba is funded by an NHMRC Scholarship and NHMRC Capacity Building Grant (57132). A.M. Eades is funded by an NHMRC Scholarship (1056434). J. Redfern is funded by a NHMRC-National Heart Foundation Health Professional Fellowship. The funder and Dr Reddy's Laboratories (provided polypills free of charge for the clinical trial) had no role in the study design, data collection and analysis, decision to publish, or preparation of the article.

Disclosures

The George Institute for Global Health recently secured an exclusive global license for the polypills evaluated in the KGAP trial, following a decision by Dr Reddy's Laboratories Ltd not to proceed with taking the products to market because of existing regulatory requirements; apart from the declared, there are no other relationships or activities that could seem to have influenced the submitted work.

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Facilitators and barriers to implementation of a pragmatic clinical trial in Aboriginal health services

Trials that address a priority health issue, have had strong health service engagement and adequate local support seem more likely to succeed

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doi: 10.5694/mja14.00581

Abstract

Objective: To identify facilitators and barriers to clinical trial implementation in Aboriginal health services.

Design: Indepth interview study with thematic analysis.

Setting: Six Aboriginal community-controlled health services and one government-run service involved in the Kanyini Guidelines Adherence with the Polypill (KGAP) study, a pragmatic randomised controlled trial that aimed to improve adherence to indicated drug treatments for people at high risk of cardiovascular disease.

Participants: 32 health care providers and 21 Aboriginal and Torres Strait Islander patients.

Results: A fundamental enabler was that participants considered the research to be governed and endorsed by the local health service. That the research was perceived to address a health priority for communities was also highly motivating for both providers and patients. Enlisting the support of Aboriginal and Torres Strait Islander staff champions who were visible to the community as the main source of information about the trial was particularly important. The major implementation barrier for staff was balancing their service delivery roles with adherence to often highly demanding trial-related procedures. This was partially alleviated by the research team's provision of onsite support and attempts to make trial processes more streamlined. Although more intensive support was highly desired, there were usually insufficient resources to provide this.

Conclusion: Despite strong community and health service support, major investments in time and resources are needed to ensure successful implementation and minimal disruption to already overstretched, routine services. Trial budgets will necessarily be inflated as a result. Funding agencies need to consider these additional resource demands when supporting trials of a similar nature.

The principles of conducting ethically sound health research involving Aboriginal and Torres Strait Islander peoples have been well documented.[1-3] There are, however, many challenges to implementation of these principles and negative experiences have been reported.[4-11] A key element to the National Health and Medical Research Council (NHMRC) guidelines for ethical conduct in Aboriginal and Torres Strait Islander health research is the notion of reciprocity — that the benefits of the research be clearly articulated, negotiated and implemented in such a way that it will build community capacity.[1] In the context of clinical trials, this includes ensuring that studies test interventions in the settings in which they will eventually be delivered, rather than contrived environments that are conducive to easier trial implementation. Such trials are often referred to as pragmatic randomised controlled trials (PRCTs).[12]

The Kanyini Guidelines with the Adherence Polypill (KGAP) study was a PRCT that tested whether a polypill-based strategy would improve prescriber and patient adherence to recommended treatments for cardiovascular disease (CVD).[13-15] The trial was conducted between 2008 and 2012 across five Australian states in 20 general practices, 11 urban, rural and remote Aboriginal community-controlled health services (ACCHSs) and one government-run Indigenous health service. Participating services were each supported by one to three nominated community pharmacies. Design features that mimicked real-life practice included the prescribing of medicines by treating general practitioners, patient copayment charges for all study and other medicines at standard Pharmaceutical Benefits Scheme rates and the dispensing through community pharmacies. A major challenge to trial implementation was attaining target recruitment rates; only 623 of the target 1000 participants were randomised.[16] This led to a longer study duration than anticipated, with concomitant budget pressures.

In this qualitative study, we aimed to identify facilitators and barriers to trial implementation in the ACCHSs and government health service from the perspective of providers and trial participants. The study forms part of a broader trial process evaluation.[15]

Methods

Fifty-three interviews were conducted with 32 health care providers and 21 Aboriginal and Torres Strait Islander patients at six ACCHSs and the government health service from April to December 2012. (Appendix 1 and Appendix 2). Five ACCHSs that were involved in the trial were unable to participate due to limited capacity at the time when interviews were being conducted. Participants were recruited purposively to yield a maximum variation sample based on location, age, sex, ethnicity, presence of CVD, and medication for patients, and location and profession for providers.

Interviews were conducted at the conclusion of the trial as part of the overall process evaluation and included exploration of experiences regarding trial implementation. Interview guides were developed and iteratively revised to explore themes and issues emerging from earlier interviews. A team of

seven researchers, including three Aboriginal researchers, from a range of disciplinary backgrounds (health economics, pharmacy, nursing and public health) who were not involved in the implementation of the trial conducted the interviews. Most interviews were conducted face-to-face, with a small number conducted by telephone for logistic reasons.

Interviews were professionally transcribed and coded by two researchers (HL and LM) using NVivo 9 (QSR International). Twelve transcripts were selected (six patients and six health care providers — pharmacists, GPs, nurses and Aboriginal health workers [AHWs]) and were coded independently by the two researchers. These researchers identified the major themes arising from these 12 interviews and developed an initial coding framework. Insights gained by the research team about the context of the interviews and the local setting were documented and used to aid interpretation. The coding framework was then discussed and refined by a multidisciplinary group comprising the study investigators and the interview team. This included two ACCHS clinicians who were site principal investigators on the trial. The two researchers then coded the remaining interviews and made minor, iterative changes to code definitions.

For this study, we analysed codes specifically relating to issues relating to trial implementation. The randomised controlled trial, including its process evaluation, was approved by seven regional human research ethics committees, including one Aboriginal-specific committee. All participants who contributed data were provided a description of the study by the interviewer and given the opportunity to discuss any concerns before obtaining written consent.

Results

Four principal themes relating to barriers and facilitators for trial implementation were derived. Appendix 3 contains additional quotes that further illustrate the findings.

Health service governance of research

Ensuring community representation in governance of the research was a dominant issue. ACCHSs were invited to participate through initial discussions with senior management and governing boards. Formal memoranda of understanding (MOUs) with the coordinating research institutes were established. Amendments were made to the standard Medicines Australia clinical trial agreement to include intellectual property rights of ACCHSs and the roles and responsibilities associated with data custodianship. The discussions associated with setting up these agreements were critical in establishing mutual roles and responsibilities, data governance, capacity building plans and establishment of funding arrangements. One participant referred to the MOU as being a "landmark document" (GP 23, urban service).

In some instances, these agreements were facilitated by local governance processes. An AHW at an urban ACCHS described how previous negative experiences with external researchers prompted the establishment of a local research committee that would scrutinise external organisations' research proposals:

> In the past, the research that's been conducted has left some scars … what has helped has been being more organised about having our own research agenda … so if you want to do research [with us then] this is what's important to us. (AHW 47, urban service)

Motivation to participate

An expectation that the intervention could tangibly address an important health issue was extremely important for both patients and providers:

> When you see people that are dying around you that are the same age as you and even younger, it's all to do with health that they died not taking medication. Maybe if they were given the one pill instead of taking half a dozen they might be still here today. (Patient 4, urban service)

Several participating services had been involved in the Kanyini Vascular Collaboration before the trial and many staff were aware of the treatment gaps documented in the collaboration's audit of patient records.[14] Consequently, there was strong support from health care providers for strategies to address these gaps.

Effectively communicating the need to address these gaps to the community was particularly important. At one urban ACCHS this was done through a community forum and launch of the trial.

A related facilitator of participation was the role played by Aboriginal staff champions. These staff were often the initial point of contact for participants seeking information and were also referred to by other staff. One AHW discussed her role:

> At first it was hard to communicate with them. But once it got mentioned once, twice, maybe three times what was in the tablet, what the benefits would be it started sinking into their brains then. (AHW 32, urban service)

Balancing service delivery and research requirements

An important aspect of the research was to incorporate the intervention into usual service delivery. Efforts to streamline the intervention included the prescribing and dispensing of the polypill within existing software platforms, timing pathology tests to coincide with scheduled visits and recruiting community pharmacies that were accessible to the participating sites. Despite these efforts to integrate the intervention into routine care processes, some GPs felt it created "confusion in their management" and "confusion about what they were on when they went into hospital".

Some providers indicated challenges balancing trial operations with existing workloads. This manifested differently in urban and remote settings. For example, in urban settings, transport services were enlisted to facilitate study visits and access to medicines, potentially leading to

limited transport availability for non-trial patients. In remote settings, fly-in fly-out doctors provided services to highly mobile populations. This created substantial challenges for clinic staff to coordinate follow-up study visits. One GP felt that the trial was more suited to urban ACCHSs:

> You cannot compare it to an AMS [Aboriginal Medical Service] in Sydney … because we are serving about 200 000 square kilometres at this AMS. … our patients might come into town but they could be based 500 kilometres away … and it's a very transient place for many of our patients. (GP 40, remote service)

Such logistic challenges inevitably resulted in delays in recruitment and follow-up. To alleviate these challenges the study team committed additional unbudgeted resources to support trial sites.

Research capacity-building challenges

A core study objective was to build health service research capacity through involvement of staff in the clinical trial. Most of those interviewed considered trial participation to be a positive experience, with many staff members describing enhancement of clinical skills, increased awareness of clinical trial processes, and deeper collaborations between the health service and pharmacies.

A key capacity-building initiative was the creation of local Indigenous research fellow (IRF) positions to perform trial coordinator duties. In practice, however, recruitment of suitably trained individuals was challenging and only four positions were filled.

> The idea was that we were going to have an [IRF] is a great idea, but it just turned that we didn't really have anyone that took it on with a passion … [The role] is quite complicated … (GP 3, urban service)

Moreover, like all clinical staff, IRFs frequently had competing responsibilities, and found it difficult to balance their research role with service delivery. This led to staff turnover in the early part of the study, which affected the trial conduct. Overall, most trial sites commented that additional on-site support from research institute staff would have been beneficial. This was easier to provide at those sites located closer to the coordinating research institutes, and those sites tended to manage the trial with fewer challenges.

Discussion

This study examined the often-overlooked views and experiences of patients and health care providers from Aboriginal health services participating in a clinical trial. The key facilitators of participation were the interrelated factors of research governance, patient and provider perception of the need for this research, deployment of effective strategies for communication to the community at large, and enlisting the support of Aboriginal staff champions. These facilitators were tempered by several challenges related to adequate integration of the intervention strategy into routine care processes, large competing demands with routine service delivery, and only partially successful attempts at building local research capacity. These challenges manifested differently due to the highly diverse settings in which the participating services operated.

In Australia, several Indigenous health RCTs have been successfully conducted through established health service–researcher partnerships, particularly in the area of child health.[17-19] Many have experienced challenges in meeting recruitment targets and implementing the trials as originally conceived. Occasionally, trials have had to be abandoned altogether due to insurmountable constraints.[20] Our findings help determine the factors that both hinder and promote successful conduct of such trials. The integration of complex trial protocols that are not supported by senior management into underresourced health service settings is a recipe for implementation failure. Conversely, trials that address a priority health issue, have had strong health service engagement and adequate local support seem more likely to succeed.

The study was an indepth exploration of issues from a sample that was not necessarily representative of all participants and providers in the trial. Fewer interviews were done in remote sites, and staff who had left the service or participants who had withdrawn by the end of the study were not interviewed.

Although this study was based on a PRCT, such a design will not always be feasible nor acceptable. Alternative designs, such as stepped wedge trials and cluster RCTs of health service interventions, have been successfully implemented in collaboration with ACCHSs.[21,22] Other designs, such as crossover studies, interrupted time series analyses and propensity score matching, are also practical and often cheaper to implement. Use of automated de-identified data extraction and opt-out consent processes can considerably reduce data collection burden and reduce demands on Aboriginal health services.[22] There is also much to be gained from observational studies, in which routinely collected clinical audits can inform the evidence base about effective health service strategies.[14,22-27]

Although community participation in prioritising the research question is of fundamental importance, substantial research infrastructure investment in health services is of equal importance. Aboriginal governance and leadership of the research agenda must be in place, and there are now good examples of how large-scale research can incorporate this from the outset.[28,29] Associated with this is clear articulation of the resource implications associated with participation and ensuring there is adequate recognition of this within study budgets. The model for capacity building had mixed success, mainly due to the excessive and competing demands on individuals and limited existing research capacity; novel models to increase research capacity are needed.

There is clearly a need for more interventional studies to build the evidence base of what works in Aboriginal health service settings.[23,30] It is important that research funding bodies recognise the factors

highlighted in this study in their grant schemes. The overall $5 million (around $8000 per randomised patient) spent on the Kanyini GAP trial was several times higher than the amount originally granted and multiple additional funding applications were required. Although guiding statements on appropriate ethical conduct of research involving Aboriginal and Torres Strait Islander peoples acknowledge these issues, project-specific funding schemes tend not to recognise the importance of long-term investments in research capacity building, beyond what is immediately required to complete the project.[1,2] In addition to non-project specific schemes, such as the NHMRC Centres for Research Excellence, project-specific loadings for research conducted in collaboration with already overstretched Aboriginal and Torres Strait Islander health services ought to be considered to support local research capacity building and establishing the governance arrangements needed to ensure community support. Such investments would build the evidence base on models associated with success and strengthen the application of reciprocity in the conduct of Aboriginal and Torres Strait Islander research.

Acknowledgements: This work was supported by the NHMRC (grant numbers 457508, 571281 and 632810). We thank Deborah Blair and Barry Fewquandie for assisting in the interviews. We gratefully acknowledge the contribution of the participating health services in this study, and of the extensive team in the design and implementation of the KGAP trial. The trial is registered with the Australian New Zealand Clinical Trial Registry (no. ACTRN12608000583347).

Competing interests: The George Institute for Global Health recently secured an exclusive global licence for the polypills used in this trial after a decision by Dr Reddy's Laboratories not to proceed with taking the products to market because of regulatory requirements. Anushka Patel, Alan Cass, David Peiris and Stephen Jan received funding from Dr Reddy's Laboratories to attend an Investigators' Meeting.

Received 15 Apr 2014, accepted 5 Feb 2015. ■

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Liu et al. Trials (2015) 16:425
DOI 10.1186/s13063-015-0956-y

TRIALS

RESEARCH Open Access

Implementing Kanyini GAP, a pragmatic randomised controlled trial in Australia: findings from a qualitative study

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Abstract

Background: Pragmatic randomised controlled trials (PRCTs) aim to assess intervention effectiveness by accounting for 'real life' implementation challenges in routine practice. The methodological challenges of PRCT implementation, particularly in primary care, are not well understood. The Kanyini Guidelines Adherence to Polypill study (Kanyini GAP) was a recent primary care PRCT involving multiple private general practices, Indigenous community controlled health services and private community pharmacies. Through the experiences of Kanyini GAP participants, and using data from study materials, this paper identifies the critical enablers and barriers to implementing a PRCT across diverse practice settings and makes recommendations for future PRCT implementation.

Methods: Qualitative data from 94 semi-structured interviews (47 healthcare providers (pharmacists, general practitioners, Aboriginal health workers; 47 patients) conducted for the process evaluation of Kanyini GAP was used. Data coded to 'trial impact', 'research motivation' and 'real world' were explored and triangulated with data extracted from study materials (e.g. Emails, memoranda of understanding and financial statements).

Results: PRCT implementation was facilitated by an extensive process of relationship building at the trial outset including building on existing relationships between core investigators and service providers. Health providers' and participants' altruism, increased professional satisfaction, collaboration, research capacity and opportunities for improved patient care enabled implementation. Inadequate research infrastructure, excessive administrative demands, insufficient numbers of adequately trained staff and the potential financial impact on private practice were considered implementation barriers. These were largely related to this being the first experience of trial involvement for many sites. The significant costs of addressing these barriers drew study resources from the task of achieving recruitment targets.

Conclusions: Conducting PRCTs is crucial to generating credible evidence of intervention effectiveness in routine practice. PRCT implementation needs to account for the particular challenges of implementing collaborative research across diverse stakeholder organisations. Reliance on goodwill to participate is crucial at the outset. However, participation costs, particularly for organisations with little or no research experience, can be substantial and should be factored into PRCT funding models. Investment in a pool to fund infrastructure in the form of primary health research networks will offset some of these costs, enabling future studies to be implemented more cost-effectively.

Trial registration: ACTRN126080005833347

Keywords: Pragmatic randomised controlled trial, Primary healthcare, Indigenous health services, Implementation, Clinical trial

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Background

Randomised controlled trials are generally seen as the 'gold standard' for assessing the efficacy of health sector interventions. Challenges in applying the evidence based on explanatory trials of interventions tested in optimal conditions have led to a growing emphasis for pragmatic randomised controlled trials (PRCTs). PRCTs involve a comparison of interventions and using health outcome measures that are relevant to 'real-world' healthcare delivery. This allows for generalisability of the PRCTs' findings which may be more accessible to decision-makers and thus be translated into practice and policy [1–6]. PRCT interventions are often multifaceted with multipurposed analyses and the provider and the recipient of an intervention may not only be the health professionals and patients respectively but can be other members in the health system [2].

Designing PRCTs is not straightforward. For instance, in primary care settings, given the broad spectrum of disease presentation and diverse practice settings, maximising generalisability in a PRCT without overly compromising reliability or accuracy has proven difficult [8]. In this regard, strategies to deal with design issues such as unblinded treatment allocation and recruiting representative participants have been suggested [9]. More recently, a tool of ten domains known as the Pragmatic-Explanatory Continuum Indicator Summary (PRECIS) was developed by Thorpe et al. as a guide for researchers in designing PRCTs [10, 11]. The ten domains include participant eligibility criteria, intervention and comparison flexibility and expertise, follow-up intensity, participant compliance and participant adherence to study protocol, selecting and analysing primary outcomes which are relevant to clinical practice [7]. It is thought that by capturing 'real-life' practice variation the evidence generated will be more relevant to policy-makers [7].

The Kanyini Guidelines Adherence with the Polypill study (Kanyini GAP) provides a recent example of a PRCT that was implemented within Australian primary care. Kanyini GAP sought to explore whether a strategy based on the use of a fixed-dose combination pill (polypill), comprising low-dose aspirin, a statin and two blood pressure lowering agents, would improve patient adherence to and provider prescribing of evidence-based cardiovascular disease (CVD) preventive medications [12, 13]. This trial was conducted in primary care rather than in hospitals reflecting the setting where, in practice, prevention and early management of cardiovascular disease is most likely to take place [14].

Kanyini GAP included a range of diverse practice sizes and settings across Australia: 12 Indigenous Health Services (IHS) (which were 11 Aboriginal Community Controlled Health Services and 1 government-run health service) and 21 private mainstream general practices. Medications were dispensed through community pharmacies with patients in both treatment groups required to pay for their medicines at the prevailing co-payment rate. By incorporating these design features, the study sought to mimic the systems through which the comparative treatments would be delivered in practice; therefore, potentially yielding more generalisable assessments of 'real-life' effectiveness. Figure 1 shows the organisation of the trial management between the research coordinating centres and primary care services. A Consolidated Standards of Reporting Trials (CONSORT) flow diagram and checklist of this completed randomised controlled trial (RCT) are included as additional documents (see Additional files 1 and 2). Despite Kanyini GAP being designed according to recommendations in the PRCT-related literature, a number of problems were encountered in implementation: recruitment fell considerably short of expected targets ($n = 623$ c.f. 1000), challenges related to stakeholders not having prior research experience yet required to comply with Good Clinical Practice [15], study duration was considerably longer than expected and the costs exceeded the projected budget.

At present, there is very little published evidence that describes the experience of implementing a PRCT in primary care from the perspectives of the participants. To address this gap in evidence, this paper aims to identify the critical enablers and barriers to implementing Kanyini GAP. Drawing on the experiences of patients and providers participating in Kanyini GAP and key trial documentation, we sought to make recommendations for the future implementation of PRCTs in primary healthcare settings.

Methods

This study uses qualitative data from the overall process evaluation of Kanyini GAP [16]. A predefined protocol for the process evaluation was used [16]. The methods are described across the three domains as specified in the consolidated criteria for reporting of qualitative studies developed by Tong et al. from a review of established guidelines and qualitative studies [17].

Research team and reflexivity

Study investigators (TU, SJ, JR, TL, DP, and AC) who were involved in the design and implementation of Kanyini GAP developed the interview guides which were iteratively revised to explore themes and issues emerging from earlier interviews. Views about the polypill strategy in CVD management, patient satisfaction or problems with the polypill, issues regarding trial implementation, and perspectives of translation of the polypill into clinical practice were key domains of the interview guides. The interviews were conducted by a team of seven interviewers. Two of the interviewers had existing relationships with some of the participants interviewed as they were research coordinators in the trial but the other interviewers were not known to the

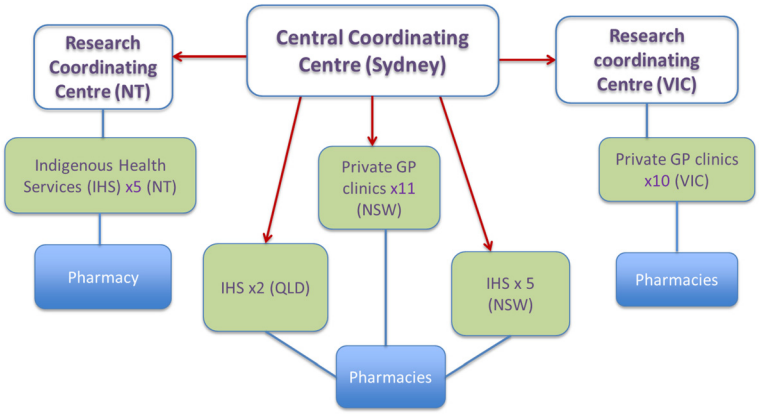

Fig. 1 Organisational structure of the Kanyini GAP study. Kanyini GAP was conducted in 33 sites across urban, rural and remote Australia and recruited 623 patients through 12 Indigenous health services and 21 private general practices. There was one central coordinating centre based in Sydney and two regional coordinating centres based in Alice Springs and Victoria, which recruited and coordinated the sites in NSW, Queensland, Victoria and the Northern Territory. Each 'site' included either a general practice clinic or an Indigenous health service and 1–3 community pharmacies

participants prior to the interviews. The team had diverse backgrounds (health economics, nursing, pharmacy, Indigenous health), varied experience in qualitative research and three were Indigenous and four non-Indigenous researchers.

Study design

Site recruitment for the Kanyini GAP trial was initiated with the general practitioners (GPs) of private practices and IHSs, as well as the board members of IHSs. A critical enabler to the recruitment of GPs was the extensive process of undertaking relationship building and leveraging existing networks amongst Kanyini GAP chief investigators. In particular, prior to Kanyini GAP, a relationship between the research-team and several of the IHSs existed as part of the Kanyini Vascular Collaboration – a chronic disease-based research collaboration between the two research institutes and participating IHSs around Australia.

Participants were purposively recruited for the qualitative study from these participating Kanyini GAP sites based on maximum variation of specified variables which were based on adherence literature which may affect participants' experience with a polypill-based strategy and also variables which may impact trial implementation. We used the sampling matrix to select patients based on these characteristics; for patients these were location, age, gender, ethnicity, primary versus secondary CVD, and self-reported adherence at baseline; and for providers variables included location and profession [18]. All health providers and patients were sent an invitation letter outlining the study and its objectives, and followed-up by a phone call by the project coordinator (LM). Five patients declined to be interviewed and two patients were not available, and all health providers agreed to be interviewed. Written informed consent was obtained from all participants.

Most face-to-face interviews, which ranged from 30 min to an hour, were conducted either at home or at the health service, and audio-recorded. Two participants from interstate were not available for a face-to-face interview. Phone interviews were conducted with these two participants and audio-recorded. One researcher LM was involved in almost all the interviews to ensure consistency [18]. She conducted 40 with another interviewer and 42 alone. LM coordinated the study and was trained in qualitative methods. She conducted preliminary thematic data analysis alongside the interviews. Thematic saturation was achieved and interviews stopped.

Analysis

Interviews were professionally transcribed. At the completion of all the interviews, two researchers (HL and LM) used NVivo 9 (QSR International, Melbourne, VIC, Australia) to code and manage the qualitative data. Using the constant comparative method [19], these researchers coded line by line the same twelve transcripts independently (six patients and six health providers across the variables) through three iterative stages and an initial coding framework was developed. Insights about the local setting, context of the interviews and empirical results of the PRCT were documented and used to aid interpretation and triangulation [20, 21]. The overarching coding framework (which is included as an Additional file 3) was developed for provider and patient interviews and refined with the study investigators and the interview team. This included two IHSs clinicians (TU and DP) who were site principal investigators on

the trial and provided respondent validation [20]. The two researchers (HL and LM) coded the remaining interviews equally, drawing up memos for each interview to provide additional context for other researchers analysing the data, and recoded the original twelve interviews. Minor, iterative changes to code definitions were made. An audit trail was kept.

To address the aims of this study, provider and patient experiences that were related to trial implementation which were coded to: 'trial impact' and 'research motivation' and 'real world', were explored.

Additionally, some triangulation of findings was obtained through a review of existing Kanyini GAP documents (e.g. Email communications, Memoranda of Understanding, and financial statements) [17].

The study was approved by 7 regional committees including 1 Aboriginal-specific committee jurisdiction (Sydney South West Area Health Service (HREC Ref. 08/RPAH/126); Aboriginal Health and Medical Research Council of NSW (642/08); Cairns Base Hospital (HREC/08/QCH/10-546); Princess Alexandra Hospital Centres for Health Research (HREC/08/QPAH/160); Central Australian Human Research Ethics Committee (2008.09.04); Northern Territory Department of Health and Menzies School of Health Research (HREC 2010–1466; Monash University Human Research Ethics Committee (CF09/2353 – 2009001370)).

Results

At the end of Kanyini GAP, 94 semi-structured interviews were conducted by the interview team with 47 providers (25 GPs, 13 pharmacists, 6 Aboriginal health workers (AHW) and 3 chronic care nurses) and 47 patients in NSW, Queensland and Victoria. There were 22 and 25 patients who were in the polypill arm and usual care arm, respectively. There were 26 non-Indigenous patients and 21 Indigenous patients.

The critical enablers and barriers to implementing this PRCT in Australian primary healthcare settings were broadly grouped within three key themes: recruitment and participation; research and primary practice settings; and participant costs. Tables 1 and 2 summarise the identified barriers and enablers to conducting a primary care PRCT within these three key categories and presents suggested strategies to overcome barriers and maximise enablers when implementing future PRCTs in primary practice settings.

Recruitment and participation

Site recruitment

The recruitment process for enlisting sites included a number of initial meetings, workshops and dinners to introduce the trial and elicit expressions of interest. This approach proved an effective way to develop and strengthen existing relationships with primary care services. Kanyini GAP also built upon previous research done with the IHSs, which found a gap in the prescribing of indicated CVD medications; thus site recruitment to Kanyini GAP was seen as a 'natural progression' (Provider 47, AHW). This is evident from the following comment from a GP based at an urban IHS:

> '*The other thing that was really helpful was the way the service was engaged by The George Institute so that the community all knew about polypill. They'd engaged with the Board very well, the Board and the service had agreement so the CEO and the manager in the service knew about it. They'd held a launch day at the service and people were asking questions, so there was a lot of engagement, a lot of patients knew about it, so there was general awareness.*' (Provider 8, GP)

Some participating GPs envisaged tangible benefits to their practice through involvement in primary healthcare research, in terms of quality improvement and staff morale. As a GP at an urban private practice site describes:

> '*Philosophically I like the idea as a practice being opened up to researchers …… I've done a lot of quality improvement with practices and one of the things that builds the team is opening it to the outside world. And, participating in research is a way of opening it to the outside world, so it's actually a plus for team building. Practices feel proud that they're actually working at this level.*' (Provider 1, GP)

In addition to staff morale, a collective increase in research capacity at the health service level was thought to be a positive impact of participating in primary care research, as one GP from an urban IHS noted:

> *'It was good for our research capacity, it was a project we all believed in and got behind. … our name came up just on the weekend at the conference that I was at … people mentioned that we were part of the Kanyini GAP trial. So I think from that point of view it was good for our health service, good for our reputation. … participating in research I think was a good experience for those workers some of whom were Aboriginal, so that's increasing the research capacity, Indigenous research capacity for (the) clinic which is a good thing.*' (Provider 33, GP)

Providers' research motivation

Motivation to take part in the research study was frequently mentioned, with many providers stating that

Table 1 Strategies to overcome barriers to implementing primary care pragmatic randomised controlled trials

Barriers	Strategies to help overcome
Recruitment and participation	
Prescriber disagreement about recruitment across sites: clinical eligibility compared to trial suitability	• Prior to implementation, identify potential sources for disagreement, provide examples and workshop solutions with providers
	• Throughout recruitment, facilitate a forum for providers to discuss with research team actual difficulties encountered
Potential negative impact of evaluated intervention on provider's business revenue	• Identify and discuss potential impacts (immediate and long-term) with providers;
	• If possible, ensure lost revenue adequately compensated
	• Educate potential providers about the value of the intervention to public good
Highly mobile patients	• Consider provision of mobile recruitment services
Research and primary practice settings	
Inadequate research infrastructure	• Ensure adequate physical space available for trial processes
	• Understand information technology (IT) capacity at sites and use study systems that can integrate with pre-existing IT, thus minimising training requirements
	• Consider using data extraction tools to minimise access time to information technology systems
	• Ensure adequate remuneration to participants for time and service provided
	• Consider provision of dedicated research coordinator at sites, particularly those already understaffed
Pre-existing workforce strains	• Adequately understand workforce-related issues at participating sites
	• Ensure adequate personnel support is available and can respond to high staff turnover
	• Ensure adequate training at practice level, and refresher training available and budgeted for
Potential miscommunication across multidisciplinary health services beyond primary care	• Provision of simple communication tools at the patient and practice levels that highlight patient involvement within the trial.
	• Adequately educating patients and carers regarding about trial and need for communicating to all healthcare providers
	• Identify participant multidisciplinary providers at enrolment and target trial communication strategies accordingly
Increased administrative burden relative to health service delivery and patient care demands	• Provide adequate research support to sites that can minimise administrative burden
	• Consider automated procedures that ensure Good Clinical Practice compliance and can integrate with current health service processes
	• Ensure site service delivery requirements are fully understood prior to implementatin
	• Provide clear education about Good Clinical Practice
	• Practice requirements and administrative needs prior to recruitment
Costs	
High trial running costs	• Ensure adequate budget for provision of research support personnel at sites to maintain recruitment timelines, ease administrative burden to sites and reduce opportunity cost to sites
	• Additional funding load to accommodate inadequate primary care research infrastructure
	• In medium to long term establish a funding pool to invest in primary healthcare research infrastructure
Opportunity cost to participants	• Understand potential costs to participants prior to implementation
	• Provide adequate remuneration to participants in light of actual time required for administration, including time spent with research nurses
	• Ensure simple processes for sites to apply for and receive remuneration

being part of a trial is for the 'greater good'. The following GP from an urban IHS outlined her motivation to take part in investigator-led research:

'*I really liked and felt comfortable and trusted the Kanyini polypill … that it was put together on the basis of what was going to be best for people with*

Table 2 Strategies to maximise enablers to implementing primary care pragmatic randomised controlled trials

Enablers	Strategies to help maximise
Recruitment and participation	
Leveraging pre-existing networks and relationships with key stakeholders	• Provide adequate pre-recruitment engagement with stakeholders and elicit expressions of interest
	• Engage with stakeholders at trial-design stage to build a sense of ownership and address research objectives of participants
Increased research capacity	• Understand research needs of sites and fulfil gaps in research capacity as requested
	• Incorporate capacity building as a key outcome for participation
	• Provide opportunity for training at health service level to build research capacity within primary healthcare.
Research as a quality service indicator and team building exercise	• Provide structured training for sites as a means for team building between and across sites
	• Research participation as a quality assurance indicator for primary practices: policy development consideration
Professional support for the intervention under evaluation and tangible benefits to the service or participant	• Understand and address professional concerns about the intervention under evaluation
	• Promote the potential benefits of trial participation to health service and participants
Personal and community benefits research participation	• Understand and promote benefits (and risks) of research to individuals and community
	• Educate participants about research goals and needs
	• Ensure participants feel sufficiently empowered to make decisions about ongoing participation
Research and primary practice settings	
Provision of research coordinator	• Prior to implementation, proactively identify site resource needs in terms of trial-related administration, communication, data management and patient management
	• Ensure adequate research and logistical support is provided

cardiovascular disease rather than the profit motive which pharmaceutical companies have to go by because they're private companies and have shareholders.' (Provider 33, GP)

Many of the pharmacists participated because they were interested in the intervention under evaluation. Several were candid about the potential negative effect a polypill strategy could have on their revenue. As described by a pharmacist in an urban site based close to an IHS:

'*Now I'm aware of different critical remarks among community pharmacists … instead of three or four dispensing fees we see one … not being a pharmacy owner … I'm less sensitive to that issue … By and large it's good for customers, it's good for compliance, it's good for the government I suppose.*' (Provider 15, Pharmacist)

For some, participating in a trial was also thought to create an opportunity for health professionals and services to improve the care given to patients while promoting collaborations with other organisations, as this next Aboriginal health worker from a remote IHS described:,

'*I'd say well it gives them (the health service) the opportunity to give their patients the best possible care that they can … offer this one more thing (that) can actually influence a lot of the patients that we have. So that offers better care for our patients. But then, you know, helping out studies also yields partnerships with people, other organisations.*' (Provider 41, AHW)

Recruitment of patients

Patient recruitment in the pragmatic trial required substantial effort due to the diversity of the health services and broad characteristics of patients expected to participate. For instance, recruitment in remote services was particularly challenging given patient populations were highly mobile and health considerations complex. A GP in a remote IHS described it as such:

'*I think there's a difference between being eligible and suitable, so I think that was something that wasn't really teased out properly. We got, I think, nearly close to our target, because we recruited a lot of eligible*

patients. In terms of suitability, I don't know whether we really picked patients that were appropriate for a trial.' (Provider 40, GP)

Moreover, for this next GP, describing the recruitment of patients with complex comorbidities from private practice, the broad patient eligibility criteria proved a source for disagreement between prescribers about recruitment:

'I was surprised that some of the patients, who others had been happy to put on it because when we looked at the problems that some had, I thought, well I wouldn't have put that person in, in the first place... Because they hadquite a complicated history and potential risks of having some problems ... I wanted them to either fit in clearly or not ... So I suppose I was looking for people who didn't really have lots of other comorbidities ... I would have said, "They're not suitable".' (Provider 36, GP)

Patients' research motivation

For patients, an overwhelmingly positive response to being involved in the trial was expressed with many claiming they were happy to be involved as 'guinea pigs' and to play a part in contributing to 'finding a cure'. Taking part in the trial was thought to not only offer potential benefit to them as individuals, but to others as well, and Aboriginal and Torres Strait Islander people in particular expressed their interest in the trial for this reason:

'*You know there's something you're contributing to, and it's not just about you; it's about how it might help the rank and file right across the nation ... if I can help my people live longer, live better lifestyles, healthier lifestyles, then I want to be a part of that. I just want to be part of that group that does that.*' (Patient 10, urban IHS)

This 'big picture' thinking translated to a willingness to be involved, to trust in the health system and a sense of doing something meaningful for others even if there were no evident or immediate benefits for themselves:

'I don't have a problem with studies. I think if it's going to ultimately benefit mankind, I'm happy to sort of be a bit of a guinea pig. It's an interest. It's also a possibility that I will suffer better health because of it, so I don't have a problem with those types of things generally.' (Patient 16, of private GP)

'*Well I did feel an obligation not to withdraw and I don't know how many people in your control group stuck it out to the end but you need a certain number to you know, validate the statistics ... But I never felt any pressure, I was always assured that I could pull out at any time if I'd had enough. But the pressure came from within, you know... I've started I should finish.*' (Patient 25, of private GP)

Research and primary practice settings

Research infrastructure

Overwhelmingly, providers cited inadequate infrastructure as a substantial barrier to trial implementation. Infrastructure considerations included: physical space to conduct patient visits, access to information technology systems, and storage space for additional supplies of polypill (for post-trial provision of polypill to participants). Time, money and human capacity were other necessary resources which were reported as being limited. A pharmacist in a remote area described such challenges:

'*... I guess from our perspective, and it came down to not necessarily The George Institute, but it was more our settings and our dispensing program and also staff education as well ...*' (Provider 42, Pharmacist)

Research and logistical support

The provision of a research coordinator at the study sites was described by many providers to be a key facilitator to trial implementation. In IHSs, the research nurse provided logistical support for the trial through trial-related communication with health service staff members, administration, obtaining informed consent, and data collection. This is evident in the following comment from a GP at an urban IHS:

'*I think it has been a good thing. It's not an added, the admin, the workload doesn't add on because we have the team for support here. So in that way it wasn't even, didn't even notice. And it's just like any other pill really, just prescribe it. It was easy enough; it was already on our system so we just prescribe it just like any other.*' (Provider 5, GP)

A GP and medical director in an urban private practice also thought that the research nurse facilitated the conduct of the study and, therefore, alleviated the effort required from the GPs in her service:

'*... she (research nurse) facilitated everything brilliantly. ... we cringe sometimes when people ask us to do studies in a busy general practice ... without the nurse it would have been a nightmare really, ... Well, I think the whole study would not have worked without her, and I think it's a real lesson for any GP research is having a research nurse is key.*' (Provider 12, GP and Medical Director)

Workforce-related issues

Some sites with particularly large patient loads, long clinic waiting times and many rotating GPs faced challenges due to potential for miscommunication between providers, and a lack of general understanding of the study across the service. Integrating the intervention within the realities of a dynamic workforce and chronic staff shortages was particularly difficult. For instance, at some IHSs, the research coordinator position proved to be difficult to replace as required, due to a complicated trial coordination handover and the need for staff re-training. A medical director of an IHS describes the effect of high staff turnover on trial conduct:

> *'I think it was more good fortune than anything else that we actually made it to the finishing line to tell you the truth … staffing's been a problem the whole way through really. I think we've actually had about three or four sort of individuals that have been identified as actually the local supports or go-to people for the trial … within a period of 18 months, 2 years.'* (Provider 46, Medical Director)

It was also acknowledged that this problem was likely compounded by the ongoing problem of workforce retention in remote settings.

Administrative demands of clinical trials

The paperwork requiring compliance with Good Clinical Practice guidelines, including the reporting of adverse events, was highlighted by some GPs as being an unacceptable additional workload. As one GP in private practice stated:

> *'"It's the paperwork (that) has driven me crazy … I don't see any future for research if that's the amount of paperwork you've got to see, … I can understand why you've got to do it but it's just insane and I think people who design these things and make the rules ought to go and have a good hard look at themselves and say you know, this is stupid … Now you know, adverse reactions are important but you know, most of them are rubbish, most of them have got absolutely nothing to do with the study.'* (Provider 10, GP)

When asked about future involvement in a PRCT, this GP in an urban setting was negative about his experience, questioning the feasibility of doing 'research on people in the "real world" … properly', (Provider 10, GP). This scepticism was based on the trial's administrative demands competing with his fundamental priority of adequate service delivery and patient care.

In contrast, some providers did not find the additional paperwork overly burdensome, acknowledging time was required to be spent on training and administrative paperwork as a condition of committing to trial participation.

Multidisciplinary care beyond primary care

Another area of difficulty identified with implementing a trial in primary care settings was that it involves patients who require multidisciplinary care that may be received outside of the primary care sites involved in the trial. In particular, difficulties with communicating information about the trial between primary and secondary healthcare was described to potentially impact patient retention, as this next GP stated:

> *'… a person that goes in and out of hospital. In which case I think it just caused a stress. Because they'd go in and then they'd have all of the interns and then the residents and registrars and everybody … What is this thing and what are you on, … And how do we, and what do we do and how we got to change this? So I had a couple of times when patients would actually come and just felt that it was too difficult because of their multidisciplinary care.'* (Provider 3, GP)

Although extensive efforts were made to inform stakeholders about Kanyini GAP at the outset (e.g. informing specialists about the study prior to commencement, explaining the polypill within referral letters and providing information cards to patients), and these were described by providers as an essential 'safeguard' against miscommunication, the above finding suggests that such measures may not have been sufficient.

Participant costs

Participants did not indicate that the incentive payments provided for participating in the Kanyini GAP trial influenced their involvement in the study, suggesting that the altruistic motivations outlined earlier were primarily considered. Furthermore, not all pharmacies claimed their entitlement offered to support the dispensing and handling of the polypill. Some pharmacists reported the 'small' payments were not worth the time and effort involved in preparing the necessary paperwork.

Despite our measures to minimise the financial impact through a remuneration of AUD$100 per patient randomised into the trial, a number of GPs from private clinics did highlight that the time involved in taking part in the trial carried a significant opportunity cost. The following comment from a GP, who was a private practice proprietor located outside an urban area, indicates that even with the provision of a research nurse, participation resulted in an opportunity cost:

'*You run a business, you really can't, (take that much time out), and even so we still spent quite a bit of time with (the research nurse)... I don't know how many appointments we missed because of time with her even though it wasn't huge, it adds up.*' (Provider 37, GP and private practice owner)

Discussion

Summary

By exploring provider and patient experiences from Kanyini GAP, and relevant trial materials, our analysis has revealed considerable barriers to implementing a PRCT in primary care. Specifically, a substantive lack of research infrastructure, limited numbers of primary care personnel adequately trained in the conduct of clinical trials, administrative burden from regulatory requirements that exceeded the demands of adequate patient care provision and the lack of coordination across all providers involved in the treatment of patients, including non-primary healthcare providers, substantially impeded implementation. Additionally, the ongoing problem of an under-resourced primary care workforce meant that centrally employed research nurses were needed to support the sites. As a consequence of these barriers, funding for this study – around AUD$5 million and sourced from multiple sponsors – ultimately proved insufficient. As a result, recruitment timelines were longer than anticipated and ultimately targets were not met.

Despite these shortcomings, participating in Kanyini GAP was generally considered a positive experience with mutual benefits stated for patients and providers involved. Benefits included professional satisfaction, increased collaboration between the different health services involved, improved research capacity and the opportunity for health services to improve patient care. In addition, patients and providers participated for altruistic reasons, being particularly motivated by the chance to contribute to the 'greater good'. The success of completing Kanyini GAP appears largely attributable to an upfront investment to build and maintain collaborations across the diverse range of Australian primary healthcare settings and, notwithstanding the additional financial cost incurred, from an intensive level of research support provided to participating sites.

Recruitment challenges in PRCT

The challenges of meeting recruitment targets particularly within PRCTs have been well-documented [9, 22–24]. A meta-analysis of interventions to promote patient recruitment to primary care concluded that organisational characteristics, especially trial infrastructure, were important [23]. Similarly, our findings indicate that a lack of such research infrastructure in Australian primary practice contributed substantially to recruitment delays. However, the high level of research motivation reported from both providers and patients that was underpinned by a sense of altruism facilitated recruitment.

Some design features of Kanyini GAP, classified with the PRECIS tool as more pragmatic than explanatory, presented further challenges to recruitment and implementation. Specifically, the 'participant eligibility criteria' domain was highly flexible in Kanyini GAP such that all patients with the condition of interest were considered eligible [10, 11]. Using these criteria to assess site feasibility on the basis of predicted recruitment targets led to an overestimation of participant numbers compared to what could be achieved in practice. Furthermore, the domain 'experimental intervention practitioner expertise' allowed for a full range of practitioners to apply the intervention within the clinics [10, 11]. In larger sites that had multiple staff on rotation, more training and logistical support for practitioners was required throughout the time frame of the study than might have occurred if selected personnel were responsible for applying the intervention. Collectively, these pragmatic design features of Kanyini GAP meant there was a need to engage more sites, extend study timelines and increase expenditure to try and meet recruitment targets. However, the use of these pragmatic criteria is necessary as they allow for real practice variation and an assessment of the acceptability and generalisability of the intervention.

Challenges unique to trial implementation in a primary care setting

Our study has identified some additional challenges which may be unique to the conduct of a clinical trial in the primary care setting. First, in contrast to research traditionally conducted in public healthcare facilities, a number of primary healthcare providers in Kanyini GAP were operating in the private sector. Although altruistically motivated to participate, the impact of the trial on revenue and time was an important consideration. Furthermore, despite establishing PRCT research partnerships that would now be classified as 'best practice', (e.g. site feasibility pre-assessment, stakeholder involvement and integration into usual practice workflow) [25], these efforts were insufficient to mitigate the burden that was experienced by some Kanyini GAP providers. In this regard, identifying and discussing the immediate and long-term financial impact of the trial with the healthcare providers is important at the outset. Compensation for such costs needs to be built into existing funding models for pragmatic trial research.

Second, as most primary care sites in Kanyini GAP were independently owned, there was substantial variation in the day-to-day operation between sites. Chronic staff shortages and high staff turnover were problematic,

particularly at rural and remote sites where some of the most disadvantaged and difficult-to-reach patients reside. To enable the streamlined integration of the trial with usual primary care processes, the provision of intensive research support is needed via trained research nurses. Research conducted in greenfield sites, involves significant investment to increase their research capacity for future studies.

Strengths and limitations

This study has identified enablers and barriers to the conduct of a PRCT in Australian primary healthcare settings by directly considering the experiences of participants. This information is vital for clinical researchers who seek to generate 'real-world' evidence to bridge the significant gaps known to exist between the controlled trial environment and practice. However, this study did not include the remote Central Australian sites involved in Kanyini GAP. Thus, the generalisability of the study's findings to such sites, and to other healthcare systems cannot be certain. So as not to influence the adherence behaviours of participants, interviews could not be conducted until the end of study. Invariably, the opinions of participants who had dropped out of the trial prior to the end-of-study visit, or sites that were approached but declined to participate, could not be ascertained. However, the rigorous methods used in this study, particularly triangulation of data sources, using more than one interviewer and coder, and the breadth of clinical and research experience of the research team favour robust results.

Conclusions

A number of key recommendations for the implementation of future PRCTs in primary care have emerged. First, significant investment in primary care research infrastructure is needed to facilitate recruitment and successful trial completion. Information technology systems that streamline data capture relating to key outcomes (e.g. hospitalisation and mortality) and that can promote communication across the various health system levels (e.g. primary and secondary care) is one suggestion.

Second, building research capacity within primary care is essential. Including research as a key performance or quality assurance indicator may increase research capacity, albeit indirectly. The increased exposure of patients and practitioners to research may ultimately lead to PRCTs being viewed as a standard feature of high-quality primary healthcare services. This is congruent with experiences of other PRCT trialists which found that conducting PRCTs has the potential to achieve greater partnerships between researchers and healthcare systems to produce high-quality studies to improve health-care [25].

A final strategic recommendation would be sustained funding for adequately resourced primary care research networks, incorporating private practices, ACCHSs and pharmacists. Based on international evidence [26], practice-based research networks (PBRN) are now starting to emerge in Australia but are currently poorly funded [27].

Notwithstanding the development of such networks, sufficient resourcing must be set aside for individual projects to cover the full costs of involving large numbers of disparate stakeholders in research. It is important to recognise that the high unbudgeted costs in the Kanyini GAP trial were to accommodate the lack of research experience and training in primary care. Substantial costs associated with running trials in primary care settings are incurred upfront, particularly when partnering with numerous centres which have had limited or no research experience. Such upfront costs should include not only costs to the study but the burden to the individual centres for which, as uncovered in our interviews, was often uncompensated for.

By initiating research across a numerous set of diverse sites, Kanyini GAP has cleared paths for easier and less costly implementation of future Australian primary care PRCTs. A key recommendation from this project, therefore, is that recognition of such path-clearing investments is required and that provision either be made (in the short term) for loadings on research funding for new projects that specifically set out to perform similar roles or (in the medium to long term) the creation of a general investment pool to fund primary care research infrastructure. Such initiatives will encourage investment in capacity that will contribute to a broader research environment more conducive in the long run to the running of much-needed PRCTs.

Additional files

Additional file 1. Populated CONSORT flow diagram of the completed RCT. (DOC 47 kb)

Additional file 2. CONSORT checklist of the completed RCT. (DOC 217 kb)

Additional file 3. Coding framework. (DOCX 21 kb)

Abbreviations

ACCHS: Aboriginal Community Controlled Health Service; AHW: Aboriginal health worker; CONSORT: Consolidated Standards of Reporting Trials; CVD: cardiovascular disease; GP: general practitioner; IHS: Indigenous health service; Kanyini GAP: Kanyini Guidelines Adherence to Polypill Study; PBRN: practice-based research networks; PRCT: pragmatic randomised controlled trial; PRECIS: Pragmatic-Explanatory Continuum Indicator Summary; RCT: randomised controlled trial.

Competing interests
The George Institute for Global Health recently secured an exclusive global license for the polypills evaluated in the KGAP trial, following a decision by Dr Reddy's Laboratories Ltd. not to proceed with taking the products to market because of existing regulatory requirements; apart from the declared, there are no other relationships or activities that could appear to have influenced the submitted work.

Authors' contributions
LM managed the study, led the data collection and analysis, and drafted the paper. HL helped managed the study, led the data analysis, assisted with the writing and revising of the paper and is responsible for the integrity of the work. SJ designed the study, helped with the data collection, analysis, and writing and revising of the paper. TL assisted with the set-up of the study, data collection, and helped write and revise the paper. AE assisted with data collection and helped write and revise the paper. AC, AP, DP, JR, KH and TU helped design the study and refine the theoretical and methodological approach, and helped write and revise the paper. All authors read and approved the final manuscript.

Acknowledgments
We would like to acknowledge the staff and participants involved in this qualitative study and in the Kanyini GAP trial. An extensive team designed and implemented Kanyini GAP which was a challenging clinical trial in the primary healthcare setting (members are listed in the main Kanyini GAP paper). The study was funded by the National Health and Medical Research Council (NHMRC) of Australia (App: 1004623). SJ and AP are funded by Senior Research Fellowships from the NHMRC. TL is funded by an NHMRC Capacity Building Grant (57132). AE is funded by an NHMRC Scholarship (1056434). JR is funded by a NHMRC Career Development Fellowship (APP1061793) co-funded with a National Heart Foundation Future Fellowship (G160523). The funder and Dr Reddy's Laboratories Ltd. (provided polypills free of charge for the clinical trial) had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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Received: 28 August 2014 Accepted: 11 September 2015
Published online: 23 September 2015

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CHAPTER 4: A PROCESS EVALUATION OF A FAMILY-LED REHABILITATION TRIAL IN INDIA (ATTEND)

Chapter Overview

This chapter contains the process evaluation of the fAmily-led rehabiliTaTion randomisEd controlled trial in InDia (ATTEND). The chapter consists of two published and one accepted manuscript titled: 1) A protocol for a process evaluation of a randomised controlled trial of family-led rehabilitation post stroke (ATTEND) in India. 2) Family-led rehabilitation in India (ATTEND) - findings from the process evaluation of a randomised controlled trial. 3) Clinical stroke research in resource limited settings: Tips and hints.

Whilst in Chapter 3 the use of a Realist lens of 'Context, Mechanisms, and Outcomes' allowed for greater interpretation of the micro to macro -level contextual factors in the process evaluation of Kanyini GAP (conducted in 2013), this chapter is informed further by the UK MRC process evaluation guidance published in 2015. The first manuscript provides the process evaluation protocol which incorporates concepts from the RE-AIM (Reach, Effectiveness, Adoption, Implementation and Maintenance) framework into the UK MRC process evaluation framework. The overarching framework and relevant data sources are described.

The second manuscript provides the findings from the process evaluation, and helps explain why the trial, which was published in the Lancet (see appendix), was neutral and the implications of the findings. As a background, the ATTEND trial was a large scale randomised controlled trial in India which involved the training of a family care-giver to provide basic

evidence-based rehabilitation to a patient post stroke. The trial was initiated by local neurologists in India and co-Investigators in Australia and the UK, and funded by the Australian National Health and Medical Research Council to address a recognised deficiency in access to stroke rehabilitation in India - a setting where there are major economic and health system barriers to formal rehabilitation services. This model of care was not found to be effective in reducing death and dependency at 6 months after stroke.

This process evaluation answers important questions raised in the wake of the trial: Was the lack of effect due to a failure of the intervention or of trial implementation, or both? What actually happened at the hospital and in peoples' homes? Given that family-led rehabilitation is a complex behaviour-change intervention with multiple interacting components and actors- examining the process of trial implementation, contextual factors and exploring health providers', patients' and carers' perspectives of the intervention could shed light on this 'black box.' Therefore, providing greater insight into the mechanisms of the intervention, and inform future research priorities.

The third manuscript aims (as stated in the process evaluation protocol) to identify the facilitators and barriers of the ATTEND collaborative group. This publication was an invited review and perspectives paper. Chief investigators of the ATTEND trial, Dr Jeyaraj Pandian and Dr Richard Lindley, were invited by the International Journal of Stroke to provide their insights and hints for conducting research in limited resource settings. The barriers and facilitators identified in the ATTEND process evaluation was incorporated in this invited narrative.

Author's contributions:

JDP suggested the original ATTEND trial idea and the steering committee (RL, GVSM, PKM, PL, LAH, MLH, MW, AF, BRS, CSA and SJ) designed the trial with a process evaluation in mind. HL developed the process evaluation protocol with extensive and significant contribution from the trial management team which includes MA, CF, DBCG, SJV, DKT, AS and RKR. HL led the process evaluation, trained the process evaluation team members in qualitative methods, contributed to the data collection and led the analysis. HL drafted the manuscripts and revised them. All authors read and approved the manuscript of the protocol and the manuscript of the findings. HL is the first author of the first two manuscripts, and the second author of the third manuscript. All authors contributed to the revisions of the manuscripts.

Manuscript details:

Liu H, Lindley R, Mohammed A, Felix C, Gandhi D, Verma S, Tugnawat DP, Syrigapu A, Krishnappa R, Pandian JR, Walker M, Forster A, Anderson C, Langhorne P, Murthy GVS, Shamanna BR, Hackett ML, Maulik PB, Harvey LA, Jan S. A protocol for a process evaluation of a randomised controlled trial of family-led rehabilitation post stroke (ATTEND) in India. BMJ open, 2016. http://www.ncbi.nlm.nih.gov/pubmed/27633636

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BMJ Open

Protocol for process evaluation of a randomised controlled trial of family-led rehabilitation post stroke (ATTEND) in India

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To cite: Liu H, Lindley R, Alim M, *et al*. Protocol for process evaluation of a randomised controlled trial of family-led rehabilitation post stroke (ATTEND) in India. *BMJ Open* 2016;**6**: e012027. doi:10.1136/bmjopen-2016-012027

► Prepublication history and additional material is available. To view please visit the journal (http://dx.doi.org/10.1136/bmjopen-2016-012027).

Received 23 March 2016
Revised 23 June 2016
Accepted 24 August 2016

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ABSTRACT

Introduction: We are undertaking a randomised controlled trial (fAmily led rehabiliTaTion aftEr stroke in INDia, ATTEND) evaluating training a family carer to enable maximal rehabilitation of patients with stroke-related disability; as a potentially affordable, culturally acceptable and effective intervention for use in India. A process evaluation is needed to understand how and why this complex intervention may be effective, and to capture important barriers and facilitators to its implementation. We describe the protocol for our process evaluation to encourage the development of in-process evaluation methodology and transparency in reporting.

Methods and analysis: The realist and RE-AIM (Reach, Effectiveness, Adoption, Implementation and Maintenance) frameworks informed the design. Mixed methods include semistructured interviews with health providers, patients and their carers, analysis of quantitative process data describing fidelity and dose of intervention, observations of trial set up and implementation, and the analysis of the cost data from the patients and their families perspective and programme budgets. These qualitative and quantitative data will be analysed iteratively prior to knowing the quantitative outcomes of the trial, and then triangulated with the results from the primary outcome evaluation.

Ethics and dissemination: The process evaluation has received ethical approval for all sites in India. In low-income and middle-income countries, the available human capital can form an approach to reducing the evidence practice gap, compared with the high cost alternatives available in established market economies. This process evaluation will provide insights into how such a programme can be implemented in practice and brought to scale. Through local stakeholder engagement and dissemination of findings globally we hope to build on patient-centred, cost-effective and sustainable models of stroke rehabilitation.

Trial registration number: CTRI/2013/04/003557.

Strengths and limitations of this study

- A strength of our study protocol includes the use of implementation theories, quantitative and qualitative research methods and our iterative approach to analysis.
- Consideration of costs to the patient is vital to assess whether a programme would be affordable outside a trial setting, which is often inadequately reported in trials. The design of this process evaluation allowing the triangulation of within-trial cost data and qualitative data will add to the limited current evidence regarding the socioeconomic burden of stroke to patients and their families in India.
- Limitations to our current approach include the overlap between the trial coordinating team and the process evaluation team. While a strength of this approach is that the team members have an in-depth knowledge of the trial and its implementation, a challenge for the process evaluation is for team members to be aware of their own biases in the conduct of the interviews for positive findings towards the trial.
- Our sampling approach for the interviews has been designed to maximise variation which should increase our understanding of the differing contextual factors. Pragmatically this is only a small sample (about 100 participants) of a 1200 patient trial. However, this is a large sample for qualitative research, and other data sources such as observations, administratively collected data and relevant policies would be reviewed to provide additional context.

INTRODUCTION

With a rapidly rising global burden of disease attributed to non-communicable diseases, access to high-quality evidence-based

healthcare is essential. Complex interventions, defined as interventions with multiple interacting components, are frequently deployed in an attempt to address health system deficiencies experienced by patients and providers.[1] Process evaluations, which are typically carried out for trials of complex interventions, can help explain for whom, how and why the intervention had a particular impact.[2] Such evaluations address the question 'Is this intervention acceptable, effective and feasible (for me or) for this population?'[3] Gaining a clear understanding of the causal mechanisms of complex interventions is vital in being able to scale up or deliver an effective intervention in other settings.

This is especially relevant for the randomised controlled trial known as the fAmily led rehabiliTaTion aftEr stroke in INDia (ATTEND), which is being conducted at 14 hospitals in India—across populations with differing languages, cultures and health systems.[4–6] The annual incidence of stroke in India is estimated to be 152–262 cases per 100 000 population, with prevalence of 0.47–0.54%.[7] This means that there is a significant burden on society due to stroke disability with limited stroke units isolated to urban areas and limited rehabilitation services.[8] Table 1 highlights some socioeconomic health indicators and available stroke incidence data in different states where our sites are based.

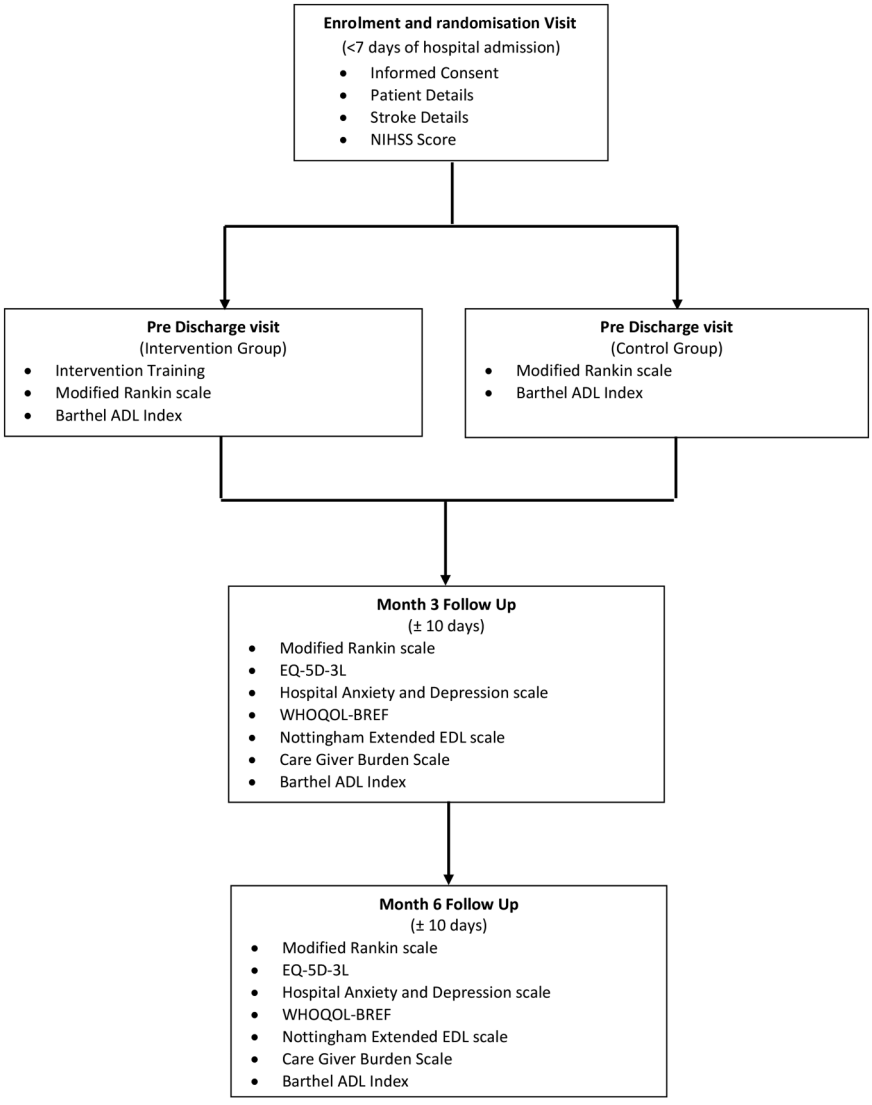
The ATTEND intervention has multiple interacting components. We developed an evidence-based rehabilitation intervention package consisting of providing information on stroke, identification and management of low mood, importance of repeated practice of specific activities, task-oriented training, early supported discharge planning and joint goal setting with the patient and nominated family. Physiotherapists employed for the trial are trained in this evidence-based rehabilitation intervention package.[6] These physiotherapists (known as stroke coordinators in the trial) provide support to the patient and family within the hospital and in subsequent home visits, with the aim of training a nominated carer and in enabling optimal rehabilitation of the patient. As such, a careful consideration of the contextual patient factors, such as health literacy, access to care and financial considerations, is needed.[9–11] The context of each patient can have an impact on the behaviour of the carer and the patient, which will affect patient improvement in disability and dependence outcomes as measured by the modified Rankin scale (mRS) and other outcome measures (see figure 1).[6] Thus, the process evaluation could help explore reasons for any variations in trial effectiveness, and address questions about the generalisability of this intervention across different settings. A deeper appreciation of the needs of patients poststroke and their families will be valuable for health system and policy reform in India.[4]

A key role of our process evaluation would be to inform how the intervention can be implemented into practice and policy, if proven effective. It is well recognised that the generation of good quality evidence does not always translate into improved patient health outcomes.[12] Financial barriers, such as high out of pocket costs for diagnostic imaging or provision of treatment, are possible reasons for an intervention not being delivered once shown to be efficacious in a trial.[13–16] Such costs are likely to frame the financial incentives of different players within the system and explain behaviour that is potentially at odds with the idealised operation of an

Table 1 Sociodemographic health indicators across the participating ATTEND sites

City/state of participating sites	Life expectancy at birth (2002–2006)* (years)	Poverty level (2004–2005)* (%)	Per capita health expenditure (in Rs)*	Age-standardised incidence rate for stroke† (from population stroke epidemiology studies)
Ludhiana, Punjab	69.4	8.4	1359	Not available
New Delhi, Delhi	Not available	Not available	Not available	Not available
Kochi and Trivandrum, Kerala	74	15	2950	135/100 000 person-years
Guntur, Andhra Pradesh	64.4	15.8	1061	Not available
Chennai and Vellore, Tamil Nadu	66.2	22.5	1256	Not available
Kolkata, West Bengal	64.9	24.7	1259	145/100 000 person-years
Tezpur, Assam	Not available	19.7	774	Not available
Hyderabad, Andhra Pradesh	64.4	15.8	1061	Not available
Bangalore, Karnataka	65.3	25	830	Not available
INDIA	63.5	27.5	1201	119–145 per 100 000 person-years

*Ministry of Health and Family Welfare, Government of India. Annual report to the People on Health. December 2011.
†Pandian J, Suhan P. Stroke Epidemiology and stroke care services in India. *J Stroke* 2013;15(3):128–134.
ATTEND, fAmily led rehabiliTaTion aftEr stroke in INDia.



*Reproduced with permission from Alim et al. Family-led rehabilitation after stroke in India: the ATTEND trial, study protocol for a randomized controlled trial. *Trials.* 2016

Figure 1 The ATTEND RCT flow chart. This highlights the outcome measures used and the study visits. ADL, activities of daily living; ATTEND, fAmily led rehabiliTaTion aftEr stroke in INDia; EQ-5D-3L, EuroQol 5-Dimensional, 3 Levels; NIHSS, National Institutes of Health Stroke Scale; RCT, randomised controlled trial; WHOQOL-BREF, WHO Quality of Life (Brief).

intervention. Understanding these cost barriers can inform how remuneration and payment systems may be shaped to facilitate implementation beyond a trial setting.[14] Incorporating an assessment of stakeholders' perceptions of how an intervention can be practically funded, delivered and scaled up is crucial.

Process evaluations can also add to the literature of how collaborations between stakeholders (ie, health providers, academics, policymakers, patients, carers) may facilitate research translation.[17] Understanding how and why an international collaboration of stroke experts came together to design and implement a feasible, locally adapted large-scale trial in India would also be helpful for future research. Lessons learnt from this trial, which is funded by the National Health and Medical Research Council (NHMRC) of Australia, with capacity building objectives in India, would be valuable in informing future international collaborative research.

The UK Medical Research Council (MRC) recommends publishing a protocol for a process evaluation so as to promote development of methodology and transparency in the reporting of the findings. In this protocol, we outline our aims, methods and study design. The core aims of this process evaluation are: *(1) to explore if the ATTEND trial was delivered as intended (eg, fidelity and dose); (2) to understand whether, how and why the intervention had an impact, through exploring providers', patients' and carers' perspectives of their usual care and of the intervention; (3) and to explore if the results are likely to be generalisable, scalable and sustainable through exploring stakeholders' (hospital stroke unit staff, providers, patients and carers) experiences of the intervention and its perceived impact. This would include an evaluation of costs from the societal perspective, including the health system and also for the patients and families. Finally, (4) we aim to explore implementation barriers and facilitators of a complex intervention by an international collaboration.*

METHODS AND ANALYSIS

Theoretical frameworks informing this process evaluation

Two theoretical frameworks with emphasis on translating evidence in the real-world setting were used to inform our methods.

The first was the RE-AIM (Reach, Effectiveness, Adoption, Implementation and Maintenance) framework. It has been used by researchers in the development, evaluation and dissemination of research, using qualitative and quantitative methods.[18] The framework's five domains highlight the need to look into the proportion and representativeness of the participants involved in the intervention, the impact of the intervention, the fidelity of trial implementation and at how a programme may be institutionalised into organisational practice after the conclusion of the trial. Thus, pending ATTEND's results, and resources permitting, there may be scope for a post-trial evaluation to explore how and why there were changes in practice and policy.[19]

The second framework that informed our methods was the Realist framework (Context, Mechanism, Outcomes).[20] It has been successfully used in process evaluations as a theoretical basis for identifying potential causal mechanisms for how an intervention works for whom, under what contexts and therefore fosters uptake of research-based knowledge into practice.[21 22] Given the complexity of the ATTEND trial from contextual macrolevel factors, such as different socioeconomic demographics, cultural differences, health system funding structures at each state, to microlevel factors such as literacy of patients and carers; the realist framework would be valuable in framing our analysis in understanding the mechanism within the 'black box' of the intervention.[23]

Our process evaluation framework and the hypothesised causal mechanisms of ATTEND

The framework (figure 2) highlights the key questions for the process evaluation, incorporating the above theories and our work plan. We have briefly outlined our hypothesised causal mechanisms of ATTEND's complex intervention within the framework as per the MRC's guidance on process evaluations.[19] The framework is divided into sections of context, implementation of the trial, mechanisms of the trial and outcomes of the trial with the final objective of reducing the burden of stroke through a sustainable model of care.

Mixed methods used to address the aims of the process evaluation

1. To explore if the trial was delivered as intended (eg, fidelity and dose)

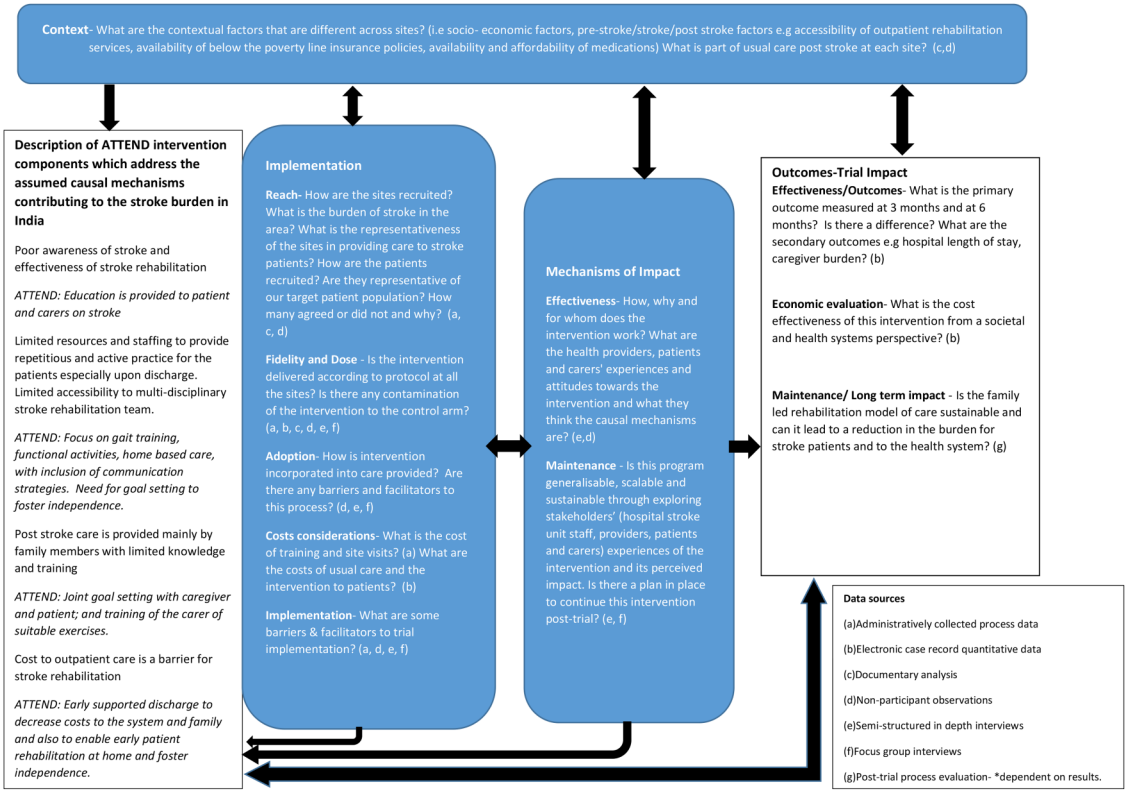


Figure 2 The ATTEND process evaluation framework. The process evaluation components are highlighted in blue boxes—exploring contextual factors, the implementation of the ATTEND trial, mechanisms of impact from the intervention. Questions informed by the RE-AIM and Realist framework fit within these components. These components are informed by the causal assumptions of ATTEND intervention and will inform the interpretation of the primary and secondary outcomes. ATTEND, fAmily led rehabiliTaTion aftEr stroke in INDia; RE-AIM, Reach, Effectiveness, Adoption, Implementation and Maintenance.

This will be achieved through an analysis of the administratively collected process data (eg, competency measures, frequency of training), electronic case record file, quantitative data and activity logs (eg, the measurement of the total time spent per patient in both arms of the trial with the usual care physiotherapist, the number of meetings and time spent with each family caregiver by the stroke coordinator during their inpatient stay and after discharge). If the analysis provides any evidence of variation between the active and control groups in terms of amount of time spent on different tasks, we will investigate and provide further training if required.

2. To understand whether, how and why the intervention had an impact through exploring the providers', patients' and carers' perspectives of usual care and of the intervention
   - Non-participant observations of all the sites to understand the contextual factors at each site, which may help explain variations in outcomes. Our observation template has been adapted from a process evaluation of a similar intervention[24] and includes issues on trial set up, trial implementation and impact. See online supplementary additional file 1 for a copy of the template.
   - Semistructured in-depth interviews will be conducted with patients, carers, stroke coordinators and the stroke unit staff of hospitals to understand their perspectives of the causal mechanisms of the intervention and to seek their suggestions on how the intervention could be scaled up or rolled out. Methods for our qualitative interviews have been described as per the consolidated criteria for qualitative research:[25]

A. Research team and reflexivity: The research team is multidisciplinary and comprises of the trial's chief investigators, the clinical trial coordinating staff and research fellows from India, UK and Australia. The team has background in medicine, physiotherapy, health economics, pharmaceutical trials and public health; with varied experience in qualitative research. In particular, three of the team members (HL, MA and SJ) have training in qualitative methods. HL who coordinated the team, organised face-to-face qualitative workshops to train the rest of the team prior to the conduct of interviews and will take a leading role in analyses. A team of six people will conduct the interviews. The team members, who are part of the clinical trial management team, have a good understanding of the trial and are known to the principal investigators, stroke coordinators and blinded assessors but will not have established relationships with the patients and their carers.

Semistructured interview guidelines based on our study objectives have been developed and pilot tested. The key areas covered include overall views of the health and socioeconomic impact of stroke on patients and families, stroke management in India, acceptability of the family-led rehabilitation intervention, the general healthcare experience of patients and their families and translation of the intervention into practice and policy. Early findings will be discussed with the study team, and minor changes made to the interview guidelines if needed. (See online supplementary additional files 2–4 for the interview guidelines for the health provider, carer and patient, respectively.)

B. *Study design*: Sampling: Participants for the interviews will be recruited using maximum variation purposive sampling. Variables to be considered for patients and carers are: usual care versus intervention arm, primary outcome (as measured by the mRS at 6 months), gender and the region of India they are from. Variables to be considered for stroke unit providers: healthcare roles (ie, neurologists, physiotherapists, nurses and the stroke coordinators), private versus public government hospitals and the region of India the hospitals are located.

A list of patients and caregivers who match our sampling criteria will be generated. They will be contacted by the local site staff (either the stroke coordinator or the 'blinded assessor') and where relevant, reasons for not participating will be elicited. They will be formally consented by the interviewer face-to-face. Interviews with carers and patients will be conducted either individually or with both together either at the participant's home or at the hospital. These interviews will be conducted in local languages and the services of an interpreter may be required. The benefits of interviewing the patient and carer separately would be to gather perspectives which otherwise may not be shared should the other be present. Healthcare providers will be invited to participate in interviews either by a letter or in person by the clinical coordinating team during their site visits, and conducted in English. Written informed consent (see online supplementary additional file 5 for a copy of the form) will be obtained from all interviewed participants. As per qualitative research methods,[26] analysis is iterative and thus the interviewer will carry out preliminary thematic data analysis at the end of each interview and discuss any highlights with the rest of the interview team. For example, the findings from the pilot interviews were discussed during the qualitative workshop, in order for the team of interviewers to explore emerging themes in subsequent interviews. It is estimated that at least five sites would be sampled, with 3–4 health providers and about 4–6 patient/carer dyads interviewed from each site. According to the sampling matrix, we will interview equal numbers from both usual care versus intervention arm, and also include sampling for gender. For example, at each site, two usual care dyads and two intervention group dyads will be invited to participate.

In addition, some of the stroke coordinators and the independent assessors at the other sites will be interviewed. That is, an estimated 80–100 interviews will be conducted though the final numbers will be determined by saturation of themes and resources permitting. Interviews will be conducted face-to-face, audio recorded

and professionally translated and transcribed verbatim. These will be uploaded into a software program NVivo V.9 (QSR International, Melbourne, Victoria, Australia) to assist with data management.

3. To explore if the results are generalisable, scalable and sustainable through exploring health providers', patients' and carers' experiences of the intervention and its perceived impact. This will include an evaluation of costs from the societal perspective including the health system, and for patients and their families. (note this is separate to the formal cost-effectiveness study which has been set out in the original trial protocol)[6]
   - One of the key domains in the semistructured interviews will be exploring participants' perspectives of what they expect post-trial in relation to this intervention. The findings related to these questions will address this aim.
   - Cost components of the intervention which will be relevant to implementation outside a trial setting will be considered. This will be extracted from the programme budget and trial contracts and includes, for example, costs of employment of a physiotherapist to implement the intervention, travel costs of the home visits and costs of any educational material required as part of the intervention. Relevant questions asked by the blinded assessor at the 3-month and 6-month follow-up visits include loss of family income (eg, number of hours of work taken off) due to carer's additional responsibility and medical costs. (Participants are encouraged to keep receipts of related medical costs.)

4 To explore implementation barriers and facilitators of a complex intervention by an international collaboration.

A research fellow not involved in the implementation of the trial will conduct focus group interviews and semistructured interviews with members of the clinical trial coordinating team and also with the trial investigators in regards to perceived barriers and facilitators to trial implementation. Findings from these interviews in addition to relevant findings from the interviews with the health providers, patients and carers will inform lessons learnt from this trial for future research collaborations.

Analysis plan for the process evaluation

Thematic analysis will be used for the qualitative analysis to code closely to the data and establish themes within the subheadings of the process evaluation framework (figure 2).[26] Constant iterative comparison between sources, for example, patient, carer and health provider will be carried out in order to identify common, as well as distinctive, themes.[26] Contextual information from observations, other process data and costs to patients and families will be used to triangulate the emerging themes.[27] The quantitative process data will help inform fidelity and the time logs of the stroke coordinator will provide descriptive data on dose. Fidelity data will be reviewed at six monthly intervals.

The process evaluation framework (figure 2) will aid in the analysis by triangulating the process's quantitative data with the relevant qualitative data addressing the questions within its subheadings.[27] For example, under the heading 'implementation—fidelity and dose', a specific question would be whether usual care is provided equally in both arms of the intervention, and thus the quantitative process data would be the time spent by the usual care physiotherapist and should be almost equivalent in both arms documented in the logs (or not), and the qualitative data would include, for example, the usual care physiotherapists' responses as to whether they did treat all the patients equally, or the neurologist's description of what happens to the study participants.

Other forms of triangulation to increase the reliability of our results include the sampling of different perspectives, that is, patient, carer, neurologists and stroke coordinators and also through the triangulation of different analysts in the team who bring their own cultural backgrounds, academic experience (eg, rehabilitation medicine, pharmacy, physiotherapy) and knowledge about different aspects of the trial into the analysis.[26]

In line with the MRC guidelines, the process evaluation data should be analysed prior to knowing the trial outcomes, first to remove bias, though there is a role for post hoc exploration of reasons for trial outcomes.[2] First, we will analyse our process evaluation data iteratively on an ongoing basis. If there are any process issues which would impact on trial integrity that need to be addressed, these will be fed back through the usual management communication channels.[28]

The framework serves as a template to consolidate the findings, and will be a dynamic structure with changes to be made if required. This means that our understanding of the causal mechanisms of the intervention may change with the iterative analysis of the process evaluation data.

There will also be a post hoc examination of the process evaluation findings, in light of the main results of the trial.[29] For example, in our experience, our assumption is that early supported discharge, as part of the intervention, will decrease costs to the system and family, enable early patient rehabilitation which may improve patient recovery (primary outcome) and result in shorter hospital stays in the intervention arm. However, in piloting our observation template at one site, we discovered that there was shortage of beds such that at that government hospital patients were discharged at the earliest possibility, for example, when they were medically stable. This may perhaps be different to developed country settings, such as UK, and ultimately may explain potential divergences in the findings of this study to that of a recent meta-analyses of rehabilitation trials (which showed positive results of early supported discharge).[30 31] A major consideration in the process evaluation therefore may be regarding the length of stay in

hospital. The examination of such secondary outcomes and contextual findings from the process evaluation is an example of how we could gain a deeper understanding of the assumed causal mechanisms of the ATTEND intervention (as depicted in the logic model in the overall process evaluation framework). Such insights will help inform the final logic model of how the intervention truly impacted the trial effectiveness outcomes, and inform the generalisability of the intervention.

ETHICS AND DISSEMINATION

Ethics

Ethical approval for the trial and process evaluation has been obtained from Research Integrity, the Human Research Ethics Committee at the University of Sydney and at each local site. See online supplementary additional file 6 for the details of ethic committees at the local sites.

The ethical implications of this scope of research include the considerations of NHMRC ethical guidelines such as research merit and integrity, beneficence and respect in relation to qualitative methods.[32]

Dissemination

Our process evaluation aims to complement a robust blinded outcome evaluation of the trial end points and inform our stakeholders how, for whom and why this model of family led rehabilitation could have an impact. This is especially relevant for India which is in 'epidemiological transition' with a diverse sociodemographic profile, and an increasing burden from non-communicable diseases which could result in greater health inequity.[4 16] A stated aim in India's key national strategy for non-communicable diseases is to increase access to healthcare to 80% with costs not being a key barrier. Strategies such as the family-led rehabilitation programme, which marshal family and community resources in the care of patients with chronic conditions will, by financial necessity, play a greater role in the future. In low-income and middle-income countries, the available human capital can form one approach to reducing the evidence practice gap, compared with the high cost alternatives available in established market economies. This process evaluation will provide insights into how such a programme can be implemented in practice and brought to scale.

The Indian Institute of Public Health has been allocated resources for the dissemination of results through the engagement of local policymakers and health practitioners. Apart from stakeholder engagement, dissemination of our findings globally will be accomplished through publishing our results in relevant journals and conferences to build on the literature in providing affordable, holistic and accessible stroke rehabilitation models of care.

We describe our protocol to encourage development in process evaluation methodology, transparency in reporting and to build on this emerging area of health services research which is much needed in addressing the complicated global health needs through sustainable, patient-centred and evidence-based complex interventions.

Trial status

In regards to the ATTEND trial, the first patient was randomised on 13 January 2014 and the recruitment surpassed the sample size of 1200 in January 2016. The ATTEND process evaluation, started in March 2015 with the observational visits of the sites and the fidelity and dose quantitative data have been reviewed in six monthly intervals since March 2015, pilot interviews were conducted with health providers in July 2015 and completion of the patient, carer and health provider interviews is expected by May 2016, with ongoing preliminary and iterative analysis.

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Contributors JDP suggested the original ATTEND trial idea and the steering committee (RL, GVSM, PKM, PL, LAH, MLH, MW, AF, BRS, CSA and SJ) designed the trial with a process evaluation in mind. HL developed this process evaluation protocol with extensive and significant contribution from the trial management team which includes MA, CF, DBCG, SJV, DKT, AS and RKR. All authors read and approved the manuscript.

Funding This study is funded by the National Health and Medical Research Council of Australia (Project grant no APP1045391). PKM is a recipient of an Intermediate Career Fellowship of Wellcome Trust-Department of Biotechnology India Alliance. MLH is a recipient of a National Heart Foundation Future Leader Fellowship, Level 2 (100034, 2014–2017). SJ is the recipient of an NHMRC Senior Research Fellowship. CSA holds an NHMRC Senior Principal Research Fellowship. HL is the recipient of a NHMRC APP1114897 scholarship to undertake her doctorate.

Competing interests None declared.

Ethics approval Research Integrity, the Human Research Ethics Committee at the University of Sydney.

Provenance and peer review Not commissioned; externally peer reviewed.

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Family-led rehabilitation in India (ATTEND) - findings from the Process Evaluation of a Randomised Controlled Trial

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ABSTRACT

Background: Training family carers to provide evidence-based rehabilitation to stroke patients could address the recognised deficiency of access to stroke rehabilitation in low-resource settings. However, our randomised controlled trial in India (ATTEND), found that this model of care was not superior to usual care alone.

Aims: This process evaluation aimed to better understand trial outcomes through assessing trial implementation and exploring patients', carers' and providers' perspectives.

Methods: Our mixed methods study included process, healthcare use data and patient demographics from all sites; observations and semi-structured interviews with participants (22 patients, 22 carers and 28 health providers) from 6 sampled sites.

Results: Intervention fidelity and adherence to the trial protocol was high across the 14 sites, however, early supported discharge (an intervention component) was not implemented. Within both randomised groups some form of rehabilitation was widely accessed. ATTEND stroke coordinators provided counselling and perceived that sustaining patients' motivation to continue with rehabilitation in the face of significant emotional and financial stress as a key challenge. The intervention was perceived as an acceptable community-based package with education as an important component in raising the poor awareness of stroke. Many participants viewed family-led rehabilitation as a necessary model of care for poor and rural populations who could not access rehabilitation.

Conclusion: Difficulty in sustaining patient and carer motivation for rehabilitation without ongoing support, and greater than anticipated access to routine rehabilitation may explain the lack of benefit in the trial. Nonetheless family-led rehabilitation was seen as a concept worthy of further development.

Word count: 4730 (250 (abstract), 3579 (main text), 926 (Ref))

Key words: Qualitative research, Stroke, Rehabilitation, Randomised Controlled Trial, Process Evaluation, India

2 Figures and 4 supplementary files

INTRODUCTION

The global burden of stroke is increasing, and in low and middle income countries (LMICs) tends to affect individuals at an earlier age than in high income countries, resulting in a significant societal burden. (1) India is in the midst of a major epidemiological transition, with an increasing stroke prevalence but limited accessibility to affordable and high quality rehabilitation services. (2-4) Task shifting through family-led rehabilitation may offer a potential sustainable solution in India and other LMICs. (5-7)

The ATTEND Trial (fAmily led rehabiliTaTion trial aftEr stroke trial in INDia) was a randomised controlled trial (RCT), which recruited 1250 patients across 14 hospitals. (8) The intervention involved a physiotherapist (known in the trial as a 'stroke coordinator') training a family carer to deliver a basic evidence-based rehabilitation intervention tailored to the Indian context. (9) The intervention had five main components including education, positioning/early mobilisation, early supported discharge planning, joint goal setting with each patient and carer, and task-orientated training. Stroke coordinators trained family carers to provide rehabilitation during hospital admission and at subsequent home visits (maximum of six) in the first two months. A culturally appropriate intervention manual documenting intervention components was provided to the patient during the first home visit. Patients and carers were followed up at three and six months by an assessor blinded to intervention allocation and its content. The recently published results indicated that this model of 'task shifting' rehabilitation to family carers compared to usual care alone did not achieve a benefit, as measured by a decrease in death or dependency. (8)

In the wake of ATTEND's neutral results, important questions remain about the future of family-led rehabilitation and uncertainty as to what transpired on the ground: was the trial result due to failure of the intervention or of trial implementation, or of both? (10)

AIMS

Our process evaluation was conducted alongside the ATTEND RCT to explore how, for whom and why this complex intervention had (or did not have) an impact. Our *a priori* aims were: (1) To explore if the ATTEND trial was conducted rigorously; (2) To understand providers', patients' and carers' perspectives of the perceived effect of the care they received or delivered; (3) To explore if the results are likely to be generalisable, scalable and sustainable through exploring stakeholders' experiences of the intervention and its perceived impact. (11)

METHODS

The process evaluation methods were pre-specified in detail in a published protocol. (11) We present a summary here.

Process evaluation framework

The design of our mixed methods process evaluation (Figure 1) was informed by two theoretical frameworks covering different aspects of the evidence generation-to-practice translation continuum. The RE-AIM framework incorporates concepts of Reach, Effectiveness, Adoption, Implementation and Maintenance to address questions of generalisability and translation into practice. (12) The Realist framework highlights potential mechanisms of action within contextual factors and is pertinent for complex interventions such as ATTEND. (13, 14) Our hypothesised causal mechanisms are stated explicitly in Figure 1 of how this intervention may impact upon proposed trial outcomes.

Data sources

We collected quantitative process data on intervention delivery, patient demographics and healthcare use data across all 14 sites. Qualitative data included semi-structured interviews with 28 health providers (seven neurologists, eight stroke coordinators, eight blinded assessors, four physiotherapists responsible for usual care and one clinical nurse), 22 patients

and 22 carers (11 usual care and 11 intervention arm dyads), observations (using a standardised template), and documentary analysis from six purposively sampled sites to enable a cross-section of geographical locations and types of institutions. (15) Patient and carer dyads were purposively sampled by patient gender and study arm, and interviews at the hospital were conducted shortly after their six months follow-up visit by interviewers who had no interactions with the dyads before the interviews. Questions covered patients' health care journey, components of the intervention and contextual factors. Healthcare providers were interviewed (by AM, HL, RL, AF, MW) in English and all patients and carers were interviewed (by AM, DG, CF, SV) in their local Indian languages where possible. There were two sites in which interpreters were used to communicate in local languages. All interviews were audio recorded. The interviews lasted on average 30 minutes and all were transcribed verbatim by professional transcribers and translators. We received ethical approval for the conduct of the health provider interviews from each study site, with one site not granting approval for patient and carer interviews and as such patient and carer interviews were only conducted at five sites. (Supplementary file 1 provides key participant characteristics and additional illustrative quotes.)

Analysis

Iterative thematic analysis of the qualitative data was conducted by the team blinded to the RCT outcomes. (14) NVivo software was used to manage the data. A coding tree based on the main headings of our process evaluation framework and line by line coding was created by HL. (Supplementary file 2) As pre-specified in the process evaluation protocol, triangulation of the qualitative findings was then conducted with baseline demographics, healthcare use and primary and secondary outcomes, and then systematically analysed against our hypothesised causal mechanisms according to the Realist configuration of Context-Mechanisms-Outcomes. (14)

RESULTS

Our results are summarised and depicted in Figure 2.

(1) Trial fidelity: trial implementation and intervention fidelity

Reach and Recruitment:

We assessed ATTEND baseline data to determine whether recruited patients were representative of the broader Indian stroke population and found that ATTEND patients had a higher level of education and monthly household income than the national population average. (8, 16) The limited feasibility for the ATTEND stroke coordinators to follow up patients living more than 50 km from the 14 participating mainly urban RCT sites (4 governmental central institutes, 4 Christian Mission and Academic Institutions, and 6 private corporate hospitals) may have contributed to this difference.

We explored healthcare use to determine the level of access to healthcare and rehabilitation by the patients recruited and found that at 6 months, most of the patients in the intervention and usual care arm continued non-trial conventional therapy i.e. either rehabilitation or medications. In both groups, about 45% reported incurring charges for outpatient rehabilitation therapy at 3 months, and about 30% at 6 months.

We synthesised our findings to better understand routine care. We found that the different types of hospitals had differing costs of treatment and available routine care in terms of stroke unit guidelines, specialist staffing, and presence of multidisciplinary outpatient clinics. In particular, we noted at 3 hospitals routine care comprised of outpatient clinics with rehabilitation provided by physiotherapists who described training family carers as part of routine care. Three hospitals had multidisciplinary outpatient clinics -including one corporate hospital which had established links (e.g. conducting capacity building workshops) with free-

lance private physiotherapists in the community who could provide rehabilitation in patients' homes.

Unblinding:

Assessors reported any unblinding to the project manager. The reports showed that unblinding occurred in 5.3% in the intervention group, and 3.3 % in the usual care group (p=0.09). An example of 'unblinding' included inadvertent incidents such as the intervention manual being seen on the table at home.

Contamination:

The potential for 'contamination' of usual care patients due to lack of space, or curtains around beds to conduct the intervention in privacy at smaller hospitals was noted during observation visits.

Intervention Fidelity:

The activity logs highlighted that the ATTEND components of goal setting, gait training and functional mobility training were implemented as per protocol. (8) Intervention dose, as indicated by duration of therapy provided, showed an average hospital training time of 2.96 hours, (SD 1.56, median 2.92), mean home training time of 3.07 hours (SD 1.69, median 2.75). Patients and carers self-reported 17.8 hours (SD 21.56) of activities in the first 30 days following hospital discharge. Activity logs of the usual care physiotherapists show that similar non-trial rehabilitation care was provided both randomised groups. Early supported discharge as a component of the ATTEND intervention was not achieved, with both groups having a similar length of hospital stay. (8)

<u>(2) For whom, how and why? To understand providers', patients' and carers' perspectives of the perceived effect of the care they received / delivered.</u>

Early supported discharge welcomed in concept

Health providers stated that the early supported discharge component of ATTEND was welcomed in concept due to potential cost savings for patients and earlier release of bedspace for the hospital. However, several neurologists described early supported discharge was not implemented due to an inadequate number of hospital beds, which resulted in patients being discharged as early as possible, or even not admitted for care, irrespective of enrolment in ATTEND. At one hospital it was estimated that 40% of patients discharged themselves from the hospital against medical advice reportedly due to the unaffordable costs of hospitalisation. With the exception of one stroke coordinator, most health providers indicated that the ATTEND intervention was not factored into the discharge planning (i.e. time of discharge) for patients in the intervention group.

Stroke education is needed

Education about stroke, stroke risk factors and the value of rehabilitation was provided to patients and carers in the intervention arm. A carer of an intervention patient described how community members had initially expected his father to die but they have since seen that *"(his father) can walk on his own…and said because of exercises only he has improved that much.*" Indeed, carers and patients in the intervention arm described a deeper understanding of the pathophysiology of stroke and a greater confidence in recovery. Most of the health providers stressed that addressing the low level of community health literacy was a priority as there was often poor management of risk factors in the community (as seen by the relatively young age of participants compared to high income countries) and delayed presentation to hospital.

ATTEND is an acceptable model of care

Many stroke coordinators and intervention carers indicated that joint goal setting with patient and carer was a key component of ATTEND and that this process was crucial in the patients'

recovery. For example, an intervention patient described how *"half of my body had become useless. But I am thankful to my children, within fifteen days they helped me...I just stood like that, with the support of their shoulders…then they instructed me to do things."* Some stroke coordinators commented favourably on the multi-disciplinary aspect of ATTEND (e.g. components of occupational and speech therapy) and the active rehabilitation (e.g. task-specific training), as compared to the passive physiotherapy they previously provided. This was evident in the activity forms, which showed a greater emphasis (as indicated by percentage of time spent) on goal setting and functional task training provided by the stroke coordinators as compared to usual care physiotherapists. (8)

Stroke coordinators liked the training of a nominated caregiver in ATTEND which encouraged continuity of the care provided to the patient. The ATTEND trial intervention manual and videos were key resources for the patients and carers. The stroke coordinators and a few neurologists highlighted that home visits added valuable contextual information for functional training. Moreover, home visits were preferred by the patients and carers as this removed the cost and travel barriers faced when attending hospital follow-up visits.

Sustaining patient and carer motivation was a key challenge

Several of the stroke coordinators reported that counselling was critical in the early stages post stroke to maintain patient motivation and overcome their initial despair. A few of the stroke coordinators suggested that more visits than the trial goal of three to six visits would be necessary to sustain patients' and carers' motivation to persist with rehabilitation. A stroke coordinator observed that individual patients' will to recover was affected by their gender roles, he described that "*males don't have much patience as they have to go earn for his family… They don't want to spend much time on bed… Usually more females are housewives, and some (lose) their hopes from getting up from bed."* The importance of this observation is

highlighted when triangulated with the finding that men appeared to benefit more than women in the trial. (8) A doctor described that carers' motivation depended on individual family circumstances regardless of education and literacy status, and that "*it just depends on how stressed the family is…there are other patients who are totally illiterate but they are so willing to learn this, so willing to do it for their relatives…I mean every patient…their situation is different."* Additionally, managing bowel incontinence, and patients' pain were also described as particularly trying for carers.

Financial stress due to loss of income and cost of treatment was iterated by many of the participants as impacting on the complexities of the patients' and carers' relationship, mental health, and motivation. For example, a female carer described selling her jewellery to tide their family through financial difficulties and saw little hope for the future. A stroke coordinator observed that "*if the stroke affects a middle-aged man, the family is [in] a disaster"* due to the decrease in household income which could lead to poverty and reduce children's educational opportunities.

<u>(3) To explore if the results are likely to be generalisable, scalable and sustainable through exploring stakeholders' experiences of the intervention and its perceived impact.</u>

ATTEND is a sustainable model of care especially for those with limited access to rehabilitation

Many participants perceived that ATTEND would be ideal for the poor and those in rural settings who could not access acute treatment and rehabilitation due to distance to services and high cost. A physician cited ATTEND as a proof of concept of a model of care for her region where there were "*no physiotherapists out there who will go to the (villagers') homes or whom patients can go to and get help."* She described that "*even before this study started,*

we were giving the relatives the education that they needed and trying to teach them to help their patients…"

When affordability was an issue, carers would seek advice from the community on managing rehabilitation at home. The source of such information included local physiotherapists, other community members who had recovered from stroke or paralysis, and traditional masseurs. For example, a control arm carer described how they could not afford the INR300 per physiotherapist visit and had pleaded with him to "*please teach us. As our condition is such we will do it ourselves. After that we do on our own. We are still doing it."*

While ATTEND was delivered free in the trial, many of the intervention patients and carers indicated they would be willing to pay a fee and would recommend this treatment to others indicating an assumption that the intervention was effective. Indeed, two ATTEND carers described providing rehabilitation for other stroke patients in their community. Some health providers suggested incorporating the ATTEND intervention into their routine practice at the stroke unit. A neurologist suggested conducting ATTEND training workshops for the free-lance physiotherapists practicing in the community. For areas with limited access to service providers, two neurologists suggested community-based models of care as potentially feasible. One described the potential to have Accredited Social Health Activists (ASHAs) trained and certified to provide the ATTEND intervention. However, other neurologists and physiotherapists stressed that such community-based models would require significant upskilling, supervision and monitoring so as to prevent exploitation by other non-licensed/untrained providers.

DISCUSSION

Our data confirm that ATTEND was a rigorously conducted trial of an intervention designed to balance existing best practice rehabilitation with local norms and economic constraints. (8,

9) Furthermore, the process evaluation was conducted with a pre-specified protocol and conceptual framework. (11) We found that intervention fidelity and adherence to the protocol was consistently high across sites with the exception that early supported discharge was welcomed in concept but not widely implemented. Using the Realist framework of Context-Mechanisms-Outcomes, we have identified two reasons for why we did not achieve the expected trial result (as depicted in Figure 2). (13) First, whilst we had hypothesised that a family carer providing rehabilitation would represent a step-up in access to care (4), our contextual findings suggest that many patients from both randomised groups already had access to rehabilitation which included rehabilitation that family members had been trained to deliver. Second, whilst we confirmed our hypothesis that a key mechanism of ATTEND was joint goal setting, we found that sustaining behaviour change for patients and carers in the face of significant emotional and financial pressures was a challenge. We also noted that stroke coordinators spent time counselling the patients and carers (which was not outlined in the protocol), and this may have decreased the time available for teaching physical training and task specific activities. Thus, the failure to reduce death and dependency over usual care is likely to be due to difficulties in initiating rehabilitation training because of the counselling needs of the patient, ongoing challenges in sustaining patient and carer motivation; and the higher than expected levels of rehabilitation may have diluted any potential benefits of death and dependency (as measured by the modified Rankin scale) and the other secondary outcome measures (such as patient mood, quality of life and carer strain).

Our findings also imply that in regions where rehabilitation is not accessible, the concept of task-shifting to community members (e.g. ASHA) and family carers has a lot of support. (2, 4, 5) The challenge lies in how the intervention could be adapted in the future for such settings, whilst ensuring that the training is standardised and certified. (17) Given the high

penetration of mobile telephones in India, mobile technology-enabled training and rehabilitation could be tried in rural settings with remote monitoring provided by specialists through video-links i.e. telemedicine. (18, 19) In addition, community-based prevention strategies including e-health may be beneficial in addressing the poor awareness of stroke, its risk factors and treatment as highlighted in this and other studies. (20-22) Critically, future versions of the family-led rehabilitation model will require increases in training intensity, duration and dose to encourage sustained behaviour. The timing of these functions should be informed by the patients' and carers' capacity to assimilate information. As such, training to provide rehabilitation may be more effective when patients and family carers are past the acute stroke crisis stage of intense shock and grief. (5, 23) Moreover, given the impact of financial stress upon patient and carers, we will further examine the economic data from ATTEND to identify critical variables contributing to out of pocket costs and household financial catastrophe.

A limitation of this process evaluation is the generalisability of our qualitative findings based on six sampled sites. Moreover, participants who agreed to be interviewed may have been biased positively to ATTEND, and we may have missed contradictory insights. However, our purposive sampling by hospital characteristics, inclusion of usual care dyads and triangulation with other data sources increases the validity of the findings. (24) The use of the theoretical frameworks especially around the topics of Reach and Maintenance, and the Context-Mechanisms-Outcomes configuration was valuable in synthesising our findings. In addition, describing the initial hypothesised causal mechanisms of the intervention provided a systematic way of analysing the data and exploring reasons for the trial outcomes. (14) In retrospect, more formative work by conducting qualitative interviews (with patients, carers and implementers) alongside the single centre pilot feasibility trial may have identified some finer details of implementation (e.g. timing for patients and carers to assimilate information)

and dosing (e.g. number of optimal visits) that may have promoted efficacy of the ATTEND intervention. (9) Such in-depth exploratory work alongside pilot trials could inform key modifications needed to improve complex interventions such as ATTEND.(25, 26)

CONCLUSIONS

Our findings indicate that family-led rehabilitation is worthy of further development especially for the poor and rural populations in India. Future family-led rehabilitation should include behavioural change and sustainability components, with an increase in the intensity and duration of effective training modules; whilst maintaining cost and logistic feasibility for populations with limited access to rehabilitation. The ATTEND trial and process evaluation is the first step for the ATTEND collaboration in further developing patient-centred rehabilitation models of care needed to address the rising burden from stroke in India and other LMICs. (27)

Acknowledgements:We thank the participants for their valuable insights; Mr Qiang Li for providing the analysis of the healthcare use data; and all the stroke coordinators, blinded assessors and trial management team in the successful completion of the ATTEND RCT.

Funding Statement: This study is funded by the National Health and Medical Research Council of Australia (Project grant no APP1045391). PM is funded by an Intermediate Career Fellowship of Wellcome Trust-Department of Biotechnology India Alliance. MLH is funded by a National Heart Foundation Future Leader Fellowship, SJ is funded by a NHMRC Senior Research Fellowship. CA is funded by a NHMRC Senior Principal Research Fellowship. HL is funded by a NHMRC postgraduate scholarship.

Competing interests: The authors declare that they have no competing interests.

Authors' contributions: JDP suggested the original ATTEND trial idea and the steering committee (RL,GVSM,PKM,PL,LAH,MLH,MW,AF,BRS,CSSA and SJ) designed the trial with a process evaluation in mind. HL developed the process evaluation protocol with significant contribution in its design, data collection and analysis from the trial management team (MA, CF, DBCG, SJV, DKT, AS and RKR). HL led the analysis and drafted the manuscript. All authors contributed to the revisions and approve the manuscript.

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Figures

Figure 1: The ATTEND process evaluation framework. Process evaluation components are highlighted in blue. *Reproduced with permission. (11)

Figure 2: Summary of the process evaluation findings (in blue italics) as compared against our hypothesised contextual assumptions and causal mechanisms (in non-italics) in impacting upon the outcomes of the RCT.

Supplementary files

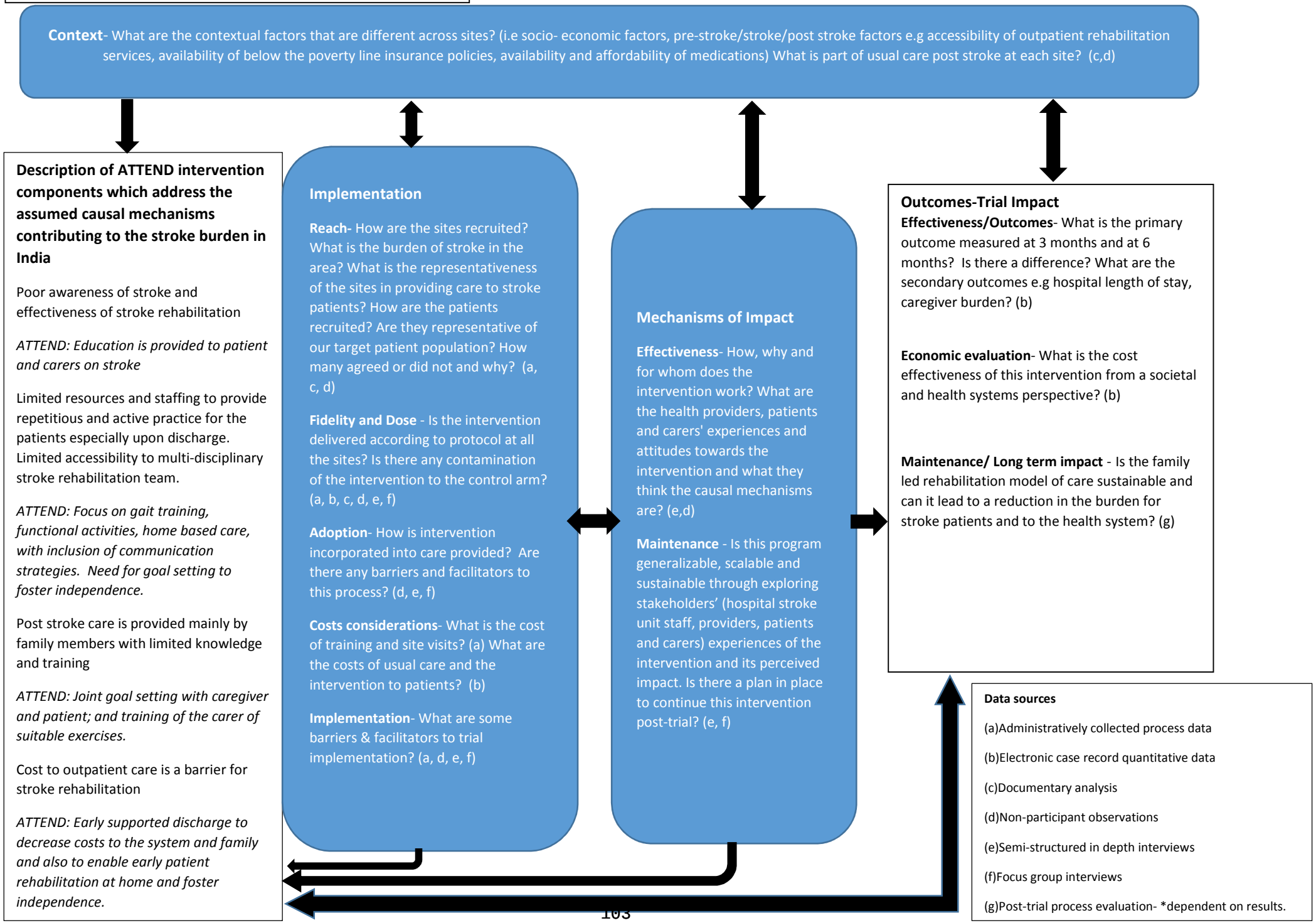
Supplementary file 1: Participant characteristics and Illustrative quotes.

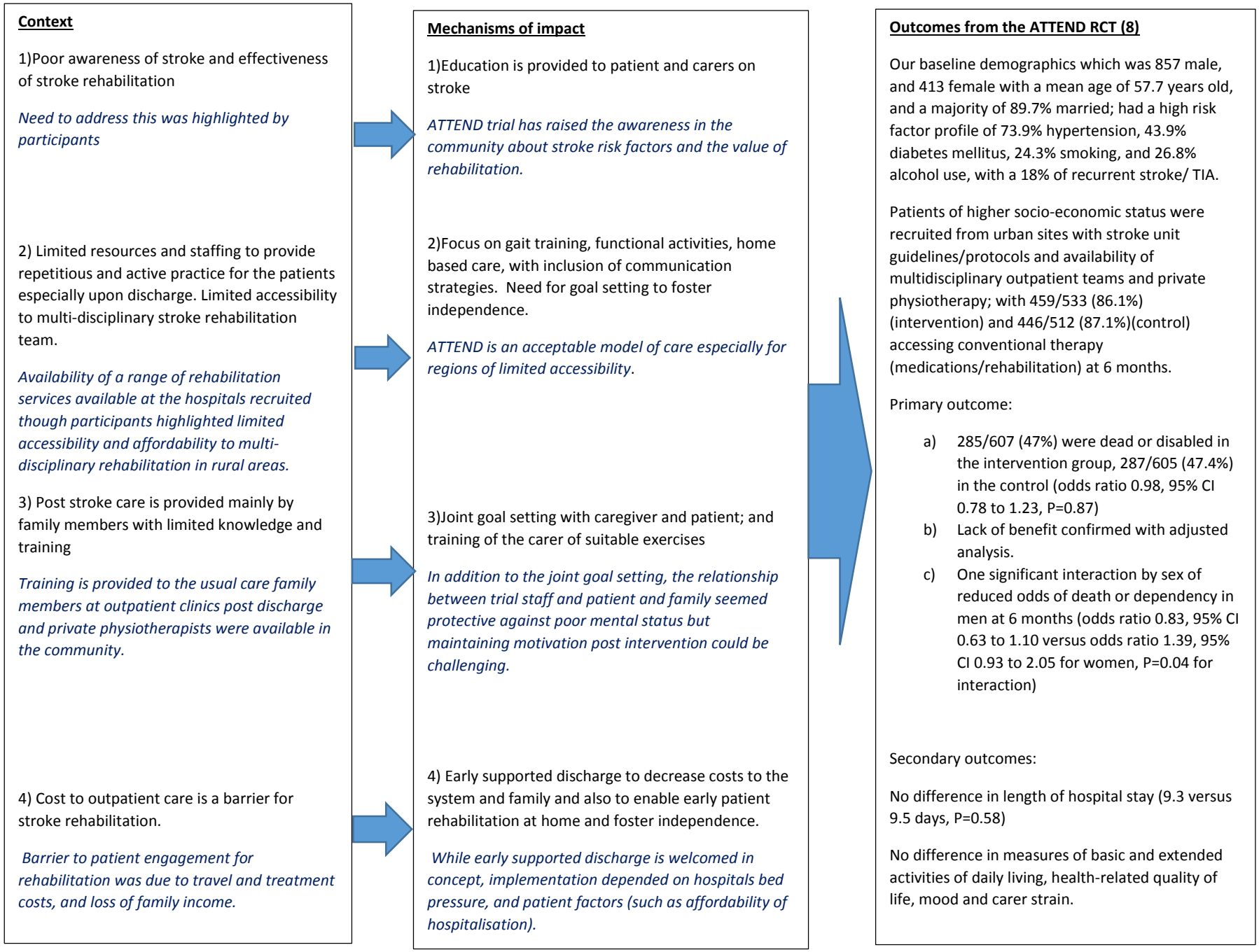
Supplementary file 2: Coding Tree

Supplementary file 3: CONSORT statement (main trial paper)

Supplementary file 4: COREQ checklist

Figure 1: The ATTEND process evaluation framework.




Context
1)Poor awareness of stroke and effectiveness of stroke rehabilitation
Need to address this was highlighted by participants
2) Limited resources and staffing to provide repetitious and active practice for the patients especially upon discharge. Limited accessibility to multi-disciplinary stroke rehabilitation team.
Availability of a range of rehabilitation services available at the hospitals recruited though participants highlighted limited accessibility and affordability to multi-disciplinary rehabilitation in rural areas.
3) Post stroke care is provided mainly by family members with limited knowledge and training
Training is provided to the usual care family members at outpatient clinics post discharge and private physiotherapists were available in the community.
4) Cost to outpatient care is a barrier for stroke rehabilitation.
Barrier to patient engagement for rehabilitation was due to travel and treatment costs, and loss of family income.
Mechanisms of impact
1)Education is provided to patient and carers on stroke
ATTEND trial has raised the awareness in the community about stroke risk factors and the value of rehabilitation.
2)Focus on gait training, functional activities, home based care, with inclusion of communication strategies. Need for goal setting to foster independence.
ATTEND is an acceptable model of care especially for regions of limited accessibility.
3)Joint goal setting with caregiver and patient; and training of the carer of suitable exercises
In addition to the joint goal setting, the relationship between trial staff and patient and family seemed protective against poor mental status but maintaining motivation post intervention could be challenging.
4) Early supported discharge to decrease costs to the system and family and also to enable early patient rehabilitation at home and foster independence.
While early supported discharge is welcomed in concept, implementation depended on hospitals bed pressure, and patient factors (such as affordability of hospitalisation).
Outcomes from the ATTEND RCT (8)
Our baseline demographics which was 857 male, and 413 female with a mean age of 57.7 years old, and a majority of 89.7% married; had a high risk factor profile of 73.9% hypertension, 43.9% diabetes mellitus, 24.3% smoking, and 26.8% alcohol use, with a 18% of recurrent stroke/ TIA.
Patients of higher socio-economic status were recruited from urban sites with stroke unit guidelines/protocols and availability of multidisciplinary outpatient teams and private physiotherapy; with 459/533 (86.1%) (intervention) and 446/512 (87.1%)(control) accessing conventional therapy (medications/rehabilitation) at 6 months.
Primary outcome:
a) 285/607 (47%) were dead or disabled in the intervention group, 287/605 (47.4%) in the control (odds ratio 0.98, 95% CI 0.78 to 1.23, P=0.87)
b) Lack of benefit confirmed with adjusted analysis.
c) One significant interaction by sex of reduced odds of death or dependency in men at 6 months (odds ratio 0.83, 95% CI 0.63 to 1.10 versus odds ratio 1.39, 95% CI 0.93 to 2.05 for women, P=0.04 for interaction)
Secondary outcomes:
No difference in length of hospital stay (9.3 versus 9.5 days, P=0.58)
No difference in measures of basic and extended activities of daily living, health-related quality of life, mood and carer strain.

International Journal of Stroke WSO

International Journal of Stroke
0(0) 1–9

DOI: 10.1177/1747493017743798
journals.sagepub.com/home/wso
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Clinical stroke research in resource limited settings: Tips and hints

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Abstract

Background: Most stroke research is conducted in high income countries, yet most stroke occurs in low- and middle-income countries. There is an urgent need to build stroke research capacity in low- and middle-income countries.

Aims: To review the global health literature on how to improve research capacity in low- and middle-income countries, provide additional data from the recently completed ATTEND Trial and provide examples from our own experience.

Summary of review: The main themes from our literature review were: manpower and workload, research training, research question and methodology and research funding. The literature and our own experience emphasized the importance of local stakeholders to ensure that the research was appropriate, that there were robust local ethics and regulatory processes, and research was conducted by trained personnel. Research training opportunities can be developed locally, or internationally, with many international schemes available to help support new researchers from low- and middle-income country settings. International collaboration can successfully leverage funding from high income countries that not only generate data for the local country, but also provide new data appropriate to high income countries.

Conclusions: Building stroke research capacity in low- and middle-income countries will be vital in improving global health given the huge burden of stroke in these countries.

Keywords

Low-income countries, ethics, funding, training, India, Asia, stroke, research

Received: 6 August 2017; accepted: 18 October 2017

Introduction

In this second paper of a five-paper series on how to do good quality clinical research, we will discuss research in limited resource settings. The Global Burden of Disease investigators estimated that 70% of incident stroke and stroke deaths, half of all prevalent strokes and nearly 80% of DALYs lost were in low- and middle-income countries (LMICs), yet most research is done in high-income countries.[1] However, LMICs have only about 3% equivalent purchasing power to fund this demand.[2] Furthermore, it has been estimated that 90% of medical research is targeted on the health needs of the richest 10% of the world.[3] [1]As stroke is occurring at an earlier age in LMICs, there is a disproportionate loss of DALYs in these countries. This has major implications for families, as those with stroke are often the breadwinners of the family, and thus stroke commonly leads to catastrophic financial hardship.[4] The resulting mismatch between burden and research has led to large evidence practice gaps in global health.[5] In addition, there is the inevitable tension in LMICs between cost effective public health strategies to reduce the burden of stroke (such as the identification and treatment of hypertension and stroke unit care), and the attraction of implementing the current "state of the art" stroke interventions, such as thrombectomy. There is a risk that piecemeal implementation of aspects of western medicine could consume all the available stroke resources, for very little public health benefit.

High-quality research is needed in LMICs to determine which local solutions work, and what is their cost-effectiveness. In this review article, we will discuss the barriers and facilitators of conducting clinical research, provide examples from our own experience, review the

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literature in this area and provide some new data from our recently completed stroke rehabilitation trial in India.

Methods

We utilized a mixed methods approach of a focused literature search, reflections from our own research careers and insights from a recent Process Evaluation from the ATTEND Trial.[6] Our literature search was performed using the search terms "stroke" "clinical research," "resource poor settings," "developing countries," "low and middle income countries" to identify relevant articles. This had to be broadened to cover all aspects of health as our initial search failed to reveal stroke specific examples, and experience from other disciplines was likely to be informative.

We supplemented this literature search with some of our findings from our process evaluation of the ATTEND trial which had an aim to identify critical facilitators and barriers in the implementation of a randomized controlled trial (RCT) in India by international research collaboration.[6] The methods of this research have been published in detail previously,[6] but in brief, this involved focus groups and in-depth interviews with thematic analysis of 8 clinical trial coordinating staff, 4 chief investigators, 26 health providers, 22 patients and 22 carers involved in the RCT.

We synthesized the main themes arising from our literature search, our own personal experience, and some of the relevant findings from the ATTEND trial process evaluation (see Box 1).

Results

The main themes identified were manpower and workload, research training, research question and methodology, and research funding.

Manpower and workload

From a survey of the 1312 members of the Indian Academy of Neurology (recorded in January 2015), it was calculated that approximately 935 million people in India had no neurologists working in their geographical area, with only 3% of members recorded to be working in rural areas (covering a further 85 million).[7] India is not unusual in this respect as the World Health Organization reported 0.03 neurologists per 100,000 population in Africa, 0.07 in South-East Asia, against 4.84 in Europe.[8] Neurologists in India (data from 2007) typically cater to 30 to 50 patients a day and approximately 15% of neurologists see more than 50 patients a day.[9] These numbers translate to a private academic institute seeing around 200 neurological patients per day, private clinics seeing 100–150 patients per day, and government institutes seeing 800 patients per day. Demand on neurosurgery is also large with an approximate seven month waiting period for elective neurosurgery at one government hospital in India.[7] These enormous clinical workloads contrast with more manageable numbers seen in high income countries, and thus leave little time for research in LMIC urban areas, and lead to virtually no healthcare provision in many rural areas of the world.

The limited number of trained professionals, and the need to cater to a large number of patients, results in a lack of "protected time" for research for neurologists in LMICs, thus limiting their ability to perform good quality research in stroke. In the process evaluation of ATTEND, we found that establishing a supernumerary research team with various roles and responsibilities (e.g. project management, data collection) with on-site training and monitoring according to Good Clinical Practice, was key to facilitating the "time poor" neurologists in conducting research, while balancing service delivery.

The lack of research training and relative lack of research funding adds to the challenges.

English et al.[10] have discussed the concept of a Learning Health System that provides an opportunity to conduct pragmatic RCTs, integrated into routine clinical care.[10] However, busy clinicians are only likely to devote a proportion of their time to research if they see the value of such research improving the health of their patients, and presumably providing an interesting and stimulating environment in which to work.

Our experience in trials conducted at Christian Medical College and Hospital Ludhiana might help beginners in establishing a good research environment. The stroke unit at our institute is functional as a multidisciplinary team and was initiated in 2008. A basic observation (by a neuro-physiotherapist of the team) of the common shoulder issues post stroke, led to the formulation of a study on the effects of shoulder taping for shoulder pain and injury post stroke.[11] The team reviewed the literature and designed a low cost, 4-centre RCT to prevent shoulder pain. Another study used an indigenously designed low cost (approx. USD7.7) mirror therapy box to be used for rehabilitation in patients with hemi neglect post stroke. This single center study provided class I evidence that mirror therapy improved hemi neglect in thalamic and parietal lobe strokes.[12] Finally, through an intramural research fund, a 7-center observational study was designed to assess the impact of pre-morbid undernutrition status on short-term stroke outcome.[13] All these studies required an appropriate mentor (see next section, Research Training) and benefited from industry

Box 1. Illustrative quotes from the ATTEND process evaluation

Manpower and workload

Team work relieving the high work load

"*You have a structured research program in the trial, each aspect of the trial is taken care of by different people, there is no burden on one person. Previously all the research work that I've done, it was all upon me. I am the coordinator, do everything is done, but here it is all structured. So I spend only one hour a week, and so I ask how many patients (the stroke coordinator) has recruited and now I identify patient and tell her, and so it's been really smooth for me, and with all other work that I have to do in the hospital and other research and that has been a great thing from my perspective.*"(Neurologist)

Research training

Lack of research training

"*There is only a few universities which speak about evidence-based practice, and it is a subject which is not taught at all. . .Many physios don't know how – what evidence means, what evidence-based practice means? They are not aware of it of how evidence works or our trials work or how systematic reviews work? What is the importance of guidelines? What is the importance of clinical pathways, protocols?*" (Physiotherapist)

Building of capacity

" *I didn't have much idea (about research) at the beginning because after I finished my bachelor's, I just came here. It was a very new experience because I had done my project work in my final year, but that was entirely different than this. My experience with the research was very little so this gave me an opportunity to have better experience and better exposure to research and how to go about things, so it was very good for me to learn. . .and it helped me to boost up my confidence with the patient interaction and how to communicate with them and how to deliver the interventions.*" (ATTEND Stroke coordinator, a physiotherapist)

Role of regular communication

"*The workshops regularly updating our skills, having a teleconference bi-monthly. It's all great to have such a thing in the trial, as sometimes we may be lost continuing to doing our work. Having such kind of thing is very good and I appreciate the administrative team and the role of people who are involved in this.*" (ATTEND Stroke Coordinator, a physiotherapist)

Respect and teamwork

"*We want this number of patients to be recruited. Look at the bigger picture. . . So (the principal investigators) have been very inspiring and you know, good messages coming across from all of us in the management team (to the sites) that this is the thing, and we will be presenting your data here. . . They are getting the constant training. . . So it helps. They know that they are being looked into. It isn't that they are on their own. They know that they are being monitored. The monitor is doing the job correctly, monitoring the site. The other people are looking into the monitor's work as well. So it's a coordinated team effort, which has gone into the trial, so it's everybody's efforts.*" (Clinical trial team member 1)

Challenges in maintaining the trained workforce

"*Actually when ATTEND finishes, we have to see whether there is any other trial we are able to get. Currently at present there is nothing in. Most of the time (for the) really good staff I will find out some study which I will try to continue. (Name withheld) has been for more than four years now, because being somebody who has been with us for sometime, it is very useful because she maintains all our data, all that prospective database, everything she keeps in, and we put in all the forms. . .That made a big difference in our quality of care.*" (Neurologist)

Research question and methodology

Research motivation

"*. . .in research we learn new things because the practical knowledge we get in the research, clinical research, we deal with the patients. The main thing is we are serving the patients. We are doing something for the betterment of the patients either directly or indirectly. . .the present patients may not get the benefit of the research but the upcoming patients they will surely get the benefits of the research. . .so they may get that proper treatment in stroke in future.*" (Trial assessor)

Improvement in care

"I *think this trial was very important, one of the biggest trial I have taken part, and I think I learnt so many things already from conducting this trial here like, for example, like when we teach something for the patient we think that they will follow it strictly, they'll go back and do it, but in many cases it's not so. One, it may be because of the lack of applicability of what we are telling them. Like suppose, for example like we had one patient who was told to do transfer, how to transfer from the bed onto the chair but later we found out the patient doesn't have even a bed at home. . ..So lot of things we found out about our patients which was totally new to us. This was a learning experience.*" (Neurologist)

Ethical dilemma

"*It is just, that I felt that certain patients, those patients who are in the control have to get certain other things. . . Because after all they are patients also; so we cannot leave that person- that you are on his own if you want to do any physiotherapy or something.* " (Stroke Coordinator)

(continued)

Box 1. Continued

Research Funding

"*You need to have that ground level experience knowing people from different backgrounds across Indian state lines and to be able to put together something of this magnitude- hundred patients across twelve to fourteen centers is a large number for a country like India where the barriers between states and cultures are so huge. Each state is a country in itself, so to bring them all together is a big challenge and a busy clinician just wouldn't have the time and you know wouldn't be that motivated. . .So, I was glad that someone actually made it happen to have the time invested into it, to have the financial resources come into it, and to have the dedication to find the right staff and to empower them, inspire them through a long period, I mean its three year study. So, that's not easy to do.*" (clinical trial team member 2)

Box 2. Case study of funding: The ATTEND trial of family-led rehabilitation for stroke in India.[18]

- 2000: Family-led stroke care developed in India.
- 2010: International collaboration initiated (European Stroke Conference, Barcelona) and developed (World Stroke Congress in South Korea).
- 2010: Medical Research Council (UK)-Indian Council of Medical Research Grant unsuccessful.
- 2010: Australia India Council Disability Workshop, Hyderabad. Strengthened and enlarged Indian collaboration, e.g. Indian Institute of Public Health involvement.
- 2011: First application to Australian National Health and Medical Research Council (NHMRC) – just missed out on funding.
- 2012: Pilot study funded (AUD$10,000) by George Institute for Global Health and re-application to NHMRC.
- 2012: Australian NHMRC funding (AUD$1.5million) obtained on second attempt.
- 2013: Indian staff appointed, regulatory approval obtained, first Investigators' Meeting (Hyderabad).
- 2014: recruitment commenced, second Investigators' Meeting (Trivandrum).
- 2015: Third Investigators' meeting (Shimla).
- 2016: February, completion of recruitment.
- 2016: 25th October final investigators' meeting Hyderabad.
- 2016: 29th October, public announcement of results (World Stroke Congress).
- 2016/7: New international collaboration formed, with leadership from University of Central Lancashire, England.
- 2017: ATTEND Trial published in the Lancet 5 August 2017.
- 2017: Follow-up stroke research utilizing the ATTEND collaborative group. Unsuccessful application to the Research Councils of the United Kingdom Global Challenges Research Fund.
- 2017: Successful application (£1.9 million) to National Institute of Health Research, Global Health Research (UK), led by Dame Caroline Watkins, University of Central Lancashire, UK.

support of other commercially sponsored trials run in parallel. This early track record was noticed by local philanthropists, who, in turn provided additional resources to improve the existing stroke care services at the institution, thus further supporting stroke research capacity.

Research training

Research training is essential to achieve high-quality research and reduce research waste.[14] Training can occur locally or internationally and there are established models for both. Local training has the advantage of usually being low cost but will remain challenging due to the competing requirements for clinical service. In cardiovascular medicine, Yusuf[15] has described the local research training by participation in a large-scale international trial during the establishment of the EMERAS (Estudio Multicentrico Estreptoquinisa Republicasde Americ de Sur) collaborative group in South America, that helped build research capacity and led to subsequent projects. The Road traffic Injuries Research Network have reported that seed grants, short-term scholarships, sabbaticals to enable staff from LMICs to work in established high-income country (HIC) units and support to present at international conferences, were successful in building research skills and capacity.[16] In our recent stroke rehabilitation trial in India, international funding allowed 35 full time staff to be employed, and their participation in the trial collaborative meetings, site training visits and participation in national and international stroke conferences provided important opportunities to learn and practice research methods (such as Good Clinical Practice guidelines).[17,18] Our process evaluation found that respect between members of the

team and the international collaborators was fundamental for the mutual learning and success of the trial implementation – a finding which has been reported by other research collaborations.[19] Regular communication between the site staff and the clinical coordinating members was highly valued by the clinical research staff on the ground. The cultivated team work approach was a facilitator to trial implementation (e.g. successful patient recruitment and follow-up) which was conducted according to study timelines and within budgeted resources. An illustration of the themes identified is given in Box 1.

While research skills can be learnt during a busy clinical post with appropriate local mentoring and training, a period of research training through scholarships and international training has also proven to increase research capacity. The advantages of an international training scholarship include the opportunity to escape the brutal local clinical workload, with time to concentrate on acquiring research skills. A disadvantage of such a program is that this can lead to a ''brain drain'' if the scholar chooses to stay in the host country! Heimburger et al.[20] have described the success of the Fogarty International Clinical Research Scholars and Fellows Program, demonstrating increasing focus on non-communicable diseases, and a good publication record and excellent subsequent grant success (two-thirds of subsequent grant applications being funded). A more organized and planned research training curriculum is needed in the three year Neurology training and allied health courses in academic institutions across all LMICs. Within LMICs, those with international stroke reputations have an important role in providing local mentorship and being a role model for their institution, and driving change to support a stroke clinician scientist career path in their country.

Research question and methodology

Many of the papers stressed the importance of locally driven research priorities from practitioners and researchers in limited resourced settings in order to truly address the contextual factors and disease burden.[21–25] Cross-sectional studies of clinical trials compared to global burden of diseases have highlighted the mismatch between disease burden and the number of trials.[24,25] For example, Condo et al.[23] highlighted that in Rwanda, clinical trials were mainly focused on HIV transmission but that testing of interventions that address the epidemiological transition from infectious diseases to non-communicable diseases, including the significant mental health trauma post genocide were needed. In a paper regarding clinical nephrology research in low resource settings, Anand et al.[22] recommended that high quality epidemiological studies and data registries be a priority in order to highlight local areas of need and channel international funding through research collaborations.

Senior researchers in a panel discussion about nephrology research in resource limited settings advised that broad areas of research questions that align with global interests and still address local needs would be strategic in securing funding.[22] For example, addressing chronic kidney disease as part of the non-communicable disease global burden. Incorporating health systems research within the research question/design to ensure sustainability and exploring issues of ''equal access'' and ''equitable financing,'' e.g. registries to inform gaps, and the collection of relevant data (e.g. health utilization data) would be ideal.[26] Such research evidence addressing broad global interests would also facilitate the ''reverse innovation phenomena'' whereby the research findings from LMIC would be applicable to high income countries.[27] The INTERSTROKE study is a good example of this ''reverse innovation phenomena''.[28]

This process of gap analysis and priority setting was reflected in our journey in India – with stroke registries set up at partner sites which helped identify the gap in service delivery and the significance of the research question for an affordable community-based rehabilitation model which was then tested in a RCT.[29] Our process evaluation found that because the research addressed an issue of local priority (the lack of access to multidisciplinary rehabilitation), it was highly motivating for Indian health providers, principal investigators, research staff, patients and carers to participate in the trial. Health providers also described improvements to clinical care, while the trial was conducted, due to the robust data collection and follow-up and greater understanding of the patients' contextual factors. Moreover, an example from the process evaluation of how evidence from high income countries may lack relevance to the local health system context was evident in how a component of our intervention (early supported discharge) was welcomed in concept but not implemented due to the health system issues like bed pressure and affordability of hospitalization.[18] As an example of the ''reverse innovation phenomena'' – in our last investigators' meeting and at the World Stroke Congress, researchers from LMIC (e.g. Uganda, Indonesia) and high income countries (Australia and USA) expressed interest in the task shifting model of rehabilitation, as they thought it would be applicable for their remote populations who also have limited access to stroke rehabilitation.

In LMICs, appropriately trained research staff are a pre-requisite to ensure that research methodology is robust, and not prone to bias.[27] There is increasing

awareness of research waste, and in a resource-limited environment, it will be essential that research is not wasting precious resources (in both opportunity costs of wasted time and also money). Dandona et al.[30] have summarized a probable strategic framework which would help in improving the quality and number of public health related research in India. Formal training institutes for public health research, exposure, and encouragement towards hands on research experience for medical and paramedical undergraduates and development of performance-based opportunities to public health research scholars for career enhancement can improve the quality of manpower available for research purposes.

In LMICs, collaborative research work has opened many channels for budding professionals to be trained and put their skills to use. Collaborative research work like the ATTEND trial in India[18]; the Headpost trial in India, Brazil, Chile, Columbia, Taiwan and Sri Lanka[31]; the RECOVER trial in China[32]; and the ENCHANTED trial in Brazil, China, Columbia, Thailand and Vietnam[33]; have all used resources from high income countries to recruit patients globally and have established stroke research networks, with resulting high impact studies. Such collaborative research work has enabled resources from rich countries to be used in LMICs in the employment of research staff.

Our own experience in the ATTEND trial[18] has shown the successful employment of 14 professional physiotherapists and 14 blinded assessors and clinical coordinators of varied health science background. Although not all of these employees had a previous formal training in research, the structured trial training and experience have empowered and motivated many of them to pursue a career in research, and contribute to research capacity development in India. Several of the principal investigators described securing additional funding through other research projects to maintain their trained clinical research staff after the completion of the ATTEND trial, and thus these staff could continue to drive local research and improve quality of care.

The current status of the ethics and regulatory systems also need to be considered, and some countries may need to establish an ethics framework before research should begin. Ensuring appropriate ethical conduct, as discussed in depth by Solbakk and Vidal, is essential and they point out the importance of a robust local ethics review.[3] Condo et al.[23] noted a key challenge for setting locally relevant clinical trial priorities for Rwanda was that local ethics and regulatory institutions lacked the local capacity and expertise to follow through the ethics, design, and integrity of clinical trials.[23] In our experience, during the implementation of the ATTEND trial,[18] the ethics and regulatory environment in India were suited to behavioral intervention trials but not for pharmaceutical trials, due to onerous requirements to compensate healthcare costs in drug trials (regulations that have now been changed to facilitate more drug trials in India). During the conduct of trial, additional ethical dilemmas may occur. For example, during the follow-up of patients and carers in the ATTEND trial, clinical trial staff described their ethical dilemma following up families who could not afford rehabilitation and were in financial strife.

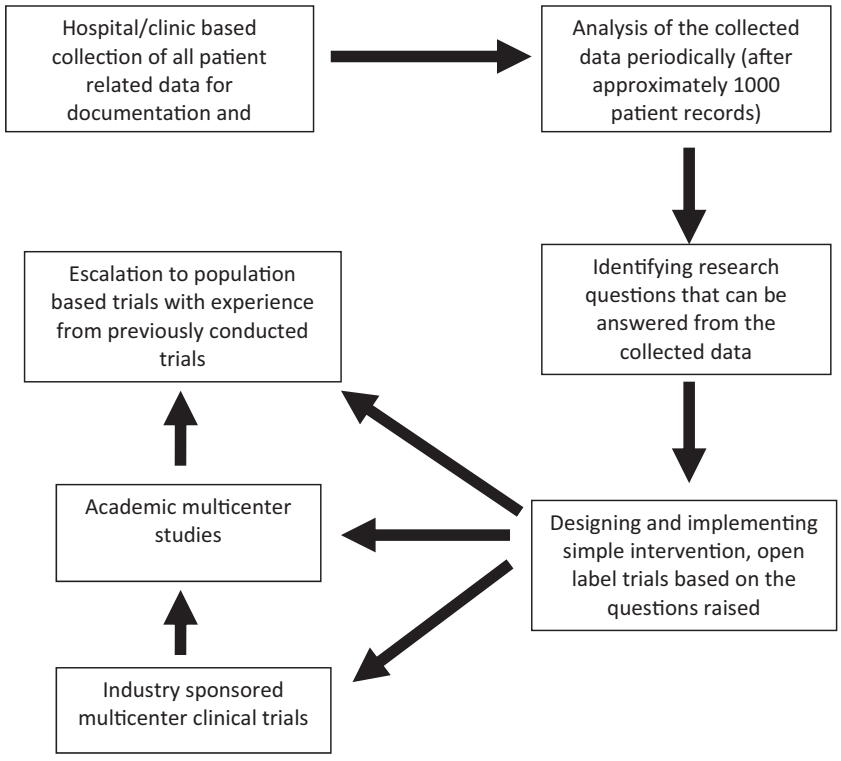
For those wishing to begin clinical stroke research, one pathway is to understand the local stroke epidemiology by obtaining local ethics approval to collect and record patient details in a systematic manner in the form of case report forms. This can be accomplished by training nurses or other ward staff who will be in contact with the patient for a longer time than the neurologist. In this manner, the local context can be described and research priorities will emerge (Figure 1). These data are also required for site surveys before commencing any industry-sponsored trials that can also help a local site begin and gain experience in research methods. Those in private practice can also collaborate with bigger institutes for large scale multicenter studies.

Research funding

High quality research requires sufficient funding which is a key challenge in resource limited settings. One solution is obtaining funding from international resources, but this potentially comes with its own challenges of ''whose priorities'' are the research actually addressing.[15,21] For example, Condo et al.[23] described the risk of ''unequal partnerships'' and the risk of research not addressing local population needs when clinical trial priorities were set by in Rwanda by local representatives (e.g. Rwandan government, academics) and international agencies (e.g. pharmaceutical companies, non-governmental organizations) with greater funding. Ali et al.[21] described a challenge of conducting cancer research in India, with potential ethical concerns with multinationals conducting pharmaceutical trials in India in regards to the lack of informed consent and the exploitation of the poor and illiterate. Such challenges related to the leverage of international funding strongly reinforce the importance of locally driven research.

International funding bodies need to team with the local researchers to ensure that their research builds local research capacity and strengthens the local health systems.[19,21,23,27] For example, Ali et al.[21] described their strategies in overcoming their challenges in 2005 due to the lack of clinical trial and regulatory

Figure 1. Creating the basic infrastructure to start research.



infrastructure (e.g. inexperience staff, no established standard operating procedures) as experienced by their INDOX (India and Oxford) cancer research network. Their strategies included the joint design and conduct of research by the principal investigators from Institute for Cancer Medicine in Oxford and leading cancer centers in India, tailoring of standard operating procedures, extensive monitoring of quality and good clinical practice at sites, dedication of site staff to help the "time poor" principal investigators in trial management and working closely with the Drug Controller General of India to obtain regulatory approval for their trial.

In the ATTEND trial,[6] the initial negative perception by the regulatory authorities of the agenda by international collaborators and Australian funding agency (and thus the relevance of the research question) was a key barrier that had to be overcome. This was achieved through extensive discussions that outlined that the research was led, initiated and piloted by a local academic neurologist and the Indian Institute of Public Health, in collaboration with academics from UK and Australia. Moreover, the research addressed an issue of local priority, which was the lack of access to multidisciplinary rehabilitation, and was highly motivating for Indian health providers, principal investigators, patients, and carers. Improvement to clinical care due to the robust data collection and follow up and greater understanding of patient contextual factors was described by health providers. Thus, our findings highlight the need for transparency, early consultation and engagement of local health, ethics and research authorities, and value of international collaborative research in strengthening health systems in limited resource settings.

Our case study of the ATTEND collaboration also highlights the importance of discussion at international stroke conferences, and we would recommend that conference organizers provide future sessions with a "research in low and middle-income countries" session theme, including plenty of opportunity for panel and audience discussion (Box 2). ATTEND also provides a good example of international funding providing initial feasibility funding, followed by more substantive funding, that built local research capacity, and then led to further international funding, thus providing more long-term research sustainability. The ATTEND trial collaborated with 14 hospitals and academic centers across India with a mix of state and central government, private, and corporate institutions. The Indian government has now funded a large Indian Stroke Clinical Trial (INSTRUcT network) constituting 27

institutes across India which are empowered to implement and run trials while employing and training research staff. With the formation of the INSTRUcT, further research capacity growth, supported by successful global grant applications, promises a bright future, with new data likely to drive local health improvement, and contribute to global health. This illustrates the importance of engaging with policy makers in creating a research culture.

Conclusions

The solutions to the challenges of research in limited resource settings are interlinked and include research training, research design and leveraging access to global research funding. Many of our own examples were driven, in part, by informal discussions at international conferences, and taking opportunities as they arose. Collegiality, and collaboration ensures we discuss the great challenges that many face in limited resource settings, and between us, we have the resources to build further research capacity for the benefit of our global citizens.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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CHAPTER 5: EXPLORING THE USE OF EVIDENCE TO INFORM INVESTMENT IN DISEASE PREVENTION

Chapter Overview

In this chapter, a qualitative study initiated by NHMRC-funded Australian Prevention Partnership Centre (TAPPC), is used to explore whether evidence is relevant to high level decision makers with responsibilities for investing in NCD prevention in Australia (from Treasury, state health departments and the insurance industry). The findings of a qualitative study examining the evidence to practice and policy gap, specifically relating to the prevention of NCDs in Australia, are presented. The chapter consists of a published manuscript titled: "Exploring the use of economic evidence to inform investment in disease prevention- a qualitative study."

In Chapters 3 and 4, examples were given of how process evaluations of RCTs provide evidence of micro to macro contextual factors explaining for whom, how and why these interventions had an impact on; and provide insights to barriers and facilitators for future collaborative research. However, a missing part of the thesis' narrative is whether the evidence generated by impact, process and economic evaluations of complex interventions, do indeed guide decision makers to invest in programs addressing NCD. This chapter provides some important insights and implications for future partnership research in tackling NCDs in Australia.

Authors' contributions: SJ, PH and AS initiated the study on behalf of the health economics group of the Australian Prevention Partnership Centre. SJ led the study and was the lead

interviewer. JM managed the study, co-interviewer and contributed to data collection, and the analysis. HL was the lead analyst of the qualitative data and a co-interviewer with SJ. HL mentored JM in qualitative methods, drafted and revised the manuscript, and all co-authors provided input in the revisions and approved of the final manuscript.

Publications details:

Liu, HM. Muhunthan, J. Ananthapavan, J. Hawe, P. Shiell, A. Jan, S on behalf of the TAPPC Economics group. Exploring the use of economic evidence to inform investment in disease prevention- a qualitative study ANZJPH (accepted on 2nd October 2017).

Manuscript:

Exploring the use of economic evidence to inform investment in disease prevention – a qualitative study

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Abstract

Objective: In the context of growing financial pressures on health budgets, cost-effective prevention strategies are needed to address the burden from non-communicable disease in Australia. We explored how decision makers use economic evidence to inform such investment and how such evidence generated can more effectively meet the needs of end users.

Methods: Thematic analysis of in-depth interviews with 15 high level stakeholders (Treasury, state health departments and the insurance industry), supplemented by documentary analysis.

Results: Types of prevention approaches and economic evidence relevant to decision makers differed by organisational perspective. Capacity building in understanding economic evaluations and research evidence that addresses the differing criteria for investment used by different organisations is needed. The task of determining investment priorities in disease prevention comes with significant challenges including ideological barriers, delayed outcome measures, and implementation uncertainties.

Conclusions and Implications for public health: Promoting the greater use of economic evidence in prevention requires more work on two fronts: tailoring the methods used by economists to better match the organisational imperatives of end users; and promoting greater consideration of broader societal and health sector perspectives among end users. This will require significant infrastructure development, monitoring and evaluation, stronger national leadership and a greater emphasis on evidence coproduction.

Key words: Health economics, qualitative research, prevention of chronic disease

Evidence-based investment in prevention is crucial in addressing Australia's rising health, economic and social burden from lifestyle-related non-communicable diseases (NCD).[1] Prevention strategies are prominent in the World Health Organization's 'best buys' in addressing this burden.[2] Despite such evidence, investment in prevention of NCDs in Australia is low compared to other countries with similar epidemiological profiles.[3,4] Such disparity in expenditure potentially reflects a low value attached to the evidence around its effectiveness and cost-effectiveness by policy makers in this country. However, we note that a recent report argues that the proportional amount of spending on prevention by a country, compared to others, may be an overly simplistic means to assess its value or worth.[5]

In the past 20 years, the use of economic evidence in Australia has been growing through the pioneering initiatives in the 1990s to introduce cost-effectiveness criterion in the listing of new drugs for government subsidy through the Pharmaceutical Benefits Advisory Committee (PBAC).[6] In spite of the recognised leadership role Australia has played in institutionalising the use of economic evidence in informing investment in healthcare (such as PBAC, as well as the Medical Services Advisory Committee [MSAC]), little has been done to promote greater use of cost-effectiveness evidence in NCD prevention.

A reason for this may be that in the prevention space, unlike that of healthcare, policy makers may be less willing to cede discretion over investment decisions to an evidence-based approach that is driven by cost-effectiveness. In principle, the role of economic evidence is to guide the allocation of resources efficiently across population groups and individuals by identifying programs that optimise social outcomes for given resources.[7] However, economic analysis tends to be underpinned by a reductionist perspective on investment decision making. In this world view, decisions are characterised by a choice to either accept or reject an investment proposal by benchmarking the observed incremental cost per unit of health outcome of the intervention against

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Submitted: March 2017; Revision requested: August 2017; Accepted: October 2017
The authors have stated they have no conflict of interest.

Aust NZ J Public Health. 2017; Online; doi: 10.1111/1753-6405.12748

an accepted cost-effectiveness threshold (in Australia this has been posited as being between $50,000–70,000 per quality adjusted life year gained). The logic underlying this is that with successive decisions made on the basis of this balancing of costs and outcomes, as a community, we are led incrementally toward a hypothetical efficiency ideal (or 'frontier').[8] One possible reason for the exception of prevention to this logic is that the outcomes of interventions are often multi-dimensional, long-term and diffuse – affecting sectors outside of health.[9] As such, while this has a high degree of acceptance as a framework for allocating resources in many parts of the health sector, it may be at odds with prevailing norms that govern the way investments are made in prevention.[10-14]

Therefore, gaining a better understanding of key actors' perspectives (as depicted in Figure 1) is vital in identifying the factors that drive investment decisions and in overcoming any perceived barriers to the implementation of evidence-based prevention strategies into practice and policy.[10,15-17] For this study, we explored how decision makers (policy makers, insurers and funders) use economic evidence to inform investment in the prevention of lifestyle related NCDs, and identified how economic evidence can better match their needs.

Methods

Our methods are outlined here according to criteria for qualitative research.[18,19]

Approach

The study was carried out and supported by a research collaboration that promotes multi-disciplinary research into chronic disease prevention, with a focus on developing system solutions. The interview guide (Supplementary file 1) was developed by health economists and covered the following key questions: What type of evidence is used when making investment decisions in disease prevention? What role does economic evidence play? What types of analyses are used? Is there scope for generating economic evidence that better matches decision makers' needs?

Setting and sampling strategy

Recruitment of the participants was purposive. We sought to elicit views from individuals within three distinct types of organisations: state health and Treasury departments and private health insurance companies. The research collaborators helped identify key individuals who were responsible for investment decisions. An ethics-approved information sheet and invitation letter were sent to potential participants. Ethics approval was granted by University of Sydney before commencement of research.

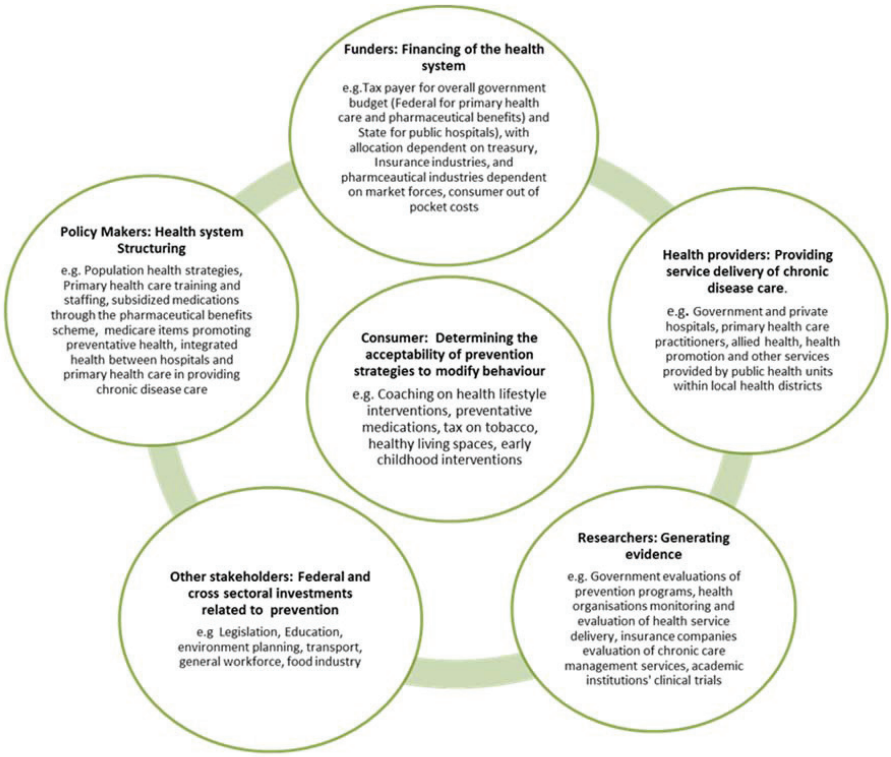
Data collection techniques

We conducted semi-structured interviews with these decision makers that lasted between 30 and 45 minutes. All participants provided written informed consent. A health economist took the lead in conducting the face-to-face interviews, accompanied by two public health researchers with backgrounds in medicine and law, respectively. Three interviews were conducted on the phone due to distance. All interviews were recorded with a digital recorder. Any supporting documents referred to by the interviewees were obtained by the team so they could be analysed.

Analysis

Interviews were professionally transcribed verbatim and managed by NVivo software. A coding framework (Supplementary file 2) was developed using a 'ground up' approach by the two public health researchers using three transcripts and iterative changes made as necessary with the coding of subsequent transcripts. The team met regularly to discuss the emerging themes. Thematic saturation was reached at 15 participants and interviews were stopped. Constant comparison across cases was undertaken as all data coded to each major code was analysed. Documents[20-31] referred to by participants during the interviews were analysed by a senior health economics researcher for the purpose of triangulating the findings.[32] The findings from the documentary analysis are provided in Supplementary file 3.

Figure 1: Contextual map of stakeholders. The complexities of the provision of prevention strategies by various stakeholders, highlighting their roles and interlocking relationships which impact upon the consumer's behaviour change.



Results

We interviewed high-level decision makers; four were from the insurance industry, eight from state health departments and three from a state Treasury department. Three key themes were derived about how organisational perspectives frame types of economic evidence used; the need to increase the accessibility and acceptability of health economics to end users; and the significant barriers to the prevention agenda. Further illustrative quotes are

presented in Box 1. Table 1 presents a summary of the identified barriers to the use of economic analysis in prevention and our recommendations to address them.

Organisational perspectives frame the preferred prevention approaches and types of economic evidence used

Industry (insurance companies) – business case and return on investment

The industry perspective focused on the use of economic evidence to justify their business case and stewardship of members' funds. Industry stakeholders wanted evidence relating to the minimisation of hospitalisation for their members and consequently defined 'return on investment' in those terms, as this was the most tangible means of demonstrating value to the business. In comparison, primary prevention or health promotion activities were highlighted by another insurer as part of their 'branding' and marketing campaign. Industry stakeholders also described how cost savings generated by their programs were often realised in the public sector (e.g. reduced pharmaceutical costs through Medicare), but indicated that these were generally not factored into the company's decision making. One option raised was the possibility of cost-sharing arrangements with government in which there were mutual benefits.

Health departments – population health approach

Health department stakeholders described using an evidence-based approach to demonstrate the potential benefits of a concerted prevention strategy with a 'range of interventions' and indicated that there was a need to incorporate other sectors. These stakeholders recognised that economic evidence would provide greater 'credibility' for what they do, although some described a reticence to use financial outcomes and a preference to only focus on health outcomes. A health policy maker indicated the advocacy value of cost of illness evidence such as "the cost of overweight and obesity being estimated to be 19 billion dollars a year" as a way of effectively framing the problem as a community rather than an individual issue. Economic evidence such as costing data (rather than cost- effectiveness evidence) was used primarily to better inform the implementation of programs, and less so to set broader priorities. Two health policy makers perceived that economic evidence that tackled allocative efficiency questions across different types of prevention strategies would be the 'holy grail' in informing their decisions.

Box 1: Illustrative quotes across themes.

Organisational perspectives frame the preferred prevention approaches and types of economic evidence used

". . . we are involved in activities which I would probably classify as primary prevention, but it's not a deliberate investment activity, it's more from a brand activity . . . So, we like to shoot positive health messages out there to the general population in regards to good diet and exercise behaviours . . ." (Insurer perspective)

"But we don't have those answers. You're getting to sort of where we get frustrated. I mean return on investment, as we are able to use it, gives us some sense of being able to compare, say one cooking program against another cooking program. It's useful in that sense in that we can get some sense of, which is the most technically efficient program if you like. And we can purchase on that basis . . . we can't compare, one type of approach to another type of approach (for example, advertising, changing environments or in advertising versus, you know, a diabetes risk assessment tool) with the tools that we have available to us or any of the return on investment analysis that I've seen anywhere. And that is the holy grail process." (Health perspective)

"We kind of take the whole of government approach ... A program might require investment through the health sectors, through the education sectors, family and community services and it's about understanding holistically. . . You've got a number of service sectors, sort of involved in this and whilst success in one sector doesn't necessarily mean, you know, success in say, education or family and community services. So, it's about looking at the whole across government, how much is it going to cost across government, what are the benefits across government." (Treasury perspective)

Increasing acceptability and accessibility of health economics to end users

"I think they (other government agencies) confuse the word economic analysis with financial analysis. There's just no way in reality that the agencies are currently geared up for that kind of thing. Completely missing that capability. We want to build up capability and understanding of those things . . . So, there's a series of opportunities there to work with government (about what) would be an acceptable kind of framework that we can all agree on so that we can sort of move the debate forward onto then what sort of things we should be funding." (Treasury perspective)

"I think from my perspective I feel like (the use of economic evidence) is an area I hardly know anything about and so I reckon that there's a role for, you know, economic evaluation 101 for senior managers . . . It would also be really helpful for me . . . in the area of overweight and obesity or tobacco control or alcohol ¬– preventing alcohol related harm – [to know] what's the current landscape, what in terms of economic evaluation of intervention and policy in those areas, is really helpful for someone in my role." (Health perspective)

"So, then what I'm looking at is my health economists have gone away and done some really nice modelling around the types of people that will be going through [a health program]. So, they're over 60 and they look like this and therefore, on average, and depending on all those variables, we have different combinations, this is what they would expect to cost . . . I'm going to say that I'm forecasting 30 to 40% reduction in patients re-admitting over a 90-day time frame that go through this program, so therefore how does that stack up?" (Insurer perspective)

Prevention agenda for NCD faces significant challenges

"So, in tobacco I think there's not so much contention around tobacco as an area where government would intervene. We've got 30 years of evidence in relation to [success], so these policy changes and these programmatic and services are an appropriate mix. Whereas, in overweight and obesity, it's not as well clearly understood, nor is it equally accepted as a place for government intervention." (Treasury perspective)

"Because we would often get a phone call from the (funders) saying okay, you've now spent this huge investment in prevention. How many kids did you stop from becoming obese? Now that's quite a hard question to answer. Not reducing . . . the number of kids who are (overweight) down into the healthy weight area, but how many did you stop from going up the scale into the unhealthy weight?" (Health perspective)

"In the health space, we know there's a kind of cost trajectory valve, and health costs are going to rise into the future. And you know, we need to be doing more about keeping people out of hospital to start with . . . there is a recognition that we need to be investing in health. it's a question of what we should be investing in . . . that the proposed [strategy], you know it's worked elsewhere, is it actually going to work here? Do we have the right conditions, capacity and capability?" (Treasury perspective)

Treasury – whole-of-government and inter-sectoral approach

Treasury decision makers stated the use of a 'whole-of-government approach' in the assessment of inter-sectoral prevention interventions and indicated they would consider costs and benefits across government. Return on investment and the 'bottom line' did come into play; however, they were also concerned with broader economic dynamics such as inter-sectoral (e.g. transport and education) contributions to investments and their roles in promoting healthy living and the economic impact of improved health status.

Increasing acceptability and accessibility of health economics to end users

Capacity building in health economics for end users

Some stakeholders in health and Treasury indicated that the health sectors' capacity to understand economic evidence was limited, and capacity should be built either through collaborations or workshops. A high-level policy maker in health stated, "there's a role for economic evaluation 101 for senior managers". Interviews often ended with requests from the interviewees for documents that synthesised the cost-

effectiveness evidence in obesity, tobacco and alcohol in order to understand the "current landscape"; to be better equipped in economic methods that would suit their needs; and to be able to confidently commission others to do so. In comparison, the insurers did not indicate this request as they had in-house personnel with skills in economics and modelling.

Increasing the relevance of health economics methodology

Many respondents described a need for economic evidence that serves as a predictive and interactive tool, which also incorporates the complexities of service delivery and health outcomes. Since many of the health insurance stakeholders described return on investment as their key driver, they were keen to have greater links between the intermediate clinical outcomes and cost savings. Another suggestion from a Treasury stakeholder was that early consultation with end users in the development of predictive economic models would be beneficial, as this would be "getting people to use this kind of data [by] helping people to understand how it's done so that it's not just a sort of impenetrable black box".

A few stakeholders in Treasury and the health departments suggested that lessons could be derived from other sectors (e.g. transport) in using economic analysis that included socioeconomic determinants. Indeed, several of the documents referred to by the interviewees (health and Treasury departments) were evaluation frameworks and government strategy documents related to policies both within and external to the health sector. The evaluation framework documents emphasise the importance of economic appraisal for efficient allocations of resources.[20,26] The documents generally recommend using cost benefit analysis (CBA) and endorse the use of cost-effectiveness analyses (CEA) only in some sectors (e.g. health) where it may be more difficult to monetise the benefits.[20,22,23] The strategy documents emphasised the importance of investing in research that includes economic evaluations and implementing cost-effective interventions.[28,30] In addition, health equity and equity in general were highlighted as objectives or guiding principles of their policies,[23,25,27-29] and government evaluation guidelines propose that equity impacts should be described and quantified when possible.[20,22]

Table 1: Identified barriers to the use of economic analysis in prevention and the prevention agenda and our suggested recommendations to overcome them.

Barriers to the use of economic analysis	Recommendations
Lack of relevance of current economic analysis to end users	For analysts to have a deeper understanding the context of the stakeholders' perspectives. In Australia: • Treasury: managing the governmental budget, thus a whole-of-government approach. Thus, a need for strong evidence and economic analysis including effects across different government sectors. • Health: a need for a holistic approach towards population health, for there to be an increasing appreciation for economic analysis and costs to be included to provide 'credibility' for their agenda. • Insurance Companies: Financial bottom line for the insurance companies in regards to reducing hospitalisation for their members.
Lack of capacity to understand health economics literature	Building capacity through workshops, in-house health economists, or collaboration, or outsourcing through commissioning Better communication of health economic evidence, to help stakeholders understand its significance, such as policy briefs, evaluation frameworks, systematic reviews.
Methodology in prevention is a 'black box'.	Co-production of economic evidence by including decision makers in the development of models and making assumptions explicit. More development needed in this area to make this economic evidence more accessible to decision makers, e.g. Modelling and links between the behavioural risk factors, the clinical risk factors and life years saved.
Health economics perceived as prioritising costs over health outcomes.	Improving capacity within organisations to understand the fundamentals of health economics (i.e. effectiveness, efficiency and equity). Equity focused economic analysis (e.g. for Indigenous health programs) are needed to provide relevant evidence for decision makers.
Barriers to the Prevention agenda	**Recommendations**
Difficulty maximising upon the different approaches of prevention as organisational perspectives frame the preferred prevention approaches.	More collaboration across sectors and health funders to provide prevention programs as a concerted effort. Priority setting across stakeholders from different sectors will be beneficial. Established institutional processes for the use of health economics (with standardised methods) in prevention. Develop diverse investment portfolios (i.e. incorporate both high and low-cost interventions with variable levels of available evidence) in prevention that consider the potential need for risk to effect return and encourages innovation.
Prevailing ideology regarding prevention as to whether it is personal responsibility or government action.	Understanding and addressing various stakeholders' views (consumers, health providers, policy makers, funders) through consultation. Building the evidence base and increasing the public awareness of cost effective prevention strategies addressing lifestyle related risk factors as this will affect political will.
Timing of funding cycle is short but prevention delivers long-term benefits and short-term benefits are less visible.	The need to use intermediate measures to show progress and modelling to show potential benefits. This requires the development of a strong infrastructure for the monitoring and evaluation of prevention strategies as a prevention platform e.g. IT infrastructure, workforce acceptance of performance metrics as part of ongoing monitoring and evaluation, data linkage, use of process data.
Use of evidence is varied across stakeholders	Evidence generated needs to be pragmatic. There should be more evidence in implementation methods, with in-depth contextual understanding. Increasing preference for co-production of evidence between academic institutions, government departments and insurance companies. More synthesis of the evidence, e.g. through reviews of economic evaluations specific to a particular area of prevention such as obesity or tobacco control. Ways to improve knowledge exchange, e.g. use of databases, policy briefs, knowledge brokers.
The need to incorporate other sectors	Including knowledge brokers and the use of economic evidence across sectors Systems approach to prevention which could be incorporated into research (so that it is not single intensity and focused only). This requires a clear picture of the current political influences, health system (private, public, out of pocket expenses), other non-health sectoral influences, e.g. market forces regarding housing, pharmaceuticals.

Prevention agenda for NCD faces significant challenges

Political and ideological considerations

Some stakeholders indicated that promoting a prevention agenda is difficult when there is a prevailing ideology that can be characterised as emphasising personal responsibility over government action. A few stakeholders suggested that when there is a change in government, support for prevention programs tends to come under closer scrutiny. As a consequence, investment in individual prevention programs is tied

with an inherent level of uncertainty. In response to this, solid evidence plays a role in addressing these uncertainties. A participant from Treasury described how a strong track record of 30 years of evidence was needed to enable smoking cessation programs to be more acceptable to government decision makers, in contrast to how "in overweight and obesity, it's not as clearly understood nor is it equally accepted as a place for government intervention".

Prevention delivers long-term benefits; short-term benefits are less visible

There was a general consensus among many stakeholders that the delay for health promotion and early prevention strategies in demonstrating 'hard' health outcomes can be problematic, due to the constant pressure to justify investments in light of competing priorities (such as acute care) within short funding cycles. The stakeholders emphasised that infrastructure in acute care allowed for more robust data collection (e.g. number of hospitalisations) than the infrastructure available to monitor and evaluate preventive care. This lack of outcome measures to show progress in prevention meant less leverage for policy makers when trying to sustain funds for prevention as compared to acute care. For example, a stakeholder in health described getting calls from funders asking questions such as: "'You've now spent this huge investment in prevention. How many kids did you stop from becoming obese?' Now that's quite a hard question to answer". Health policy advisors suggested that identifying valid "proxies, [such as] people's behaviour, people's participation, people's motivation to change" may be needed to "predict the future [of that] program outcome" and to enable these potentially long-term effects to be reflected in investment decisions.

Enabling the commitment to prevention requires significant infrastructure

Another key barrier to the prevention agenda was the generalisability and scalability of effective programs. A Treasury stakeholder recognised that "there's a kind of cost trajectory valve, and health costs are going to rise into the future" but that the question they had was "what we should be investing in … you know it's worked elsewhere, is it actually going to work here? Do we have the right conditions, capacity and capability?"

Most participants emphasised that enabling evidence-based investment in prevention requires advancements in infrastructure, including the availability of informative (baseline and process) data, processes for ongoing data collection and workforce capacity building. There was also a stated need to leverage other available resources (e.g. from primary healthcare, insurance companies, hospitals, primary health networks). All this would facilitate improved monitoring and evaluation, which would allow for continued funding and expansion of the projects.

Discussion

Our results highlight the significant political and pragmatic challenges faced by decision makers in investing in prevention. It is within this context that 'economic' data can sometimes be in a form that does not resemble the traditional way that cost-effectiveness evidence is defined, even though it is used routinely by stakeholders. The types of evidence used, framed by prevailing organisational perspectives, include forward estimates of budgetary impacts and 'return on investment', i.e. range of benefits as specific to the organisational imperatives of the stakeholders (e.g. decrease in hospital admissions for the insurers). Furthermore, economic evidence tends to be used to support activities such as advocacy, financial management and communication between stakeholders, which fall outside the functions economic evaluations are typically designed to inform. Indeed, the finding that prevention is seen as part of the branding activity by health insurers (regardless of prevention's economic benefit) fits with the observation that decision makers often hold knowledge to have more symbolic value than instrumental value.[33]

The limited capacity of conventional economic evaluation methodologies and cost-effectiveness metrics to provide all the information decision makers need is well recognised in the international literature.[10-12,34,35] A solution may lie in an adoption of an evidence co-production approach,[36] which means that research is characterised as a joint enterprise rather than as the end-product of a process in which it is 'delivered' by researchers to a group of decision makers.[37] Conversely, more work can be done to encourage decision makers to look beyond their organisational perspectives and to take on board evidence of societal and sector-wide impacts. This may include promoting recent initiatives in the health economics literature such as the use of cost consequences analyses of 'social impact inventories', which represent evaluation techniques that take multi-dimensional social outcomes into account.[38,39]

Another key implication is that economic evaluation tools could potentially address some of the barriers faced by prevention programs (e.g. short-term benefits are less visible). Thus, an area for further development is for health economic researchers to re-orient analyses in prevention so that evidence can be used to guide future action, rather than as a means of evaluating past decisions. This requires greater use of modelling techniques based on epidemiological evidence to provide decision makers with stronger predictive capabilities. In addition, the use of priority setting tools such as program budgeting and marginal analysis that involve the decision maker in the process[40,41] and studies[41,42] that synthesise existing evidence and incorporate a broader concept of benefit would be useful in prospectively informing investment decisions.

Given the dynamic nature of the political and ideological context around prevention, stronger national leadership and establishing processes for the use of health economics within organisations may be needed.[43,44] Advances in the use of economic evaluations in policy in Australia have mainly been in the field of health technology assessments for drugs and devices. We had expected this to filter through to prevention, but our evidence suggests that this has not happened to any major extent. A reason inferred from the findings was that implementation of prevention programs (e.g. taxation of soft drinks) faces political and ideological challenges and that consumer acceptability is key in this process. While a universal PBAC-type system for assessment of new prevention 'technologies' may be challenging given the diversity of funders and organisational imperatives that drive decision making in the prevention sphere, the evolution of the partnership between UK Department of Health and the National Institute for Health and Care Excellence (NICE) to provide evidence-based recommendations for public health practitioners and policy makers indicates that such challenges can be overcome.[6,45,46] As indicated in this study, much of the evidence sought by those charged with investing in prevention falls outside the purview of what is conventionally

considered health economic evidence and is specific to organisation. Part of the solution is in encouraging the application of existing methods of economic analysis that are sympathetic to what it is that prevention achieves, and the other part is to create the incentives for decision makers to factor into their investment decisions outcomes that are broader than their narrow organisational perspectives.[1,7]

A limitation of the study may be the small number of participants, although it should be recognised that our focus was on senior-level decision makers, and that we did achieve thematic saturation. Sampling from the different organisations also provided triangulation from different perspectives given the relevance of the public and private sector in the prevention agenda. It is possible that a level of social desirability may have biased the findings, given that the interviews were led by a health economist. However, we found respondents to be candid and openly critical of economics and often highlighted organisational shortcomings in addressing issues raised.

Conclusion

To ensure the better use of evidence in investment in prevention in Australia, researchers need to be attuned to the varied organisational imperatives faced by the various organisations who are players in this space. Evidence needs to be fit for such purposes but, at the same time, more can be done to encourage potential funders to take into account cost-effectiveness evidence that highlights cross sector and societal impacts. This will require significant infrastructure development, monitoring and evaluation, stronger national leadership and a greater emphasis on evidence co-production.

Acknowledgements

We would like to thank all participants who gave so generously of their time and for their valuable insights. This research was supported by The Australian Prevention Partnership Centre through the NHMRC partnership centre grant scheme (Grant ID: GNT9100001) with the Australian Government Department of Health, NSW Ministry of Health, ACT Health, HCF, and the HCF Research Foundation. HL is funded by a NHMRC postgraduate scholarship, SJ is funded by a NHMRC Senior Research Fellowship. AH was funded through NHMRC #571372.

The authors acknowledge the contribution of The Australian Prevention Partnership Centre (TAPPC) Health Economics Group. Stephen Jan co-authored the paper on behalf of TAPPC, and other group members comprise of: Andrew Milat, Beth Stickney, Alison Hayes, Thomas Wai-Chun Lung, Rob Carter, Louise Sylvan and Tracey-Lea Laba.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Supplementary Table 1: Interview Guide.

Supplementary Table 2: Coding Tree.

Supplementary Table 3: Documentary analysis.

CHAPTER 6: SUMMARY AND IMPLICATIONS

Chapter Overview:

This chapter comprises of three sections. First, the results of the thesis as a whole will be summarised and the common findings presented across macro, meso and micro levels. Second, the three main overall implications from the thesis will be discussed. Third, the strengths and limitations of the thesis will be discussed through an appraisal of the PE framework used, a researcher's lens of reflexivity and synthesising the three key strengths of the thesis.

SUMMARY

In this thesis I present a body of work which demonstrates that process evaluations (PE) play an important role in articulating the needs of end-users (patients, providers, practitioners, and policy-makers) within their local context, and doing so, further inform intervention design and implementation strategies needed for the sustainability and scaling up of locally relevant interventions. This was done through examining the methods and findings of published PEs of primary care interventions, two PEs of secondary and tertiary interventions; and exploring the use of evidence by end-users in investing in prevention.

Chapter 2

In the systematic review in Chapter 2, we used the MRC PE guidance to appraise and synthesise the methods and findings from published PEs of primary care interventions. We found that greater consistency is needed in the reporting, and the methods of PEs. In particular, there should be greater use of theoretical frameworks to inform intervention theory. The main strengths were robust sampling strategies, and the triangulation of qualitative and quantitative data to understand intervention's mechanisms. Findings were synthesized into three key themes: 1) a fundamental mismatch between what the intervention was designed to achieve and local needs, 2) the required roles and responsibilities of key actors were often not clearly understood and; 3) the health system context – factors such as governance, financing structures and workforce- if unanticipated could adversely impact implementation.

Chapter 3 and 4

Using the Realist evaluation and modified MRC PE framework alongside RCTs of secondary and tertiary interventions, I was able to systematically examine important individual to policy (i.e. micro to macro) level contextual factors impacting on the outcomes of the intervention. For example, at the patient level- in Kanyini GAP, we found that the other factors that affect patient's adherence should be considered when prescribing the polypill. And that in hindsight, the polypill strategy does not seem to address a patient need for those who are on established medications, have a routine and are fully compliant. In ATTEND, we found that sustaining behaviour change for rehabilitation by patients and their carers in the face of significant emotional and financial pressures was a challenge. Therefore, in the development of future models of care, more ongoing emotional support will be required, and the timing of training (e.g. of mobility exercises) should align more appropriately with the stages of grief. These insights provided a deeper understanding of the how, for whom and why the intervention worked for.

At an organisational level, in the PE of Kanyini GAP, providers described that using a model of the absolute CVD risk assessment and prescribing of the polypill was acceptable but found the prescribing inflexibility a barrier. The health providers at Indigenous health services recognised that the polypill suited their chronic care model. In the PE of ATTEND, through the analysis of the participants' health care use, we were able to determine that patients from both randomised groups already had access to rehabilitation, which possibly diluted the effect of the intervention. However, the PE highlighted that the training of a family carer was an acceptable model of care and necessary for those with limited access to rehabilitation, and a future priority would be how to feasibly reach these populations. These micro to macro contextual findings resonates with the findings in Chapter 2- that greater emphasis on

formative research in designing primary care interventions is needed to align the intervention with the needs and responsibilities of local key actors, and to minimise unanticipated consequences due to context-specific barriers to implementation.

However, the manuscripts on the facilitators and barriers of collaborative research (in Chapters 3 and 4) also emphasised how such pragmatic trials are resource and time intensive for practitioners having to balance service delivery with research duties. This was a common theme across the practice-based research with general practitioners in private practice and in Aboriginal health services, community pharmacists (for Kanyini GAP); and in the context of busy stroke units in across India (for ATTEND). Therefore, a key implication is that investment in practice-based research infrastructure, capacity building of staff knowledge and expertise, is absolutely needed to enable effective generation of 'real-world' evidence with health practitioners. (1-3)

Chapter 5

In Chapter 5, we found that the economic evidence used in decision making differed from conventional notions of cost-effectiveness and was determined by specific institutional imperatives. Participants described that investing in disease prevention came with significant challenges, which included ideological barriers, delayed outcome measures, and implementation uncertainties. Whilst recommendations such as capacity development and dissemination have been well set out previously, the findings of this chapter suggest that we need to go further in reconciling the objectives of decision makers with the evidence that is generated. This requires more work on two fronts: tailoring the methods used by economists to better match the organisational imperatives of decision makers; and promoting amongst decision makers greater understanding and consideration of broader

societal and health sector perspectives. This will require significant infrastructure development to allow for ongoing monitoring and evaluation of population health strategies; and a greater emphasis on evidence co-production in order to overcome challenges unique to the prevention agenda.

Common findings (macro, meso, micro levels) and specific implications

Therefore, a common finding across Chapters 2 to 5 is that co-production of evidence between key stakeholders is needed to generate evidence relevant to the needs of the end-users (patients, providers and policy-makers). In Table 1, I summarise the results of Chapters 2 to 5 into categories of patient (micro), organisational (meso) and policy (macro) level factors, and I outline the specific implications of each study, which informs the overall implications of the thesis, discussed below.

Summary of Chapter findings by micro, meso and macro level factors	**Specific implications**	**Overall implications from the thesis**
Examples of micro (i.e individual) level		
Systematic review: Stakeholders were generally motivated to adopt/implement the complex intervention if it addressed the contextual gap in care i.e. intervention fit.	More emphasis on formative research in designing interventions is needed to align the intervention with the needs of local stakeholders.	*Use of a process evaluation framework to facilitate iterative stakeholder co-production of intervention theory will be beneficial.*
Kanyini GAP: For patients who do not have a routine for adhering to multiple medications and experience significant pill burden and costs, the polypill can facilitate regular taking of indicated therapy. In addition, providers found that using a model of the absolute CVD risk assessment and prescribing of the polypill was acceptable but found the prescribing inflexibility a barrier. The health providers at Indigenous health services recognised that the polypill suited their chronic care model and Indigenous patients found the polypill acceptable. The dosages of the polypill trialled were more suited to high risk CVD prevention patients.	The context of other factors that affect patient's adherence should be considered when prescribing the polypill. In hindsight, the polypill strategy does not seem to address a patient need for those who are on established medications, have a routine and are fully compliant. Other forms of the polypill could allow greater flexibility in prescribing. Incorporating the absolute CVD risk assessment with prescribing of the polypill would be an acceptable model of care. Future research on the cardiovascular polypill should include these considerations in their inclusion criteria and intervention development.	
ATTEND: The model of care was deemed necessary for those with limited access to rehabilitation. Sustaining behaviour change for patients and carers in the face of significant emotional and financial pressures was a challenge.	Majority of those recruited into the trial had access to non- trial rehabilitation though the intervention was hypothesised to be most relevant for the population with limited access to rehabilitation. Future work is needed to develop a way to feasibly reach populations with limited access to rehabilitation Moreover, while the model of care was acceptable, it could be improved to consider timing of patients' and carers' stages of grief. Greater emotional and possibly financial support may be needed in addition to the existing model of joint goal setting, mobility training, communication practice, and functional task training. A question remains, as to whether the intervention and recruitment might have been modified before the phase 3 trial if interviews with patients and carers was conducted alongside the pilot trial. Such in-depth exploratory work could inform development of intervention theory and implementation. The	

	process evaluation framework could potentially be used to facilitate the communication between stakeholders for the co-production of evidence in this iterative process.	
Examples at the meso (i.e organisational) level Systematic review: The extent to which key actors believed in and adopted their 'assigned' roles and responsibilities as part of implementing the complex intervention was a key theme. ATTEND: Though a key assumption was that the family-led model of care would address the lack of access, patients from both randomised groups already had access to rehabilitation.	Greater emphasis on formative research in designing primary care interventions is needed so that they are clearly aligned with the needs of local stakeholders and that the roles and responsibilities of key actors are better understood, and implementation strategies are in place. Using individual-level patient collected data on health care use to triangulate the qualitative findings was informative in identifying the access to non-trial rehabilitation. However, on hindsight, this was resource intensive to collect and may not always be feasible depending on project funding. Streamlining data collection with existing systems may be beneficial.	*Use of a process evaluation framework to facilitate iterative stakeholder co-production of intervention theory will be beneficial.* *Innovative and efficient methods of capturing health system context (such as access to care) are needed*
Kanyini GAP: Despite strong community and health service support, major investments in time and resources are required to ensure successful pragmatic RCT implementation in primary care and minimal disruption to already overstretched, routine services. ATTEND: Enablers such as respect, high level of intended research capacity building, and local leadership were essential to the successful completion of the large scale RCT. Challenges identified included the perceived ethical dilemma in conducting RCTs for those with limited resources; and the need for transparency, early	Researchers and funding agencies need to consider these additional resource demands in collaborative research with Aboriginal health services and in primary health care. Given the need to conduct pragmatic trials and the challenges in implementing such research across diverse stakeholder organisations- Investment in research infrastructure such as primary health care research networks will contribute to future studies being conducted more cost-effectively. International collaborations can generate locally relevant evidence but need to be locally driven. Investment into local leadership, providing adequate research support and funding and capacity building is key to successful collaborative research	*Ongoing research infrastructure and funding, and relational principles (e.g. respect and equality) required for effective co-production of research*

consultation and engagement of local health and research authorities in international collaborative research.		
<u>Examples at the macro i.e. policy level</u> <u>Systematic review:</u> Health system structures such as governance, health financing structures and workforce, were often mentioned as impacting on intervention implementation. <u>Prevention of NCDs:</u> Barriers to the investment in prevention include ideological considerations, lack of evidence of long term outcomes within short budget cycles, and the need monitoring and ongoing evaluation to justify for ongoing funding into prevention in the face of limited health budgets.	Greater ongoing exploration of policies, health financing structures should be done such that unanticipated consequences arising from context-specific barriers to implementation can minimised. Evidence needs to be fit for purpose through a greater emphasis on evidence co-production. At the same time more can be done to encourage stronger national leadership in prevention, for significant *infrastructure development for monitoring and evaluation* and for potential funders to take into account cost effectiveness evidence that highlights cross sector and societal impacts.	*Innovative methods of capturing health system context are needed and the need for stakeholder co-production across sectors.*

IMPLICATIONS FOR RESEARCHERS, POLICY MAKERS AND PRACTITIONERS

(1) An iterative end-user ('ground-up' and top-down') co-production of intervention theory would be beneficial

Ground up approach for local priorities

The PEs of both ATTEND and Kanyini GAP highlight how ground-up approaches are essential in the development of an intervention that addresses a local priority. Reflecting on Kanyini GAP and ATTEND, the underlying mechanisms for both trials was the use of evidence-based practice through implementation strategies (of a combined cardiovascular pill to improve adherence, and family-led rehabilitation to improve access to rehabilitation, respectively.) The question remains as to whether interviews with patients and carers earlier (e.g. during the pilot studies) may have led to modification of intervention theory and the target population (i.e. limiting recruitment to those with poor adherence to medication and with limited access to rehabilitation, respectively). (4) Therefore, as reflected in our discussion in ATTEND PE, researchers should invest more in the earlier phases of theory building of the complex intervention, a recommendation which is in line with recent literature. (5-7)

Top-down approach for sustainability

However, both cases also exemplify how 'top-down' approaches, are necessary to sustainably address NCDs, and improve health outcomes beyond a research project. Using Kanyini GAP as an example, 5 years post-trial, despite the intervention's effectiveness in reducing prescribing gaps and improving patient adherence to indicated therapy, and its potential cost savings to the health system (8, 9)- the intervention was *not* implemented into practice post-trial. Key barriers included the lack of a commercial case for polypill

manufacture, and hurdles related to pharmaceutical regulation in Australia. (10) Similarly, the systematic review in Chapter 2, provided evidence that policy and organisational level contexts (e.g. financing structures, workforce allocation) have to be carefully considered in the design and ongoing implementation of interventions.

Iterative co-production of intervention theory by different level stakeholders across time

In chapter 5, we spoke with Australian decision makers who highlighted how stronger national leadership is needed for a more concerted effort in prevention, and to inform investments of cost-effective interventions from a societal perspective. However, examples from UK have also shown the limitations of such top-down approaches (e.g. improving care through NICE recommended evidence-based guidelines) can also fail to improve outcomes if the end users (patients, health providers) do not find them useful or acceptable within their local contexts. (11) Therefore, as mentioned above, a 'bottom up' and 'top-down' approach is concurrently needed to strengthen health systems to effectively tackle NCDS. Globally, this is reflected in the growing recognition of the value of collaborative research, and in engaging communities in health systems research to enable patient-centred care, and effective dissemination and uptake of research evidence. (12-14)

The co-production involving different stakeholders would ideally be conducted together and concurrently, so that there is a shared understanding of the 'other's' perspectives and a common solution can be found. Future work lies in how to facilitate this co-production of evidence across multiple stakeholders in an effective and efficient manner, and identifying what suitable research tools (e.g. nominal group technique, online surveys) could be used.

My findings are in line with the co-production literature that states that the consultation with the key stakeholders should take place from the start. This includes the identification

of the problem, and the generation of the solution including the implementation strategies. This proposed iterative, co-production of complex interventions with key stakeholders have parallels with the qualitative improvement work (e.g. Plan, Do, Study, Act cycles) initiated by the health providers/ managers in the public and health sectors. The slight differences lie in the scope of who are engaged in the co-production of the interventions. For example, quality improvement initiated by managers using routine data and discussed with health practitioners- would often result in local individual and organisation (i.e. micro and meso) level strategies to improve outcomes. For example through discussion and education in regular morbidity and mortality meetings. In comparison, co-production of complex interventions in research may be between external researchers, clinicians, policy makers and consumers to develop the intervention content and implementation strategies, which would be trialled, adapted to local context, and then scaled up to other settings if found effective.

Therefore, for research to have an impact in the real world- more work needs to be done such as advocacy, active post-trial monitoring and co-production of research evidence by engaging with policy makers from the onset to help overcome health system barriers. (15) Using the PEs to explicitly examine contextual factors may be a way to generate evidence relevant to the breadth of stakeholders who are necessary in the co-production of affordable, effective and accessible models of care for the prevention of NCDs.

(2) Innovative and efficient methods to evaluate complex interventions is needed to inform end-users

Limitations of RCTs

In Chapter 5, we spoke to decision makers who highlighted that other approaches such as modelling may be particularly informative for guiding investment of population-based complex interventions targeting NCDs.(3) This suggestion fits into the recent discourse as to whether RCTs are suitable study designs for complex interventions. This is partly due to the dynamic change in the local context over the timing of a RCT. (16-18) For example, in Kanyini GAP, some health providers cited the emerging evidence (about the controversial use of aspirin for diabetic patients) as a barrier to the use of the combined polypill. Similarly, while the investigators had assumed the polypill strategy would address the cost barrier for the consumer who would pay for one medication instead of four- a government pharmaceutical reimbursement policy introduced during the trial meant that the cost barrier was not a contextual problem anymore. This re-emphasises the value of explicitly exploring 'contextual factors' as per the MRC framework, and the iterative approach so as to be more responsive to contextual changes. (19-22) Moreover, in ATTEND, some local health providers questioned on hindsight, whether RCT was a suitable study design. They described their ethical dilemma since patients in the control arm will have significant out of pocket costs in order to access rehabilitation.(2) These examples from the thesis highlight how in some circumstances, RCTs may not be a good fit for the evaluation of complex interventions.

Innovative methods required

While this thesis confirms that PEs of RCTs do provide relevant evidence for health systems strengthening- other innovative methods may provide more timely evidence for research translation. (13, 23, 24) Other suggestions in the literature include complex system science to investigate how an intervention interacts with the system at multiple points, the use of modelling tools to inform policy on complex public health interventions and the conduct of pragmatic PEs of interventions already in practice but may have a limited evidence base. (4, 25) Therefore, future research as to how co-production of evidence facilitated by innovative methods such as modelling, may inform the iterative development of cost-effective and patient-centred interventions.

(3) Co-production of evidence requires ongoing significant funding, time and resources for research infrastructure and relationship building

Facilitators to co-production

Being part of three collaborations, provided me a unique perspective of what the barriers and facilitators to effective collaborative research are. In Chapter 3 and 4, through the individual interviews and focus groups, I found that a crucial facilitator of effective collaborations was the stakeholders' shared motivation (researchers, practitioners, and local communities) to address a local priority. Other facilitators identified included stakeholders respecting each other's unique knowledge and expertise ('equality' and respect), to enable mutual knowledge exchange and capacity building to identify solutions. For example, in TAPPC, I observed that the common priority in exploring how to effectively address the rising NCD burden with limited resources enabled a constructive dialogue between policy makers in Treasury, health departments, health economists, health services researchers and insurance industries. This process of co-production provided the greater insights of the context (e.g. institutional imperatives, political considerations) which decision makers face, and how economic evidence generated could better suit their needs. Similar principles such as active end-user participation, facilitative leadership, equality amongst all stakeholders, and acknowledging that they can do more together (i.e. reciprocity and mutuality) have been reported in the literature to be the 'active mechanisms' of effective co-production. (12-14, 26, 27) (1, 2)

Barriers to co-production

However, I also observed that there were significant challenges in the implementation of such relational principles and values when the collaboration consist of stakeholders from

different disciplinary, cultural and social backgrounds. For example, the Indigenous research fellows in the Kanyini Vascular Collaboration shared their difficulties in 'researching' their own community and 'over-promising' the impact of their proposed research. They described how "*We remained anxious about our ability to do justice to the stories with which people had entrusted us. We feared that, as Indigenous people working for major research institutes, we might interpret people's experience as the white fellas expected us to*." (28) (1) The established relationships between all team members, and the leadership of a senior Aboriginal academic enabled such open communication in a 'safe space', (28) facilitated the critical discussions to address such concerns. (29) Similarly, for the ATTEND, the Indian neurologist had to have extensive discussions with the Indian research ethics committee, to be finally given permission for the conduct of the ATTEND trial. This was because the ATTEND RCT was mistakenly perceived initially as a 'foreign' driven research agenda due to the overseas funding and international collaborators. This led to a significant delay to the start of the trial. (2)

Anticipate additional time, resources required for effective co-production

Therefore, to enable effective co-production of evidence with end-users- funding bodies and researchers have to recognise and plan for the additional time, personnel and resources needed to build strong and respectful relationships through community consultation and effective communication. (1, 30, 31) From our experience, supporting research through structured processes will facilitate communication and co-production. This includes for example strong project management, regular updates facilitated by a core group, and the use of staged research processes such as focus groups (facilitated by the PE objectives) with stakeholders where concerns can be addressed and processes altered as required.

In addition, funding research infrastructure (including time, and personnel) would be beneficial due to the competing service delivery requirements while research is being conducted. (1, 2) In the Kanyini GAP PE, we found that despite strong community and Indigenous health service support, major investments in time and resources were needed during Kanyini GAP to ensure successful implementation and minimal disruption to already overstretched, routine services. (1)

Benefits of investment into research infrastructure for ongoing co-production

Importantly, investment in practice-based research infrastructure encouraged future ongoing research. For example, an Indian stroke research network (INSTRUcT) was formed as a direct result of the successful conduct of the ATTEND trial. The INSTRUcT network was established to address local research priorities and improve service delivery through mutual knowledge exchange. (2) Similarly, the Kanyini Vascular Collaboration and TAPPC have successfully received ongoing funding, for co-production with end users' (with local Aboriginal community health services, and policy makers respectively) to generate contextually relevant evidence. Therefore, to sustain locally driven and relevant research, it will be strategic to capitalise on existing network and infrastructure formed from individual project research funding. Findings from PEs of individual projects can inform future research priorities and facilitate an iterative stakeholder ('ground-up' and top-down') co-production of intervention theory to address NCDs.

STRENGTHS AND LIMITATIONS

1) Appraisal of PE framework

To inform the conduct of future PEs, I reflected on the thesis and appraised the ATTEND PE framework's strengths and limitations based on criteria of coherence/ completeness, applicability, usefulness and ease of application. (32) Box 1 provides further details, summarises my reflections, and implications for future PEs.

Completeness and internal coherence? Intervention theory and context

In ATTEND, I described the intervention theory through explicitly stating the broader contextual assumptions (e.g. lack of access), and the hypothesised intervention mechanisms to address them (e.g. training family carers can provide greater access to rehabilitation). I found this useful in guiding the analysis of a huge dataset, in explaining the variation of outcomes. However, I remain uncertain as to what is a meaningful level of detail that should be reported.

Five criteria from a pilot study to assess global health interventions such that the evidence generated is relevant for global health policy makers, seems to provide some clarity, and resonates with the findings of this thesis. (33, 34) The criteria include: intervention source (i.e. locally vs. externally driven), intervention theory (i.e. hypothesis of how it addresses the problem), rationale for the components (i.e. existing evidence), and a detailed description of the intervention as implemented (e.g. any adjustments, similar to TIDieR), and costs associated with implementation. For example, reporting the 'intervention source' is important because of the need for locally driven research to ensure better intervention fit

and its sustainability. Therefore, for future PEs, it would be helpful to test the inclusion of these criteria within the PE framework.

As noted in Chapter 2, the reporting of contextual factors in published PEs has been inconsistent, and guidance that is more explicit is needed on top of the MRC guidance and PE framework. In Kanyini GAP and ATTEND, I had categorised context as micro to macro level factors to aid data collection and analysis. In Chapter 2, key questions are presented (i.e. about intervention fit, roles and responsibilities and health system structures) that will be helpful to examine context in detail. Therefore, for future PEs, it would be helpful to include the use of a standardised template with key questions to facilitate a systematic examination of micro to macro contextual factors.

Advance theory? Development of intervention theory with stakeholders

In my application of the UK MRC PE guidance for health systems research, I found that this guidance has similarities to other implementation frameworks with the emphasis of a cyclical feedback loop, early and ongoing stakeholder engagement to better inform intervention theory and implementation. (22, 35, 36) Being explicit about the intervention theory from the start enables an iterative process i.e. an ongoing modification of intervention theory according to documented outcomes as the study progresses. This could facilitate a more nuanced understanding of for whom, how and why in different contexts an intervention is effective, beyond the binary outcome of 'is this effective?'

Applicability? Examination of Context

A key strength of the PE framework is exploring the interaction of the complex intervention with contextual factors. (37) Such evidence is needed to inform decision makers for whom,

how and why an intervention is suited for. By examining the micro to macro context, other gaps in care can be identified and inform future research priorities. For example, the PE of the ATTEND trial highlighted how policy level factors such as the health financing structures significantly impacts on patients' out of pocket costs; and is key to the impact and sustainability of the new model of care. These findings imply that there is need to review current funding policies to identify and implement funding models necessary to provide affordable care. Therefore, evaluating access and the policies underpinning service delivery and financing structures provide additional context. (38) However, such data collection (e.g. individual-level health care use) can be highly resource intensive, which may not always be feasible. (39) Streamlining and combining PE data collection with existing systems where possible may be beneficial. This would provide more timely data collection for a more responsive health system.(3)

User friendliness? Limitations of my approach, future research needed

In my experience with the ATTEND PE and the systematic review, I have found the MRC guidance and the modified PE framework to be '*user friendly*'. I have learnt and built on my experiences in the use of Realist principles firstly as a tool to pull the thematic findings from the Kanyini GAP PE into a coherent narrative. This experience reinforced to me the benefits of using the Realist principles in the synthesis of the findings. Therefore, I was keen to use the MRC framework which is heavily influenced by the Realist principles for the ATTEND process evaluation. I found that context-mechanism-outcome configuration provided a useful and adaptive framework for the systematic examination of our contextual assumptions and hypothesised causal mechanisms to provide plausible explanations for the variations in the trial outcomes.

Assessment criteria	Findings from the thesis	Implications
Completeness and coherence of framework i.e. Are definitions clear? Is the framework comprehensive?	Systematic review: Ambiguity in the reporting of context and intervention theory. ATTEND: Initial difficulty in describing the intervention theory. A useful strategy was describing the contextual assumption that the intervention specifically addresses. Nevertheless, still uncertain about the level of detail to report on.	Use of PHC template from Chapter 2. Incorporate contextual assumptions and intervention components in the description of the intervention Future research to test the inclusion of other criteria such as source, details of implementation and costs.
Development and advancement of theory i.e. Is the framework compatible with existing theories, and does it advance theories? Does it show the relationship between components of the frameworks?	Systematic review: PE framework encourages the use of existing theoretical frameworks and advancing the intervention theory for whom, how and when it works. ATTEND/KGAP: refined our understanding for whom the interventions are applicable for.	Encourage the use of relevant existing theoretical frameworks specific to research question. Greater consistency in the reporting of hypothesised intervention theory is needed in PEs.
Applicability i.e. Can the framework be applied to different types of interventions? Can the framework be applied to systematic reviews and different study designs? Does the framework portray complexity?	Systematic review: Successfully applied to the synthesis of different types of primary care interventions. ATTEND/KGAP: applied to different interventions and portrays micro to macro level factors as seen in Table 1.	Encourage the use of the PE framework outside the field of NCDs. Data collection can be resource intensive, streamlining and combining PE data collection with existing systems where possible may be beneficial.
User-friendliness i.e. Can the framework be applied feasibly and easily?	It has been applied in this thesis and in other projects.	Future research documenting researchers' collective experiences of the MRC PE framework needed. Future research to investigate if the PE framework can be a useful tool in the co-production of evidence through an iterative approach.

Abbreviations: ATTEND: Family-led rehabilitation post stroke in India randomised controlled trial ; KGAP: Kanyini-Guidelines Adherence with the Polypill randomised controlled trial; MRC: Medical Research Council; NCD: Non-communicable diseases; PE: Process Evaluations; PHC: Primary health care.

I found that the PE framework seemed to provide an intuitive approach to investigate different types of complex interventions and study designs, as it has been easily adapted to other projects that I have been involved in (e.g. implementation studies, cluster RCTs). Future research documenting researchers' collective experiences of the MRC PE framework will further ascertain its' user-friendliness and advance its' methodology.

A limitation of this body of work is that while I highlighted the role of PE in formative work, this was not part of the case studies in Chapters 3 and 4 due to the timing of the PEs. Future research is needed to determine whether an iterative approach using this proposed PE framework to develop and intelligently adapt interventions over time would produce greater impact on practice and policy.

2) Reflexivity

As stated in the preface, through my previous experiences, I have an underlying assumption that primary health care which is affordable, accessible and of high quality is necessary to reduce health inequity and inequalities. Therefore, a limitation of this thesis is that this assumption may potentially bias my interpretation of the interviews. To mitigate this, there has been a strong emphasis on reflexivity by all PE team members in the conduct of the interviews and analysis. Another strategy to minimise such bias has been having another researcher to code and analyse the interviews together with, and critically assess each other's interpretation prior to knowing the trial results.

However, my previous clinical experiences also provide a deeper appreciation of the complexities of health systems research and the importance of 'context.' For example, when working at the HIV clinic in Uganda, I asked that a patient have an electrocardiogram done, not realising the impact of the significant out-of-pocket costs that resulted for the family.

This oversight was because I was used to ordering such investigations in the context of Australian public hospitals, where such costs are covered fully by government reimbursements. It was that informative experience among others, which influenced me to explore the impact of costs in PEs.

I acknowledge that I am from a different cultural, socio-economic and professional background from the study participants, which may influence my interpretation of the interviews. For the PE of Kanyini GAP, I am heavily indebted to the Indigenous research fellows who welcomed me into their communities and guided me to conduct the research in a culturally safe manner, and an Indigenous researcher who provided the much-needed confirmation of our analysis. Similarly, for the PE of ATTEND, the local Indian staff were essential in checking my underlying assumptions, and in providing the critical triangulation of their assessment of the PE findings. For the TAPPC qualitative study, I found that my 'outsider' perspective (i.e. not being a policy maker, or health economist) was valuable. It enabled me to have a non-biased approach (i.e. about the value of economic evaluations) in aligning both the perspectives of the policy makers and health economists in the synthesis and write up of the manuscript.

3) Key strengths of the thesis

First, that the overall findings are based on primary data from all levels of stakeholders (consumers, practitioners and policy makers) to triangulate and inform the overall theme that both top-down and bottom- up initiatives are concurrently required for research to have impact in practice and policy. Second, is the unique benefit of hindsight over time as to the longer- term impact and limitations of collaborative research beyond the funding of an individual research project. Third, is to be able to critically appraisal the MRC framework

based on the findings of the systematic review and strengths and limitations of the Kanyini GAP and ATTEND case studies.

CONCLUSION

In the thesis I demonstrate that PEs are needed to explore for whom, how and why a complex intervention has an impact- and in doing so, help to strengthen health systems. This is in the context of a rising global NCD burden due to complex proximal and distal determinants. I found that to effectively address NCDs, 'ground-up' approaches alone are not sufficient and concurrent 'top-down' approaches are needed. This requires greater co-production of evidence with the breadth of stakeholders (in addition to patients and practitioners) involved in the prevention of NCDs. Policy makers and funders have to be engaged from the onset of research to ensure health system barriers (such as financing structures, health workforce, costs of medications) can be overcome. However, to effectively co-produce high quality evidence, *significant investment* is required. This includes investment in practice-based research infrastructure, time, capacity building and recognising the time and efforts needed to build critical relationships between stakeholders.

PEs with its focus on iterative stakeholder input to develop a clear intervention theory within the local context can be a useful tool for the effective co-production of locally relevant evidence. Reflecting on the application of the MRC PE framework through the systematic review and the ATTEND PE, I found that its strengths are that it *advances theory*, is *applicable* and is '*user friendly*'. The micro to macro contextual findings can also inform future research priorities, and improve the health system through capitalising on research networks formed. (13, 40) However, to further improve on this PE framework and make it more complete and internally coherent- there needs to be greater clarity in definitions and

reporting of context and intervention theory. Such modifications should improve the transferability of interventions and promote a more systematic examination of proximal and distal contextual factors.

Future research should include greater emphasis on formative and developmental work, to ensure that the intervention meets local needs, and minimise implementation failure due to unanticipated health system factors. I envision that the continual use of PE will strengthen health systems through facilitating co-production of much needed patient-centred complex interventions, and using the intelligence gained from such evaluations to enable an ongoing process of intervention improvement. As the global community continues to tackle chronic health conditions with complex holistic solutions using implementation science, it is likely that the demand for innovative health system research using co-production and iterative evaluations (such as PEs alongside pragmatic trials), will increase. This will enable effective complex interventions to be sustainably implemented- hopefully making small but essential steps in strengthening the local health system such that health care is affordable, accessible and of high quality *for all*.

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APPENDIX 1: AUTHORSHIP ATTRIBUTION STATEMENT

The work contained in this thesis has benefitted from collaboration with a number of other researchers. The contributions of all co-authors has been detailed at the start of each chapter. In addition to these statements, in cases where I am not the corresponding author the manuscripts presented as Appendices to this thesis, permission to include the published material has been granted by the corresponding author.

Hueiming Liu  29 June 2018

As supervisor for the candidature upon which this thesis is based, I can confirm that the authorship attribution statements contained in each chapter are correct.

Stephen Jan  29 June 2018

APPENDIX 2

Appendix Overview

This appendix comprises of 3 publications from the Kanyini Vascular Collaboration (KVC) titled: (1) Facilitating engagement through strong relationships between primary healthcare and Aboriginal and Torres Strait Islander peoples. (2) Effectiveness of chronic care models: opportunities for improving healthcare practice and health outcomes: a systematic review. (3) Factors influencing the implementation of chronic care models: A systematic literature review.

KVC conducted a program of research which included a large qualitative study across Aboriginal community health services in Australia, and a systematic review of chronic care models of care. The qualitative study aimed to understand what an ideal health system would look like, through the perspectives of Indigenous community participants and health practitioners. The first manuscript reports on the health system factors affecting engagement with Aboriginal and Torres Strait Islander peoples. The second and third manuscript reports on the effectiveness, and the implementation barriers and facilitators of chronic care models.

Authors' Contributions:

Qualitative study: AC, AB conceived the idea for the study, and obtained funding. AC, AB, JB, JDVries, BF, SI, RM, PS, BR, ST, HL, DP conducted the interviews, and contributed to the analysis. All authors provided critical input in the analysis, synthesis of the findings and interpretation. CD drafted the manuscript, and its revisions with input from other authors.

Systematic review: CD participated in the design of the study, the literature search, assessment of quality and bias, extraction of findings and drafting the manuscript. JB participated in the extraction of findings and drafting the manuscript. HL and MT participated in the literature search, assessment of quality and bias and extraction of findings. SP participated in the design of the study, the literature search, assessment of quality and bias, and extraction of findings. AB participated in the design of the study. All authors read and approved the final manuscript.

Publications details:

Davy C, Cass A, Brady J, DeVries J, Fewquandie B, Ingram S..**Liu H** et al. Facilitating engagement through strong relationships between primary healthcare and Aboriginal and Torres Strait Islander peoples. Australian and New Zealand journal of public health. 2016

Davy C, Bleasel J, **Liu H**, Tchan M, Ponniah S, Brown A. Effectiveness of chronic care models: opportunities for improving healthcare practice and health outcomes: a systematic review. BMC Health Serv Res. 2015 May 10;15(1):194.

Davy C, Bleasel J, **Liu H**, Tchan M, Ponniah S, Brown A. Factors influencing the implementation of chronic care models: A systematic literature review. BMC family practice. 2015

Manuscripts:

Facilitating engagement through strong relationships between primary healthcare and Aboriginal and Torres Strait Islander peoples

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Abstract

Objective: Given the high prevalence of chronic disease, it is of concern that access to and sustained engagement with primary healthcare services by Aboriginal and Torres Strait Islander Australians is often far lower than would be expected. This study sought to explore ways in which relationships can support sustained engagement with healthcare services.

Methods: Semi-structured interviews were conducted with 126 Aboriginal and Torres Strait Islander participants with and without chronic disease and 97 Aboriginal and Torres Strait Islander and non-Indigenous healthcare providers, healthcare service managers or administrative staff.

Results: Our findings indicate that when faced with acute health issues, Aboriginal and Torres Strait Islander participants did prioritise care, provided that the service was both physically and emotionally welcoming. Trustworthiness of healthcare providers and strong relationships with patients were the most important factors for encouraging sustained engagement overtime.

Conclusions: Responsibility for sustaining relationships does not rest solely with Aboriginal and Torres Strait Islander patients. Rather, healthcare providers need to commit to the process of building and maintaining relationships.

Implications: First and foremost healthcare providers should take time to establish and then maintain relationships. Healthcare services can also contribute by ensuring facilities are welcoming for Aboriginal and Torres Strait Islander peoples.

Key words: primary health care, Indigenous health, chronic disease, service delivery

There are significant disparities in health status and life expectancy between Aboriginal and Torres Strait Islander peoples and non-Indigenous Australians. Chronic conditions account for the bulk of these disparities.[1] Cardiovascular disease is the single leading cause of death,[2] diabetes is at epidemic levels,[3] and rates of chronic kidney disease are also disproportionately high compared to other Australians.[4] Given the high prevalence of chronic disease, it is of concern that access to and use of primary healthcare services by Aboriginal and Torres Strait Islander Australians is often far lower than would be expected.[5-7] Furthermore, as chronic disease is, by definition, often a permanent condition in a person's life,[8] sustained engagement with primary healthcare is important for long term management and wellbeing in the face of illness. Rates of sustained engagement with healthcare services over time are, however, also far lower than would be expected given the high burden of chronic disease experienced by Aboriginal and Torres Strait Islander peoples.[5]

A number of researchers have investigated the reasons why engagement rates are suboptimal. Some of the broad reasons Aboriginal and Torres Strait Islander peoples are dissuaded from engaging with care include the lack of culturally appropriate healthcare services, racist or discriminative behaviour by healthcare staff, the cost of seeking healthcare and a lack of time or ability to attend appointments.[9,10] Aboriginal and Torres Strait Islander peoples in remote communities may be particularly disadvantaged due to the lack of availability of a broad range of healthcare services.[11,12] Where services do exist, it is often difficult to build lasting relationships with healthcare providers due to the high turnover of staff.[13] According to the 2008 National Aboriginal and Torres Strait Islander Social Survey, almost 30% of Aboriginal and Torres Strait Islander peoples over the age of 15 living in

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Submitted: November 2015; Revision requested: December 2015; Accepted: March 2016
The authors have stated they have no conflict of interest.

Aust NZ J Public Health. 2016; 40:535-41; doi: 10.1111/1753-6405.12553

urban environments have also experienced problems accessing healthcare services.[14]

Some researchers have suggested various ways in which access could be better facilitated. For example, ensuring that Aboriginal and Torres Strait Islander peoples are employed within healthcare services can enhance relationships with patients and promote access.[15] Creating a healthcare service that belongs to and is part of the community also improves access to healthcare services for Aboriginal and Torres Strait Islander peoples.[16] For remote communities in particular, outreach services through which care is provided within the community setting have also been shown to improve rates of engagement with patients.[17] Few researchers, however, have specifically considered the question of how to support sustained engagement within this context.

This paper draws on findings from the Kanyini Qualitative Study (KQS) to identify how sustained engagement between Aboriginal and Torres Strait Islander peoples and their healthcare services can be better supported. The KQS is one of a series of discrete yet inter-related studies conducted by the Kanyini Vascular Collaboration (KVC) team (http://www.kvc.org.au/) with Aboriginal and Torres Strait Islander communities and primary healthcare partners in New South Wales, Western Australia, South Australia, Queensland, the Northern Territory and Australian Capital Territory.

Methods

Four ethics committees approved the KQS, one in Central Australia, one in New South Wales and two in Queensland. Five healthcare service sites agreed to participate in the study. According to the Australian Standard Geographical Classification System,[18] two services were in capital cities (RA1), two were in major regional centres (RA2-3), and one was in a remote area (RA4). Three of the participating healthcare services were Aboriginal Community Controlled Health Organisations (ACCHOs), and one was a government-administered Aboriginal healthcare service. The final site had services provided by a number of government healthcare services as well as four ACCHOs.

Our research team comprised a group of geographically dispersed Aboriginal and Torres Strait Islander and non-Indigenous researchers, many of whom were also clinicians. The team also included five Aboriginal and Torres Strait Islander Research Fellows (ARFs), four of whom were embedded within KVC partner healthcare services as half-time Aboriginal Health Workers whilst also working half-time on this study. The fifth ARF was employed within a collaborating research organisation but had been an Aboriginal Health Worker prior to participating in the research. Our team also included a further five research staff who had experience in undertaking qualitative research. One researcher identified as an Aboriginal Australian while the remaining four were from a variety of cultural backgrounds.

From July 2008 to February 2010, the ARFs and the qualitative researchers within our research team conducted semi-structured interviews with 223 participants (Table 1). Of the 126 Aboriginal and Torres Strait Islander community participants, 111 identified as Aboriginal, 10 as Torres Strait Islander and five as both Aboriginal and Torres Strait Islander. A further 97 participants who were Aboriginal and Torres Strait Islander or non-Indigenous healthcare providers, healthcare service managers or administrative staff also participated in the study (Table 2). A purposive sampling technique[19] was utilised in order to gain perspectives from a range of both community members living with chronic disease and their carers, as well as a variety of clinical, administrative and management staff working in the services that provided care. Community participants were invited to participate in the study by the ARF in their area, while healthcare providers were invited to participate at opportune moments including during staff meetings. While written informed consent was obtained from all participants, records were not kept in relation to the number of community members or staff who chose not to participate. Interview guides were developed and piloted prior to the first interview. Separate guides – one for community members and one for healthcare professionals – contained on an average of 13 questions incorporating suggested 'prompts'.

Our entire research team was involved in data analysis which began soon after the initial interviews were completed. Although the qualitative analysis computer software program NVivo 8 was used to assist with organisation of data in subsequent stages of our analytic process, initially a 'manual' approach was used to inductively code interview data to emergent themes, in order to establish the underlying principles of qualitative data analysis for team members not familiar with this research method. After reading and re-reading the interview transcripts, themes were

Table 1: Summary characteristics of all study participants.

	Aboriginal and Torres Strait Islander participants (n=126)	Healthcare providers (n= 97)	Total participants (n=223)
Female	71 (56%)	62 (64%)	133 (60%)
Male	55 (44%)	35 (36%)	90 (40%)
Urban	43 (34%)	30 (31%)	73 (33 %)
Regional	27 (21%)	38 (39%)	65 (29%)
Remote/Very Remote	56 (45%)	29 (30%)	85 (38%)

Table 2: Summary of healthcare provider participant characteristics.

		Aboriginal Identity		Type of Healthcare Service		
Healthcare Provider Participants	No.	Aboriginal and Torres Strait Islander	Non-Indigenous	ACCHO[a]	Gov[b]	NGO[c] Private Sector
Aboriginal Health Worker	17	17	-	16	1	-
Nurse	29	4	25	13	14	2
Doctor	10	-	10	8	1	1
Allied Health	6	1	5	5	1	-
Registered Nurse manager	4	1	3	2	2	-
General Practitioner manager	6	2	4	4	2	-
Aboriginal Healthcare Worker manager	3	3	-	1	2	-
Non-clinical manager	5	3	2	3	2	-
Board member	2	2	-	2	-	-
Chief Executive Officer	4	3	1	4	-	-
Administrative staff (receptionist, driver, etc.)	9	7	2	6	3	-
Healthcare adviser	2	-	2	-	-	2
TOTAL	**97**	**43**	**54**	**64**	**28**	**5**

a: Aboriginal Community Controlled Health Organisation
b: Government-run Service
c: Non-Government Organisation

identified which then became the subject of multiple and enthusiastic team discussions. These discussions were integral to our iterative analytic approach and, critically given the nature of this research, allowed team members to compare perspectives, interpretations and understandings. Commensurate with interviewers' skills and experience, themes highlighted during these discussions were explored during subsequent interviews across the sites. Although at the outset informed by grounded theory techniques,[20] our analytic process became subject to real-world challenges, in particular resourcing and time constraints, which arose from conducting a large, complex, multi-site study with a geographically-dispersed research team. Analysis and interpretation of data at the between-sites level was undertaken from May 2012 to July 2013. Findings from this between-site analysis are presented and discussed below.

Results

Our findings indicate that a number of factors sustained engagement between Aboriginal and Torres Strait Islander peoples and their healthcare services. We also found that competing demands and the stress associated with being diagnosed with chronic disease meant that care was not always a priority. However, when faced with acute health issues, Aboriginal and Torres Strait Islander peoples did prioritise care if the healthcare service was physically, relationally and emotionally welcoming. In particular, healthcare providers who were able to build strong and trusting relationships and who cared for more than just the physical needs of their patients encouraged care seeking. While strong relationships were also one of the keys to sustaining engagement, when relationships broke down as a result of discrimination or distrust, Aboriginal and Torres Strait Islander peoples were likely to disengage from healthcare services. This in turn impacted on future engagement.

Healthcare – 'Health' was not always a priority

Our study identified a number of reasons why Aboriginal and Torres Strait Islander community members did not always engage with primary healthcare services. In many cases these were related to the number of competing demands that Aboriginal and Torres Straits Islander peoples negotiate on a daily basis. It appeared that there was rarely just one problem, but a whole range of needs that required attention before people could think about seeking care for themselves.

> *Because sometimes people miss out on their appointments because they don't have cars, they don't have money because they're all on welfare. And then there's a lot of children in the house, you've got to find a babysitter, you've got to take some kids with you, and there's a problem, and a lot of our people miss out on appointments that are very, very vital to their health issues, and they've got to go ...we definitely need transport for our customers.* (Aboriginal, Community participant, Female, Urban)

For those living in remote areas, maintaining engagement with required treatments often involved an inability to participate in cultural activities, moving away from family and community and dislocation from their Country. The term Country is used in relation to the spiritual connections that Aboriginal and Torres Strait Islander feel with the land. Many community participants found this separation unsustainable, to the extent that some prioritised their connections with family and community over opportunities to prolong their life.

> *People get homesick when they go into town to stay on the [dialysis] machines. They miss their bush food, they miss everything. Even their family members, they've got to like be split apart... Some people I know from [community names withheld] they just gave up hope and just came back to the communities and just long stay with the families, they just passed away...They miss out on a lot.* (Aboriginal, Community participant, Male, Very Remote)

As perceived by a healthcare provider participant, even when treatment was available closer to home, it did not necessarily mean that healthcare providers understood either the client or the social and kinship contexts in which they lived.

> *It's also just the momentum of the system to get the most overwhelmed person and put them in the most overwhelming situation by virtue of the fact that none of the Australian graduates want to work in this little Aboriginal community "Well we'll just get someone from Nigeria and just plonk them there without any understanding of Medicare, Australian medications, the prescribing system, the health care system, with minimum orientation and no cultural orientation".* (Non-Indigenous, Practitioner, Female, Remote)

The possibility of being diagnosed with chronic disease was so stressful for some that they chose not to engage with services.

> *I don't know, I don't want to know what's wrong with me half the time, I'm getting around fine and that, you know … you kind of get around fine and then go to the doctors and get a test done … they find what's wrong with you … and then you start stressing out about it … that's the way I am, I think what you don't know, you know, whereas [my husband] he's different … he's got to go and … I even said to him if I get taken to hospital and they tell me I haven't got long to live … don't tell me … I don't want to know … I just really stress out …* (Aboriginal, Community participant, Female, Urban)

Reprioritising – Opportunities to engage

Until the seriousness of their condition became undeniable, for many community participants leading busy lives, healthcare had not been a major focus.

> *Yeah, that was me exactly before, I was exactly like that [finding it hard to maintain motivation to stay healthy]. I'd walk every now and again, but it's not until something drastic or dramatic happens to you and then it makes you reassess your life and then you can see the path you were going down. Like when you are sitting in a bed and you have got three or four doctors doing different things… that's an eye opener, you know. I thought, "Oh, shit I was doing something wrong".* (Aboriginal, Community participant, Male, Regional)

In many cases, community participants described engaging with healthcare services only after acute events such as a heart attack. Some were also motivated to engage after others in their family or community experienced a life-threatening episode.

> *[When a bloke I played touch football with] had the heart attack it really made me sit up and think … we took it for granted, our health. We thought we were immortal. We could just live forever. But when he had the heart attack … I went and got checked up … But you know, that was one story where what happened to them changed a lot of the way people thought … Now men are starting to see well, you know, you need to look after it [your health] …* (Aboriginal, Community participant, Male, Urban)

These types of traumatic events often proved to be turning points in peoples' lives. One community participant spoke of reassessing his life after a sudden heart attack and described engaging more regularly with healthcare providers, which in turn helped him manage his health.

No I didn't [have a regular doctor]. You know what black guys are like, they don't like seeing doctors … Yeah [since my heart attack] I see the doctor quite regularly … it makes me feel good every time I go around and see the doctor, and [he] checks all my weight and everything and my size around the waist and it's all coming down, so that's good … so I was sort of getting in tune with my body. (Aboriginal, Community participant, Male, Regional)

Some healthcare provider participants attributed the increasing awareness of the impact of chronic disease to direct experiences within the patient's family and community, especially when *"[t]hey can see there're a lot of people that are dying young around them."*(Aboriginal, Practitioner, Female, Regional). These providers reaffirmed the community perspective that life-threatening events frequently proved the catalyst to long-term engagement.

One of those guys…he's just such a great success story in that…I mean it's terrible he had his big scare and went into hospital and nearly died, but he's quit smoking and he's just taken his life into his hands as a result, and he's so happy … And it's really lovely to see him thriving. (Non-Indigenous, Practitioner, Female, Regional)

Welcoming spaces – Continued engagement

While acute events may motivate people to engage with care, both community and provider participants believed that having the right type of healthcare service in place was crucial to supporting continued engagement. Welcoming spaces where community members felt comfortable, accepted, and able to build strong and trusting relationships with healthcare providers encouraged people to remain engaged with care. This 'welcoming space' did not just represent the physical place but also encompassed emotional (feeling supported and cared for), and relational (the quality of relationships between patients and providers) elements. One of the most important aspects of a welcoming space was the presence of Aboriginal and Torres Strait Islander staff.

Community members needed to feel the healthcare service was *"their place"* (Non-Indigenous, Manager, Female, Regional) and noted the importance of feeling well treated.

I can only answer you for myself, but you could ask any other Aboriginal person that wants to be cared for and improve their health and to stay healthy, they'll tell you that the Doctors that work for the Aboriginal Medical Service, to my way of thinking and talking is they're good people. They really care for the Aboriginal people. And [name withheld] I'm not only saying that because I'm a regular and we know one another, I'm saying this from my heart and I know the people who attend this place and come here for their check-ups. They're very pleased with how they're treated. (Aboriginal, Community participant, Male, Urban)

The use of health posters depicting Aboriginal and Torres Strait Islander people, as well as paintings and other artefacts that demonstrate the commitment of staff to providing culturally appropriate healthcare, were also considered to be important.

… It's right from when you walk through the door, brother. It's when you walk in, you see the paintings up there, you see the artefacts, you know. All that sort of stuff makes you feel welcome and makes you want to sit in the waiting room for an hour to wait … half an hour, five minutes, whatever. Because you feel that, you know, you're okay there. Yeah. And the ladies in the front, they're lovely. They're all good. Really good crew. I don't think I've had a bad experience over there … (Aboriginal, Community participant, Female, Urban)

Aboriginal and Torres Strait Islander staff – whether doctors, nurses, healthcare workers or administration officers – were key to creating the much needed feelings of belonging and acceptance.

So, it's very important to have your own people and you feel open to talk to, that sort of stuff. You go to a non-Indigenous doctor and they look at you sometimes indifferent, and you can't be sort of more open to them, sort of thing. (Aboriginal, Community participant, Male, Urban)

Sustained engagement wasn't just about Aboriginal and Torres Strait Islander staff however. Strong relationships with all healthcare staff were fundamental to community members' long-term engagement with a healthcare service.

You fellas in there [staff in the health centre] give us, the community members, a reason to come in. I don't know whether youse even know that. But because of the way you fellas handle all your responsibilities, you make us want to come there. There are lots of places in our state, in our nation, where it's because of the people within the organisation that people don't attend … You look at those organisations where people aren't going, why is that? (Aboriginal, Community participant, Female, Urban)

Relationships with healthcare staff were considered by many participants to be just as - if not more - important than the type of building or the quality of medical care on offer. When healthcare providers understood patients' care needs and demonstrated genuine interest in the peoples' lives, community participants reported feeling welcomed, respected and accepted.

They're [medical staff] caring, first of all. They care what's going on. Like everything. Like they'll ask, first of all health and they ask about home. And then with me, like I said, like time is the biggest thing that I don't have and they just take the time out just to say, something nice, like you know, like I'm anaemic so my doctor will look up [my blood results] and say, "Oh you're getting it up there, yeah very good woo hoo!" And I'll feel better just walking in, I didn't come in to see you about that, but that's good, like a help for me. (Aboriginal, Community participant, Female, Urban)

Closely aligned with building relationships were the provider's ability to be flexible and their commitment to maintaining a connection with patients. Providers who focused on taking "*a motivational interviewing approach*" (Non-Indigenous, Manager, Male, Urban), treating each encounter as an opportunity to help support behavior change, if not on that day, then at another time in the future, believed that this was particularly successful in supporting sustained engagement. Community participants also emphasised the need to achieve understanding within care encounters.

I think a good doctor and a good nurse is someone that actually talks to you and not talk at you … not just babble on and keep talking and you don't have a clue and they're not going to stop and help you understand. (Aboriginal, Community participant, Female, Remote)

Services that were able to provide this more holistic approach to care were highly valued.

Yeah. It's the holistic approach over here. It's the whole bundle. You know, it's the environment, it's the people, it's the care, you know, the service, right through to, the whole lot. From admin right through to your doctors and where you're sitting. It's really good. (Aboriginal, Community participant, Female, Urban)

Healthcare services that went beyond merely providing medical treatment to become part of the community were held in particularly high regard. This, in turn, encouraged sustained engagement.

They've got a high-quality preschool next door. They charge us bugger all compared to the rest of them. They pick them up and drop them off. They'll pick me up. They'll look after me. They look after my teeth. They look after me. If I need a lift, no worries. They'll come and pick me up. They'll actually be concerned. Like, I've got more people caring about me here than I've had in my own neighbourhood in the last five years, you know…And this year, I have been using them. And I've been a lot better off. (Aboriginal, Community participant, Male, Urban)

Hindering engagement – Distrust and discrimination

Often trust between Aboriginal and Torres Strait Islander communities and their healthcare services did not come easily, with both clients and providers having to *"work hard for it"* (Aboriginal, Practitioner, Female, Regional). Interruptions to patient-provider relationships occurred as a result of a breach of this trust, which then needed to be regained over time in order to re-establish the same level of engagement.

As workers, if we break our connection with people, we can go back to 'delicate' [engagement] from 'robust' very easily. That just because we think we've achieved a robust relationship, if we then disengage for any reason … then we actually go back to at least 'delicate'. We don't remain in the 'robust'. We've got to re-earn our 'robust' credentials … And I think that does show how profoundly underlying is the basic distrust, however much people may know that they have to rely on outside service providers. (Non-Indigenous, Practitioner, Female, Remote)

While some people were deterred by the stories they heard from others, distrust also resulted from firsthand encounters of racism or inferior treatment.

… a lot of people didn't want to go there [the local mainstream health service] because they felt the place was unfriendly, the staff were not friendly towards them and there was a lot of attitudes happening, people felt they were discriminated against, and the place was very sterile … it wasn't like a, it wasn't a comfortable environment … and people spoke … didn't speak in the way we speak … like very abrupt, loud and abrupt, communication wasn't there too, you know? Just that lack of understanding in how you talk, the tone you use for Indigenous people … so there was that, where there was no probably no cultural knowledge with the staff … Yeah, like discrimination, racism, or you know, just ignorance and no sensitivity and no understanding of Indigenous health issues … (Aboriginal, Community participant, Female, Urban)

Community members as well as healthcare staff participating in this study dwelt on the emotional impact of these situations. Some described 'losing faith' in healthcare services and people walking away from necessary care as a result.

I don't think the community have a lot of faith in mainstream, and I have to admit I've seen it where I've taken a client, or a couple of clients, to the hospital, and they're just treated atrociously. And I don't think it was because of their condition … It was because they identified as being Aboriginal … one of our clients was admitted because he had a heart attack, and she [one of our nurses] went in to visit him, and she could actually hear the nurses in the hallway speaking about him. And she walked out and she tore strips off them, because they were just so derogatory to him. And he ended up getting up and walking out. (Aboriginal, Manager, Female, Urban)

Yet, healthcare providers were often perplexed and frustrated when patients disengaged from care. Some were concerned with people's apparent resistance to engaging with care, believing that it was about not "*being dominated by white people*" *(Non-Indigenous Practitioner, Male, Remote)*. Other providers realised that there may be many reasons why people choose to disengage and importantly, recognised that healthcare services may need to apply multiple strategies to support patients to remain engaged.

But when you've got people who are clearly already disempowered, and disadvantaged, to say that they should be taking responsibility … "It's up to them to come into the clinic, and if they don't present, well then that's their own decision". How can we say that they've made an informed decision? That's, you know, another ethical question. … And there's absolutely no one strategy … one doesn't fit all sort of sizes. So you've got to have a range of strategies. (Non-Indigenous, Manager, Female, Remote)

Discussion

Our study found that a number of factors supported sustained engagement between Aboriginal and Torres Strait Islander peoples and their healthcare services. These included opportunities that arose after life-threatening events. Nevertheless, accessing healthcare services and remaining engaged in care is likely to require more than simply the availability of medical facilities in times of need. Sustained engagement was most likely when community members felt that the healthcare service was part of their community and where patients could have faith in and develop strong relationships with healthcare providers. These relationships needed time to develop and were built on the foundation of trust and respect. Importantly, sustaining these relationships required flexible approaches to care which acknowledged and accounted for competing interests, accepting that people may not always prioritise their own healthcare needs.

While Aboriginal and Torres Strait Islander staff were more likely to form a strong connection with patients,[21] participants in this study also acknowledged the importance of developing relationships with non-Indigenous healthcare providers.[22] Patients often found relationships more difficult to form with non-Indigenous healthcare providers, needing a willingness on the part of these providers to understand healthcare from the perspective of Aboriginal and Torres Strait Islander patients and their broader community and kinship contexts.[23]

Developing these types of relationships went well beyond the use of a patient-centred care approach. Defined as care that is "respectful of and responsive to individual patient preferences, needs, and values and ensuring that patient values guide all clinical decisions",[24,p6] patient-centred care does little to acknowledge the importance of building relationships with the community in order to better understand the social and cultural context in which the patient lives. Examples of tailored services include the use of local language wherever possible when communicating with patients or providing appropriate healthcare facilities and services that accommodate cultural sensitivities and expectations. The notion of tailored care also assists with prospectively planning to meet the particular needs of the local population rather simply responding to the patients that walk through their door.[25]

Developing and sustaining these types of relationships will take time.[26] In the context of colonial history and perpetual racial discrimination experienced by Aboriginal and Torres Strait Islander peoples,[27,28] healthcare providers will need to demonstrate respect for their patients, their patients' family and the communities they serve. Community members will also need to make time to develop trust and faith in their healthcare services. Time is also needed to establish

effective communication strategies, ensuring that healthcare providers understand their patients and that patients understand their healthcare providers.[29,30] Finally, time is necessary for healthcare providers to engage with and understand the social and cultural aspects of the local community in order to better understand the needs of their patients.[31] All are especially important for non-Indigenous healthcare providers who have little previous knowledge of the social or cultural contexts in which they practice.

Health systems can support or inhibit this type of engagement. The strategies that systems could employ to support healthcare providers include ensuring that providers have the time to connect with patients, their families and the community;[26] providing cultural safety training and ongoing professional development to ensure that providers not only understand but take responsibility for their own cultural impositions to ensure they can provide culturally appropriate care to the community they serve;[30] and designing employment contracts that facilitate the flexibility necessary for providers to deliver the type of care that communities need.[32] Healthcare services could be better supported with the required resources to engage appropriately with communities. Employing and providing educational and career opportunities Aboriginal and Torres Strait Islander staff would assist with ensuring that patients feel welcomed and comfortable in engaging with services.[33]

Strengths and limitations

A large number of Aboriginal and Torres Strait Islander community members and healthcare providers participated in this study. Participants came from a mix of remote, regional and urban contexts. Healthcare providers were drawn from the same healthcare centres that provided services to the Aboriginal and Torres Strait Islander community members who were involved in this study. Despite the large number of participants and the variety of contexts in which the study was conducted, it should not be assumed that the findings are necessarily transferrable to all primary healthcare services. The wide diversity of Aboriginal and Torres Strait Islander communities in Australia, each with locally specific healthcare and community needs, requires a contextualised approach to improving healthcare services.

The research team that undertook this study comprised a group of geographically dispersed Aboriginal and Torres Strait Islander and non-Indigenous researchers, many of whom were clinicians with medical, nursing or health worker qualifications. All of the team members brought a wide variety of perspectives and understandings to the research which further enriched the analysis and interpretation of the data collected. One of the most important strengths of our multicultural, multi-disciplinary research team was the ability to listen to and respect each other's point of view and then discuss potential solutions until members were in agreement with the outcome. In particular, this provided an opportunity to discuss what was clear (explicit), and also what was not (tacit), in the stories being told by both community and healthcare provider participants.[34] We also acknowledge that working within this research space was not without some costs. The process of negotiating the research space[35] continued throughout analysis and interpretation. Considerable effort was therefore made, particularly in the early stages of data analysis, to create a safe space to jointly exchange, consider, discuss and debate perspectives.

Conclusions

The challenge for healthcare providers is clear. Improvements in Aboriginal and Torres Strait Islander health will not be achieved by simply providing 'more' services. Instead, enhancing and maintaining relationships between patients and providers appears to be at the heart of the potential for sustained engagement. Relationships in turn depend on a number of factors associated with both the provider and the service. Time to build trust and faith in the healthcare provider is essential. So too is the need for healthcare providers to demonstrate respect for and engage with not just patients but also the wider community. For healthcare services, ensuring that Aboriginal and Torres Strait Islander peoples feel welcomed and accepted and employing Aboriginal and Torres Strait Islander staff will support the development of these important relationships. Given that chronic disease is a long lasting condition that can be managed but rarely cured, sustained engagement with appropriate primary healthcare services will result in better health outcomes for Aboriginal and Torres Strait Islander peoples.

Acknowledgements

We acknowledge the contribution that Jeannie Devitt and Michael Howard made to the KQS. This research is a project of the Australian Primary Health Care Research Institute, which is supported by a grant from the Commonwealth of Australia as represented by the Department of Health. The information and opinions contained in it do not necessarily reflect the views of the Australian Primary Health Care Research Institute or the Department of Health. This research was also supported by a health services research program grant from the National Health and Medical Research Council (Grant ID # 402797). Maree L Hackett is a recipient of a National Heart Foundation Future Leader Fellowship, Level 2 (100034, 2014-2017).

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Davy et al. BMC Health Services Research (2015) 15:194
DOI 10.1186/s12913-015-0854-8

BMC Health Services Research

RESEARCH ARTICLE Open Access

Effectiveness of chronic care models: opportunities for improving healthcare practice and health outcomes: a systematic review

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Abstract

Background: The increasing prevalence of chronic disease and even multiple chronic diseases faced by both developed and developing countries is of considerable concern. Many of the interventions to address this within primary healthcare settings are based on a chronic care model first developed by MacColl Institute for Healthcare Innovation at Group Health Cooperative.

Methods: This systematic literature review aimed to identify and synthesise international evidence on the effectiveness of elements that have been included in a chronic care model for improving healthcare practices and health outcomes within primary healthcare settings. The review broadens the work of other similar reviews by focusing on effectiveness of healthcare practice as well as health outcomes associated with implementing a chronic care model. In addition, relevant case series and case studies were also included.

Results: Of the 77 papers which met the inclusion criteria, all but two reported improvements to healthcare practice or health outcomes for people living with chronic disease. While the most commonly used elements of a chronic care model were self-management support and delivery system design, there were considerable variations between studies regarding what combination of elements were included as well as the way in which chronic care model elements were implemented. This meant that it was impossible to clearly identify any optimal combination of chronic care model elements that led to the reported improvements.

Conclusions: While the main argument for excluding papers reporting case studies and case series in systematic literature reviews is that they are not of sufficient quality or generalizability, we found that they provided a more detailed account of how various chronic care models were developed and implemented. In particular, these papers suggested that several factors including supporting reflective healthcare practice, sending clear messages about the importance of chronic disease care and ensuring that leaders support the implementation and sustainability of interventions may have been just as important as a chronic care model's elements in contributing to the improvements in healthcare practice or health outcomes for people living with chronic disease.

Keywords: Chronic care model, Integrated care, Chronic disease, Primary healthcare

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Background

Chronic diseases have a substantial impact on the lives of people living in both developed and developing countries. Of the 57 million deaths in 2008, 36 million (63%) were a direct result of chronic diseases, principally cardiovascular disease, diabetes, cancer and chronic respiratory diseases. Nine million of these deaths occurred in people under 60 years of age and ninety per cent of these premature deaths occurred in low- and middle-income countries [1]. It is also the case that disadvantaged and marginalised communities in developed countries suffer an increasing burden of chronic disease [2].

As a way of combating this growing health crisis, researchers have attempted to develop comprehensive strategies to manage chronic disease and to deliver improved chronic disease care. The primary aim of many integrated care or chronic disease management programs is to reduce fragmentation while at the same time improving health outcomes at an acceptable cost to the healthcare system [3,4]. Many of the current chronic disease management strategies were first identified by MacColl Institute for Healthcare Innovation at Group Health Cooperative, commonly referred to as the Wagner chronic care model (Wagner CCM), which was based on six key elements [5-7]. These elements focus on mobilising community resources, promoting high quality care, enabling patient self-management, implementing care consistent with evidence and patient preferences, effectively using patient/population data, cultural competence, care coordination, and health promotion [8]. Yet while the broad elements may be similar to the Wagner CCM developed by the MacColl Institute for Healthcare Innovation, what constitutes a CCM and how it is implemented and delivered within healthcare services, has continued to evolve [9,10].

A number of systematic literature reviews have already focused on which of the elements or combination of elements included within a CCM were effective in improving healthcare practice and health outcomes. One of the first systematic literature reviews to include all six elements of the Wagner CCM focused on the provision of care to chronic obstructive pulmonary disease (COPD) [11]. While the review found that the implementation of two or more elements was likely to reduce healthcare usage by COPD patients, the authors also identified significant heterogeneity between the ways in which each of the elements were implemented. Another systematic literature review [12] looked at the association between improved performance and the implementation of integrated quality management models which included a CCM. Again, there was some evidence that implementing interventions based on a CCM improved performance and health outcomes. Other systematic reviews have identified small to moderate improvements in health outcomes associated with diabetes [13], improved adherence to inhaled corticosteroids among asthmatics [14], and improvements to mental and physical health outcomes for patients with mental disorders such as depression [15]. Pasricha et al [16] also conducted a systematic literature review focusing on effectiveness of two of the elements included within the Wagner CCM - decision support and clinical information systems. These authors found that the implementation of either or both elements resulted in modest improvements to care provided for people living with HIV.

These previous systematic reviews have tended to focus on effectiveness for improving health outcomes. They have also limited their inclusion criteria to evidence from randomised [11,14,15] and/or non-randomised trials, cross sectional studies and cohort studies [13,16]. This systematic literature review broadens the work of other reviewers in two ways. First, it focuses on healthcare practice as well as the health outcomes associated with implementing a CCM. This is particularly important as the quality of healthcare practice is a key determinant of health outcomes for patients [17]. Improvements to healthcare practice not only benefit the patients in terms of improved health outcomes but also ensure considerable savings to the healthcare system [18].

The second feature of this systematic literature review is that case series and case studies have also been included. To our knowledge only one other systematic literature review has included case studies [12]. While the main argument for excluding this type of literature is that they are not of sufficient quality or generalizability, case studies and case series have been included on the basis of completeness. Rather than dismissing any study based on methodology alone, we have instead focused on presenting information about the quality of these and other featured studies.

Method

Review objective and questions

The objective of this systematic literature review was to identify and synthesise relevant international evidence on the effectiveness of CCMs elements for improving healthcare practices and health outcomes. The questions asked by this review were:

1. What elements of a CCM have been implemented into a PHC setting?
2. Do the identified elements improve healthcare practices delivered to patients living with chronic disease?
3. Do the identified elements improve the health outcomes of patients living with chronic disease?

Inclusion criteria

Types of participants

This review considered studies that either focused on people with or healthcare providers that cared for people

with a non specific chronic disease or alternatively with at least one of the following specific chronic diseases - cardiovascular disease, chronic kidney disease, chronic respiratory disease, type 2 diabetes mellitus, depression and HIV/AID -) in a primary healthcare setting.

Primary healthcare is generally defined as first-contact, accessible, continued, comprehensive and coordinated healthcare provided by a single practitioner (e.g. GP, nurse practitioner) or a multidisciplinary team of professionals in a community practice. For the purposes of this review however, primary healthcare is first-contact, accessible, continued, comprehensive and coordinated care. First-contact care is accessible at the time of need; on-going care focuses on the long-term health of a person rather than the short duration of the disease; comprehensive care is a range of services appropriate to the common problems in the respective population and coordination is the role by which primary care acts to coordinate other specialists that the patient may need [19]. Primary healthcare also includes primary care settings that have only one health professional, i.e. a general practitioner.

Elements of a chronic care model

In order to identify elements that should be included as part of this review, a scoping exercise of published chronic care models was undertaken. This scoping exercise identified two additional key elements - case management [20] and family support [21] which had previously been included as part of a chronic care model, bringing the total number of elements included within this review to eight. Studies which had implemented at least two of the these eight elements were included in this review:

1. Facilitated community support (CS) to meet the needs of patients
2. Facilitated unpaid/informal family support (FS) to meet the needs of patients
3. Self-management support (SMS) to meet the needs of patients
4. Health system (HS) improvement to meet the needs of health-care providers
5. Delivery system design (DSD) to meet the needs of health-care providers
6. Enhanced health care professional case management (CM) support to meet the needs of patients
7. Decision support (DS) to meet the needs of health-care providers
8. Clinical information systems (CIS) to meet the needs of health-care providers

Types of outcome measures

In addition to describing the elements included within a CCM, outcome measures for effectiveness included any reported changes (improvements or declines) to healthcare practice, or the health outcomes of patients as a result of the implementation of a CCM.

Types of studies

This review focused on quantitative (e.g. randomised and non-randomised control trials, cross-sectional and cohort studies, case studies and case series) and qualitative studies.

Search strategy

Seven electronic databases (MEDLINE, Cinahl, Embase, Informit Online, PsycINFO, Scopus, and Web of Science) were searched for articles published in English language between January 1998 to April 2013 and met the above inclusion and exclusion criteria. The Medline search strategy is provided in [see Additional file 1] was originally set up in MEDLINE and then modified for the other databases.

Study selection

Four authors (CD, HL, MT, SP) were involved in study selection. For each paper, two of these authors independently scanned the identified studies and excluded studies according to the criteria above, on the basis of titles and abstracts. Full text copies of the papers deemed to meet the inclusion and exclusion criteria were these retrieved and two of the review authors reviewed these publications. Authors of relevant papers were contacted if the full text article were not available. If there was uncertainty or disagreement, consensus was reached by discussion and consultation with the review authors.

Bias appraisal

Four authors (CD, HL, MT, SP) were also involved in the Bias Appraisal. Two of these authors independently assessed the risk of bias onall of the papers included in this review. The Cochrane Handbook for Systematic Reviews of Interventions was used to assess bias for randomised and non-randomised control trials, cross-sectional and cohort studies [22]. The Joanna Briggs critical appraisal tool was used to measure the bias of case studies and case series [23]. As the first objective of the review was to identify elements of a CCM which have been included in studies, and then identify the effectiveness of these elements for improving health outcomes and the provision of healthcare, studies were not excluded based on this appraisal [see Additional file 1: Table S1–S5].

Data extraction

Data was extracted from primary studies and included in pre-defined data extraction tables by the four review authors (CD, JB, HL, MT). The extracted data included specific details about the geographical context, study methods and disease focus [see Additional file 1: Table S6], elements included in the intervention, study participants,

and outcomes of significance to the review questions [see Additional files 1: Table S7–Table S11]. Data has been presented in narrative form including tables and figures to aid in data presentation where appropriate.

Results

Literature search

The search of information sources returned 3492 articles from the initial searches of electronic databases. The majority of these studies were subsequently excluded based on their title or abstract because they clearly did not meet the inclusion criteria for this review. A total of 226 full text articles were obtained and a further 149 were excluded as they also did not meet the inclusion criteria. This resulted in the inclusion of 77 published peer-reviewed papers which were ultimately included in this review (Figure 1).

Description of chronic care models

The majority of studies were conducted in the Americas, including United States of America, Canada and Mexico [24-76]. A number of studies were also conducted in Europe including United Kingdom, Spain, Belgium, Italy, Denmark, Netherlands and Germany [20,77-88]. A further six studies were conducted in Australia and New Zealand [21,89-93], one study was conducted in Taiwan [94], one in the United Arab Emirates [95] and one in South Africa [96] [see Additional file 1: Table S6].

The majority of studies focused on the provision of care for diabetes [21,24,26,27,29,31,33-38,40-42,44-53, 55-60,62,65-70,72,75,76,79,80,83-87,90,91,93,94,96]. Included studies also focused on cardiovascular disease [20,25,28, 30,32,39,43,54,61,63,64,71,73,88,89,91,95], depression [34,51, 53,74,76,90], respiratory disease [90], including chronic obstructive pulmonary disease [77,81,82,92,93], and renal disease [21,90]. Other studies [20,25,28,30,32,39,43,54,61,63, 64,71,73,88,89,91,95] focused on the provision of care to patients with chronic diseases more generally [see Additional file 1: Table S6].

While a range of CCM elements were used across the papers reviewed, the most commonly used element was SMS, while only two papers included FS (Table 1). However, there was substantive variation between studies in both the combination of included elements and also in how these elements were implemented. For example, descriptions of SMS implemented in primary care settings included development of care guides and individualised patient action plans [25,28,92], individual counselling or

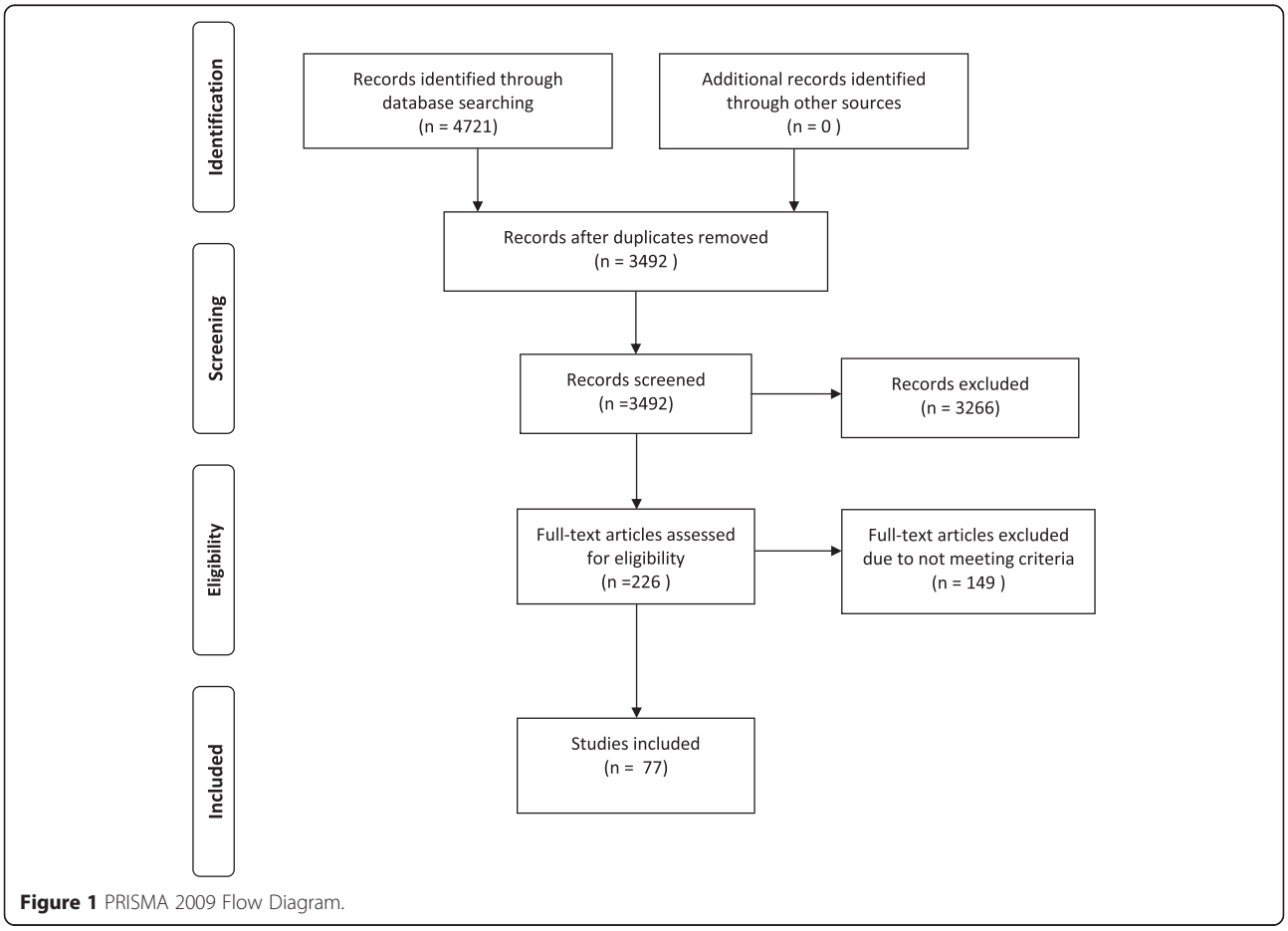

Figure 1 PRISMA 2009 Flow Diagram.

Table 1 Overview of CCM Elements Reviewed

Element	Number of Papers
Self-Management Support	50
Delivery System Design	39
Clinical Information Systems	37
Decision Support	36
Case Management	19
Health System	13
Community Support	13
Family Support	2
CCM - Elements Not Specified	4

coaching, [25,42,74,97], education programs on disease management [28,31,33,51,58,62,74,77,86,89,98,99], programs on empowerment, goal-setting and motivation [26,42,51,58,79,92], and use of support groups [62,98,99]. Descriptions of how other CCM elements were implemented also differed substantially between studies, meaning that between study changes to healthcare practice and health outcomes as a result of implementing CCM elements were not easily comparable.

Effectiveness of chronic care models

To explore the effectiveness of CCM elements, the review focused on the analyses of randomised controlled trials (RCTs), non-randomised controlled trials (non-RCTs), retrospective cohort studies, as well as case studies and case series. Measures of effectiveness relating to health outcomes relevant to specific chronic diseases (e.g. improvements to HBA1c for diabetes) as well as healthcare practice appropriate to the management of chronic disease (e.g. concordance with clinical guidelines), were reported by 63 of the 77 studies included in this review.

In a small number of studies [35,70,75] the Assessment of Chronic Illness Care (ACIC) was used to assess level of implementation of CCM elements in primary healthcare settings. The ACIC contains 28 items across the six elements within the Wagner CCM: CS, HS, SMS, DS, DSD and CIS, with each assigned a numeric score from 0 to 11. Individual providers or healthcare teams were asked to rate level of implementation through self-report. The equivalent patient self-reporting tool (Patient Assessment of Care for Chronic Conditions) was also used in three studies [47,66,87] to measure quality of healthcare based on five sub-scales: patient activation, DSD, DS, goal setting, problem solving/contextual counselling and follow up/coordination.

Findings pertaining to the quality of the included papers and the reported effectiveness associated with specific CCM elements for improving health outcomes and healthcare practices are presented below by study type.

Randomised controlled trials

Of the 13 RCTs that measured the efficacy of a CCM as defined by our search criteria, the majority (n = 8) were conducted in the USA [25,26,28,42,51,62,69,74]. Control groups generally either received usual care or received less intensive intervention. Six studies focused on diabetes [24,26,42,62,69,79], two studies on COPD [77,92], one study on depression [51], and four studies on non-specific chronic disease or multi-morbidity [20,25,28,74].

A significant potential risk of bias was identified in many of the included RCT papers [see Additional file 1: Table S1]. Of particular concern was the risk of detection bias which was assessed as either high or unclear for all but two of the papers [69,74].

Findings of significant healthcare practice or health outcome improvements associated with CCM interventions were inconsistent [Additional file 1: Table S7]. While many studies reported significant changes in health outcomes from baseline in the intervention group, significant between-group differences were often lacking [42,92], and a number of studies reported no intervention effect for any health outcome [26,28,51,69,74]. Randomised control trials that reported significant changes in health outcomes from baseline for the intervention groups had implemented the following elements:

- SMS [62,77]
- DSD [62]
- CIS [77]
- DS [62]
- CM [24,77]
- HS [24]

Two RCTs reported on healthcare practice change. One reported a significant improvement in monitoring of symptoms and risk factors was associated with CM and HS [24], while the second study identified a deterioration in patient education [77].

Non-randomised control trials

Two non-RCT papers were also reviewed, one conducted in the USA focusing on COPD [32] and the other in Europe which focused on chronic disease more generally [97]. Only one of these studies looked at effectiveness [see Additional file 1: Table S7], demonstrating significant reductions in mortality in an intervention group referred to a nurse care manager equipped with specialised information and IT tools, however findings were not significant after two year follow up [32]. The second study evaluated implementation of CIS, SMS and DSD elements into primary healthcare practices and reported on the proportion of elements that had been implemented at two year follow up [97]. While reporting bias was low, the risk of selection, sampling, detection

and attrition bias for non-RCT papers was considered to be, at best unclear, if not high [see Additional file 1: Table S2].

Retrospective cohort studies

All six observational cohort studies were conducted retrospectively using chart reviews of electronic patient health records, registries and patient databases to evaluate CCM elements implemented at a practice or practice group level. Four of the studies were conducted in the USA [31,33,49,61] and two were conducted in Europe [83,85]. Five studies focused on diabetes [31,33,49,83,85] and one focused on non-specific chronic disease risk factors [61].

The risk of selection and sampling bias was assessed as high or unclear for all but one study [31]. Likewise, the risk of detection bias was also considered to be high or unclear for all but one other study [61] [see Additional file 1: Table S3].

Three of the studies reported improvements to healthcare practice as well as health outcomes for diabetic patients [31,33,85] while one study [61] only reported on improvements to health outcomes for diabetic patients [see Additional file 1: Table S9]. Improvements were found to be associated with the following CCM elements.

SMS [31,33,85]
DSD [31,33,83,85]
CIS [31,33,83]
DS [31,33,83,85]
CM [31,33]

Cross-sectional studies

Of the 11 cross-sectional studies identified in this review, all but one study [91] included elements implemented to support diabetic care. In addition, only two studies [87,91] were conducted outside of the USA.

Eight of the 11 cross-sectional studies [13,35,40, 45,46,66,70,87] either did not have sufficient information to make an assessment, or were considered to be at high risk of selection bias. Only four of the cross-sectional studies met the criteria for being at low risk of detection [45-47,70] or attrition biases [35,46,60,70], while seven were assessed as low risk for reporting bias [35,45-47, 60,75,87] [see Additional file 1: Table S4].

Three of the cross-sectional papers reported associations between implementation of CCM elements and improvements to clinical outcomes, [35,66,91] with one study reporting improvement in clinical outcomes and healthcare practice [60] [see Additional file 1: Table S10]. Improvements were found to be associated with the following CCM elements.

- SMS [35,60,66,91]
- DSD [35,60,66,91]
- CIS [35,60,66,91]
- DS [35,60]
- CM [66]
- HS [35,91]
- CS [35]

Case studies and case series

Similar to papers presented above, the vast majority of case studies and case series (25 of 31 papers) included diabetic patients when assessing the effectiveness of CCMs for improving health outcomes of, or health care practice [21,27,29,36-38,44,48,50,53,55-57,65,67,72,76,84,90,91,93, 94,96]. The majority of these case studies and case series (20 of 31 papers) were conducted in USA [27,29,34,36-38, 44,48,50,53-57,63,65,67,72,76].

None of the case studies and case series papers included in this review met all of the nine critical appraisal criteria defined by the Joanna Briggs Institute [23]. Of particular concern was that nine of these studies did not sufficiently define the inclusion criteria, and only two of the 31 papers identified confounding factors [Additional file 1: Table S5].

Twenty two of the case studies or case series papers reported associations between improved health outcomes [21,29,34,36-38,44,48,54,63,65,67,72,78,84,90,91,93-95] and the implementation of SMS [see Additional file 1: Table S11]. In addition, associations were also found for improved health outcomes and the implementation of the following elements.

In addition, associations were also found for improved health outcomes and the implementation of the following elements.

- DSD [21,29,36,37,54,65,67,72,84,95]
- CIS [21,29,37,54,65,72,76,95]
- DS [29,36,37,44,65,67,72,76,93,95]
- CM [29,34,36,44,78,90]
- HS [38]
- CS [21,29,48]
- FS [21]

Two case studies [67,95] found an association between implementing CCM elements and a decline in a health outcome (decreased high-density lipoprotein and increased low-density lipoprotein respectively). However, out of 77 papers included within this review, these were the only studies to report a negative health outcome associated with the implementation of CCM elements.

Twenty five of the case studies or case series [21,27,29, 30,36-38,44,48,50,53-57,67,73,78,81,84,93-96] reported an association between improved healthcare practices and the implementation of the following elements.

- SMS [21,27,29,30,36-38,44,48,50,54-57,67,78,81,84,93,95]
- DSD [21,27,29,36,37,50,54,56,67,81,84,94-96]

- CIS [21,27,29,30,37,50,54-57,81,95]
- DS [27,29,93,95]
- CM [29,36,44,78]
- HS [27,38,96]
- CS [21,27,29,48,50,94]
- FS [21]

Only one case study [57] out of the 77 papers included within this review suggested an association between implementing elements of a CCM and a decline in healthcare practices (documentation).

Discussion

Of the papers which did include measures of effectiveness, the majority found an association between the implementation of CCM elements and improvements with healthcare practice or health outcomes for people living with chronic disease. Only two papers [67,95] reported association between implementing CCM elements and a decline in any of the health outcomes measured (decreased high-density and increased low-density lipoproteins respectively), while one paper [57] suggested an association between the implementation of CCM elements and a decline in healthcare practices (documentation).

One of the primary findings of this systematic literature review was considerable study variability, both in the combination of and ways in which CCM elements were implemented. For this reason it was impossible to clearly identify any optimal combination of the eight CCM elements that could lead to improvements in either healthcare practice or health outcomes. A direct relationship between any combination of CCM elements and improvements to either healthcare practice or health outcomes was further placed into doubt by the RCT studies that compared outcomes from the implementation of two different combinations of CCM elements [38,44]. Despite differences in the combination of elements included, researchers were unable to find any significant variation in outcomes. Similarly, studies that focused on the implementation of self-selected elements across multiple sites found very little between site differences in either the type or strength of healthcare practice or health outcome improvements [50,57,78,95]. This suggests that factors other than or in addition to the implementation of CCM elements may play a role in improving healthcare practices and health outcomes for people living with chronic disease [100].

One of the benefits of including case studies in this systematic review was that they tended to provide a more detailed account of how CCM elements were implemented. Of the 19 case studies that described these processes in more detail, eight specifically utilised the Plan-Do-Study-Act cycle [27,37,54,65,72,93,95,101], while a further five developed various learning collaboratives [29,50,53,57,76] as part of the development and implementation process. One of the key findings of these studies was that Plan-Do-Study-Act cycles and learning collaboratives appeared to be associated with the development of contextually relevant interventions. In addition, these methods often meant that the healthcare providers involved in the implementation process were engaged with development, encouraging a sense of ownership and consequently responsibility for the success of the intervention. The authors of these papers also described how healthcare providers who were involved in the development process had an opportunity to reflect on, gaining for example, a more nuanced understanding of how the care they provided could address the needs and priorities of the communities they served.

Reflective practice is a key component for developing clinical knowledge and skills [102] and can, in and of itself, lead to significant improvements in healthcare by assisting to bridge the gap between theory and practice [103,104]. Importantly for the implementation of interventions including CCM elements, reflective practice also encourages healthcare providers to identify anomalies between the ways in which they currently practice and organisational priorities for the future [105]. Within a healthcare setting, this involves analysing one's own experiences and modifying behaviour based on these reflections in order to improve the way in which healthcare is provided. While not without some challenges, an individual's reflective practice is enhanced when there is an opportunity to work with others in a group setting [106]. The methods, including the Plan-Do-Study-Act cycles and learning collaboratives described in this systematic review, can assist this process by developing collegial environments within which this reflective group practice can occur.

Although not specifically addressed by papers in this review, spending the time and resources to develop and implement a CCM may have also underpinned both healthcare practice and health outcome improvements by signalling to staff that improving chronic disease care was a priority for their healthcare service. Yet simply communicating these messages may not be sufficient to ensure improvement. What was evident in a number of papers, was the key role that leaders played in guiding the development and implementation process. Once started, leaders within these organisations needed to be committed to the implementation and sustainability of a new CCM [27,31,43,52,54,71,72,93]. As was highlighted in the Wagner CCM under HS [107], without this commitment, any improvements to either health outcomes or healthcare practices were likely to have been lost [43,52].

Providing a collegial environment which supports reflective practice, sending clear messages about the importance of chronic disease care and ensuring that

leaders support the implementation and sustainability of interventions appear to contribute to the health outcomes and healthcare practices identified in papers included in this review. However, this list is by no means complete and further work is required to identify other facilitators and barriers which could influence the implementation of similar interventions. However, the findings in this systematic literature review do suggest that other models of care, including alternatives to CCM elements included in this review could be equally successful in improving the health outcomes and healthcare practices within primary healthcare services, particularly when they address the particular needs of patients within each context [95].

Contextual relevance is especially important given that although the burden of chronic disease is highest within disadvantaged populations, the majority of studies which have implemented the eight CCM elements included in this review have focused on interventions within advantaged populations living in developed countries [see Additional file 1: Table S6]. In particular, FS which was the least utilised CCM element (Table 1) may be particularly useful within, for example, Aboriginal peoples living with chronic disease [21]. Whether this or any other CCM elements can help to improve healthcare practices and health outcomes for disadvantaged populations more generally is not as clear. Outcomes from this review suggest that targeted approaches whereby leaders provide clear direction and support [108] and also encourage healthcare practitioners to reflect on how their own practices may need to change to meet the needs of particular populations are more likely to stimulate improvements to health outcomes and healthcare practice.

Limitations

There are a number of limitations to this review. Of particular concern was the high risk of bias in the RCT, non-RCT, retrospective cohort and cross sectional studies. In addition, the quality of the case studies included in this review was considered to be poor. In addition, as previously noted the interventions differ from one study to another, meaning that generalizations were impossible to make and which suggestions based on existing evidence have been made for why a CCM might lead to improved healthcare process and health outcomes these are yet to be tested.

Conclusions

The key finding from this systematic literature review was the wide variability between the elements included within CCMs and the way in which these elements were implemented. While the majority of papers reported improvements to either healthcare practice or health outcomes as a result of implementing a CCM, it was not possible to identify which elements or combination of elements led to these improvements. Rather these results suggested that factors other than or in addition to the implementation of CCM elements may play a role. While not exclusive, these may include collegial environments which support reflective practice, sending clear messages about the importance of chronic disease care and ensuring that leaders support the implementation and sustainability of interventions. Given the high prevalence of chronic disease in disadvantaged populations including Indigenous communities, elements including FS could play a greater role in improving the management of and outcomes from chronic disease for these peoples.

Additional file

Additional file 1: Search strategy. Table S1. RCT risk of bias. **Table S2.** Non-RCT risk of bias. **Table S3.** Retrospective cohort study risk of bias. **Table S4.** Cross sectional study risk of bias. **Table S5.** Case study and case series quality appraisal. **Table S6.** Description of chronic care models. **Table S7.** RCT study outcomes. **Table S8.** Non-RCT study outcomes. **Table S9.** Retrospective study outcomes. **Table S10.** Cross sectional study outcomes. **Table S11**. Case study and case series outcomes.

Abbreviations

ACIC: Assessment of chronic illness care; CM: Case management; CCM: Chronic care model; COPD: Chronic obstructive pulmonary disease; CIS: Clinic information system; CS: Community support; DS: Decision support; DSD: Delivery system design; S: Family support; HS: Health system; RCTs: Randomised control trials; SMS: Self-management support.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CD participated in the design of the study, the literature search, assessment of quality and bias, extraction of findings and drafting the manuscript. JB participated in the extraction of findings and drafting the manuscript. HL and MT participated in the literature search, assessment of quality and bias and extraction of findings. SP participated in the design of the study, the literature search, assessment of quality and bias, and extraction of findings. AB participated in the design of the study. All authors read and approved the final manuscript.

Acknowledgements

This research and the researchers working on this study were supported by a Centre for Research Excellence Grant from the Australian Primary Health Care Research Institute. AB is supported by a post-doctoral fellowship from the National Heart Foundation (#PR 08 M 4207) and a senior medical research fellowship from the Viertel Charitable Foundation. This research was also supported by National Health and Medical Research Council (NHMRC) Grant No 1061242. The published material are solely the responsibility of the individual authors and do not reflect the views of NHMRC.

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Received: 24 December 2014 Accepted: 27 April 2015
Published online: 10 May 2015

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Davy et al. BMC Family Practice (2015) 16:102
DOI 10.1186/s12875-015-0319-5

BMC Family Practice

RESEARCH ARTICLE Open Access

Factors influencing the implementation of chronic care models: A systematic literature review

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Abstract

Background: The increasing prevalence of chronic disease faced by both developed and developing countries is of considerable concern to a number of international organisations. Many of the interventions to address this concern within primary healthcare settings are based on the chronic care model (CCM). The implementation of complex interventions such as CCMs requires careful consideration and planning. Success depends on a number of factors at the healthcare provider, team, organisation and system levels.

Methods: The aim of this systematic review was to systematically examine the scientific literature in order to understand the facilitators and barriers to implementing CCMs within a primary healthcare setting. This review focused on both quantitative and qualitative studies which included patients with chronic disease (cardiovascular disease, chronic kidney disease, chronic respiratory disease, type 2 diabetes mellitus, depression and HIV/AIDS) receiving care in primary healthcare settings, as well as primary healthcare providers such as doctors, nurses and administrators. Papers were limited to those published in English between 1998 and 2013.

Results: The search returned 3492 articles. The majority of these studies were subsequently excluded based on their title or abstract because they clearly did not meet the inclusion criteria for this review. A total of 226 full text articles were obtained and a further 188 were excluded as they did not meet the criteria. Thirty eight published peer-reviewed articles were ultimately included in this review. Five primary themes emerged. In addition to ensuring appropriate resources to support implementation and sustainability, the acceptability of the intervention for both patients and healthcare providers contributed to the success of the intervention. There was also a need to prepare healthcare providers for the implementation of a CCM, and to support patients as the way in which they receive care changes.

Conclusion: This systematic review demonstrated the importance of considering human factors including the influence that different stakeholders have on the success or otherwise of the implementing a CCM.

Background

The increasing prevalence of chronic disease faced by both developed and developing countries is of considerable concern to a number of international organisations [1, 2]. Many of the interventions to address this concern within primary healthcare settings are based on the chronic care model (CCM) which was first developed by MacColl Institute for Healthcare Innovation at Group Health Cooperative in the early 1990s [3–5]. The elements included in this original model focused on mobilising community resources, promoting high quality care, enabling patient self-management, implementing care consistent with evidence and patient preferences, effectively using patient/population data, cultural competence, care coordination, and health promotion [6].

The implementation of complex interventions such as CCMs requires careful consideration and planning. Success depends on a number of factors at the healthcare provider, team, organisation and system levels [7]. Implementation strategies should also take into account contextual factors [8]. As a result, primary healthcare services need to consider the range of interacting factors

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at many different levels and consider the possibility that multiple often interacting factors will largely determine whether a CCM is implemented and whether this intervention succeeds in improving health outcomes for people living with chronic disease [9].

A vast number of theories have been developed to inform the implementation of complex healthcare interventions [10]. Process theories focus on the activities and organisation of the change process, stage-of-change theories consider how the steps taken to implement the change differ according to the healthcare providers involved and impact theories describe how the intervention will facilitate change. There are theories that focus on individuals within the change process including cognitive, educational and motivational theories. There are also theories that relate to social interaction encompassing communication, social learning, social networking, team effectiveness, professional development and leadership theories. Finally, there are theories at an organisational level including integrated care and quality management, both of which underpin the development and implementation of CCMs [9].

A number of systematic literature reviews have already considered the effectiveness of CCMs [11–17]. None, however, have specifically focused on what impedes or promotes the successful implementation of CCMs. This systematic literature review goes some way to addressing this gap by identifying the facilitators and barriers to implementing CCMs within primary healthcare settings, from the perspective of both patients' and healthcare providers'. The intention is that the outcomes from this review will assist both policy makers and practitioners working within a primary healthcare setting, to implement CCMs.

Objectives

The specific purpose of this review was to systematically examine the scientific literature in order to understand the facilitators and barriers to implementing CCMs within a primary healthcare setting from the perspective of healthcare providers and patients. The question asked by this review was:

> What attitudes, beliefs, expectations, understandings, perceptions, experiences, resources and knowledge according to healthcare providers and patients support (facilitators) or inhibit (barriers) the implementation of CCMs within a primary healthcare setting?

Method of the review

A three-step search strategy was used in this review. An initial limited search of MEDLINE and CINAHL was undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe article. A second keywords and index term search was then undertaken across Embase, Informit Online, PsycINFO, Scopus, and Web of Science. Duplications were then identified and the most complete record retained for subsequent review on inclusion criteria. Additional file 1 provides an example of the Medline search strategy.

Inclusion criteria

Population and context

This review considered studies that focused on patients with one or more of the more prevlant major chronic diseases as defined by the World Health Organisation - cardiovascular disease, chronic kidney disease, chronic respiratory disease, type 2 diabetes mellitus and depression [18, 19] - receiving care in primary healthcare settings, as well as all primary healthcare providers such as doctors, nurses and administrators.

Primary healthcare is generally defined as first-contact, accessible, continued, comprehensive and coordinated healthcare provided by a single practitioner (e.g. GP, nurse practitioner) or a multidisciplinary team of professionals in a community practice. For the purposes of this review however, primary healthcare is first-contact, accessible, continued, comprehensive and coordinated care. First-contact care is accessible at the time of need; ongoing care focuses on the long-term health of a person rather than the short duration of the disease comprehensive care is a range of services appropriate to the common problems in the respective population and coordination is the role by which primary care acts to coordinate other specialists that the patient may need [20]. Primary healthcare also includes primary care settings that have only one health professional, i.e. a general practitioner (GP).

Phenomena of interest/intervention

The phenomena of interest were the attitudes, beliefs, expectations, understandings, perceptions, experiences, resources and knowledge of healthcare providers and patients about what supports (facilitators) or inhibits (barriers) the implementation of CCMs within a primary healthcare setting. To be included studies must have also referred to a CCM which included at least two of the following elements:

1. Facilitated community support (CS) to meet the needs of patients
2. Facilitated unpaid/informal family support (FS) to meet the needs of patients
3. Enhanced health care professional case management (CM) support to meet the needs of patients
4. Self-management support (SMS) to meet the needs of patients

5. Health organisational change (OC) to meet the needs of health-care providers
6. Delivery system design (DSD) to meet the needs of health-care providers
7. Decision support (DS) to meet the needs of health-care providers
8. Clinical information systems (CIS) to meet the needs of health-care providers

Outcome

Finally, this review only considered studies that included attitudes, beliefs, expectations, understandings, perceptions, experiences, resources and knowledge according to healthcare providers support (facilitators) or inhibit (barriers) the implementation of CCMs.

Types of studies

This review focused on both qualitative and quantitative studies (e.g. randomised and non-randomised control trials, cross-sectional and cohort studies, case studies and case series). Papers were limited to those published in English between 1998 and 2013.

Data collection

Data was extracted from primary studies and included in the review using a set of pre-defined tables. The extracted data included specific details about the chronic care model, populations, study methods and outcomes of significance to the review questions and objectives. Extracted data included:

- Study type
- Chronic disease
- Study setting (country and region)
- Chronic care elements

These data on the included studies are presented in an additional file [see Additional file 2].

Critical appraisal

Two reviewers independently assessed the quality of the papers prior to inclusion in this review. The Cochrane Handbook for Systematic Reviews of Interventions was used to assess bias for randomised and non-randomised control trials, cross-sectional and cohort studies [21, 22]. The Joanna Briggs critical appraisal tool was used to measure the quality of case studies and case series [23]. As the objective of this review was to facilitators and barriers to implementing CCMs, studies were not excluded based on these critical appraisals.

Data extraction

Data was extracted where possible by themes identified by the authors of each study. Where themes were not identified within the study, findings were extracted from the narrative discussion by a reviewer (CD) in the form of a definitive statement made by the authors and supported by the presentation of data. Qualitative findings and the quantiative findings presented in narrative form were pooled. Findings were first inductively grouped into categories that were created on the basis of similarity of meaning; categories were then subjected to a meta-aggregation in order to produce a single comprehensive set of synthesized findings that could be used as a basis for evidence-based practice which would inform policy makers and practitioners on the facilitators and barriers associated with implementing a CCM [23].

Results

Description of studies

The search of information sources returned 3492 articles. The majority of these studies were subsequently excluded based on their title or abstract because they clearly did not meet the inclusion criteria for this review. A total of 226 full text articles were obtained and a further 188 were excluded as they did not meet the criteria. Thirty eight published peer-reviewed articles were ultimately included in this review (Fig. 1).

The majority of studies were conducted in the Americas, including United States of America, Canada and Mexico [24–47]. Nine studies were also conducted in Europe including United Kingdom, Spain, Belgium, Italy, Denmark, Netherlands and Germany [48–56]. Four studies were conducted in Australia and New Zealand [57–60] and one study in Africa [61].

While all studies described in the included papers were conducted within a primary healthcare setting, the majority focused on the provision of care for diabetes [24, 26, 28–30, 32–34, 36, 37, 39, 40, 42, 45, 47, 49, 53–55, 60, 61]. Included studies also focused on cardiovascular disease [28, 48, 60], depression [32] and chronic obstructive pulmonary disease [50, 52, 60]. Other studies [25, 27, 31, 35, 38, 41, 43, 44, 46, 51, 56–59] focused on the provision of care to patients with chronic diseases more generally.

Though a range of CCM elements were used across the papers reviewed, the mean number of elements across the 38 papers included in this review was four, with only one study including seven of the elements. None of the papers included studies utilising FS. While the most commonly included element was SMS (Table 1), there were substantive between study variations both in the elements used and how these elements were implemented. For example, descriptions of SMS implemented in primary care settings included development of care guides and individualised patient action plans [36, 48] individual counselling or coaching [52, 54], education programs on disease management [29, 32, 39, 50], web-based patient portals [30] and programs on

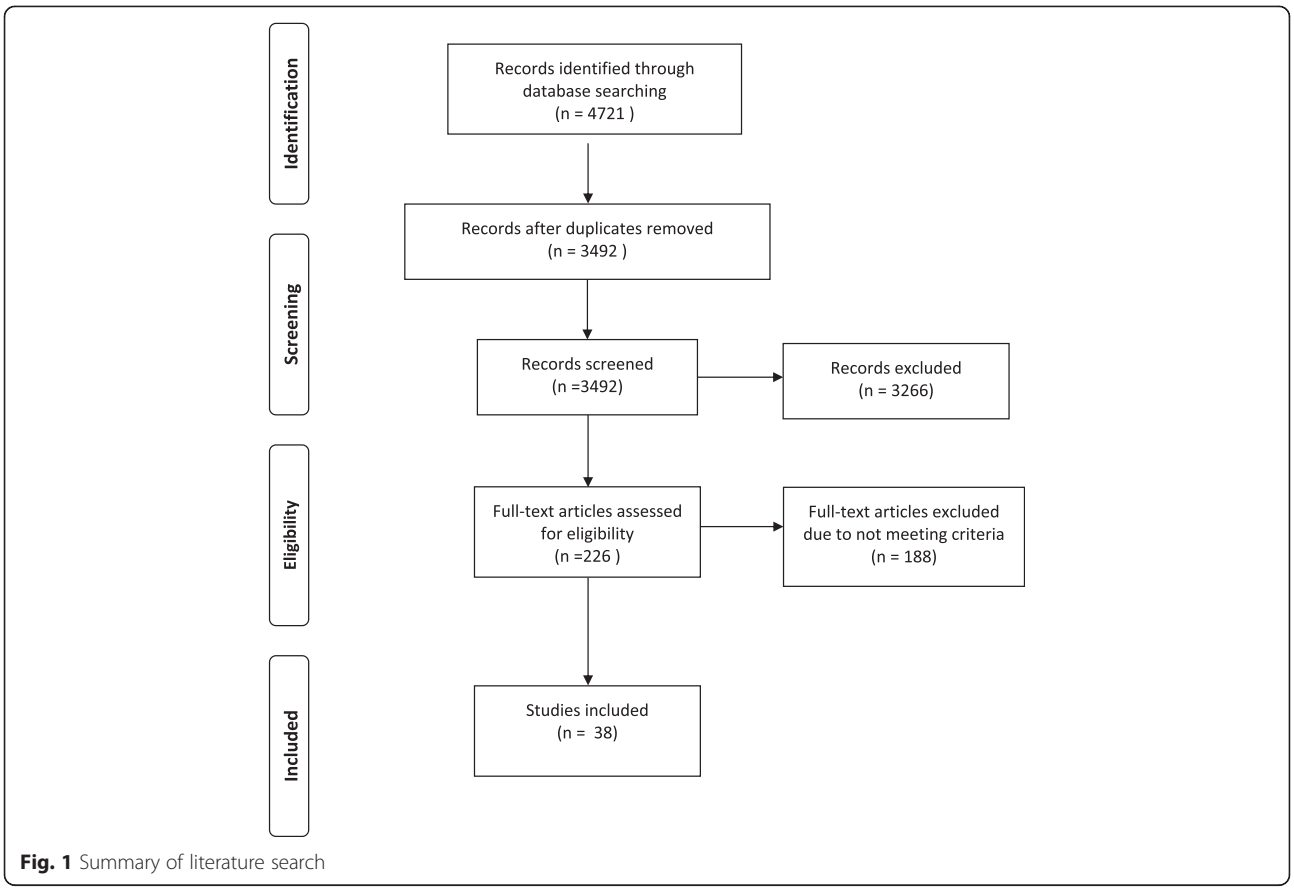

Fig. 1 Summary of literature search

empowerment, goal-setting and motivation [35]. More generally, a number of papers in this review reported using plan-do-study-act or learning collaborative approaches which resulted in context specific implementation strategies for all included elements [24, 33, 35, 42, 60] (Table 1).

Methodological quality

All 38 papers were critically appraised. The Cochrane Collaboration's tool was used to assess risk of bias in randomised controlled trials, non-RCT quantitative studies, non-RCT qualitative studies and mixed-methods evaluations [21]. Case studies and case series were assessed in accordance with the Joanna Briggs Reviewers' Manual [23]. Additional files present the results of the appraisal process applied to all studies [Additional files 3, 4, 5, 6 and 7].

Table 1 Overview of CCM Elements Reviewed

Element	Number of Papers
Self-Management Support [SMS]	31
Delivery System Design [DSD]	27
Decision Support [DS]	26
Clinical Information Systems [CIS]	25
Health Organisational Change [OC]	10
Case Management [CM]	9
Community Support [CS]	9
Family Support [FS]	0

Facilitators and barriers

The objective of this review was to identify the facilitators and barriers to implementing chronic care models. Of the 38 papers included in this review, four reported on randomised control trials [25, 32, 47, 51], three on cohort studies [26, 53, 54], two on cross sectional studies [28, 59], 11 on qualitative studies [27, 30, 31, 34, 41, 44, 45, 49, 54, 56, 57] and 17 case studies or case series [24, 29, 33, 35–40, 42, 43, 46, 48, 50, 58, 60, 61]. All findings related to identifying facilitators and barriers to implementing chronic care models regardless of perspective, disease or geographical locations were pooled to generate one cohesive set of synthesized findings (Table 2). As such, the syntheses represent provider and provide perspectives.

From the 38 included papers, findings pertaining to both facilitators and barriers to the implementation of CCMs in a primary care setting were extracted. Qualitative as well as quantitative findings presented in a narrative

form were grouped into ten categories and which were then meta-aggregated into four synthesized findings.

Synthesised finding 1 – acceptability of CCM interventions

One of the most prominently reported factors influencing the successful implementation of CCMs was acceptability. Generally referred to using terms such as "satisfaction", 15 of the 38 papers included in this review reported on acceptability from the perspective of healthcare providers [24, 36, 43, 52], patients [25, 30, 32, 38, 49, 58] or both providers and patients [35, 37, 41, 48, 53]. The majority of these participants felt that the CCM implemented in their setting was acceptable.

Category: Acceptability of the CCM intervention for healthcare providers

The majority of papers considered acceptability from the point of view of the healthcare providers [24, 35, 36, 48, 53]. These papers report high levels of support for CCM elements, which in turn facilitated their implementation. Not all, however, provided reasons for why healthcare providers felt these CCM elements were acceptable. Those that did suggested that healthcare providers found them to be helpful to their work [24] and perhaps more importantly, believed that they would make a positive impact on their patients' health [48]. One paper also reported that healthcare providers experienced greater work satisfaction and had access to additional resources as a result of the model's implementation [35]. Finally, one paper focused on the acceptability of the training used to prepare staff for implementation, rather than focusing on implementation of CCM per se [43].

Table 2 Summary of Synthesised Findings

Synthesised Finding 1 - Acceptability of CCM interventions
• Category: Acceptability of the CCM intervention for healthcare providers
• Category: Acceptability of CCM interventions for patients
Synthesised Finding 2 - Preparing healthcare providers for a CCM
• Category: Information about the change
• Category: A reason to change
• Category: Appropriately qualified and experienced chronic care staff
• Category: Leaders and champions for success
Synthesised Finding 3 - Supporting patients
• Category: Patients supported and encouraged to engage with care
• Category: Acknowledging patient differences
Synthesised Finding 4 - Resources for implementation and sustainability
• Category: Time needed to implement and sustain CCMs
• Category: Information and communication
• Category: Sufficient funding
• Category: Collaborations with other healthcare services
• Category: Monitoring and evaluating

Category: Acceptability of CCM interventions for patients

Of the studies which did measure patients' perspectives, the majority found that CCMs were acceptable [35, 37, 38, 49, 51, 53]. Nevertheless, two RCTs found no statistically significant differences in levels of satisfaction between intervention and control patients [25, 32]. Another qualitative study identified a range of both positive and negative responses in relation to a study which aimed to provide patients with online information as part of SMS [30]. Positive responses in this study included patients feeling empowered as a result of the readily available online information, as well as a greater understanding of how lifestyle choices impacted upon their health. On the other hand, patients in this study also reported a number of inefficiencies which reduced the acceptability of the system, including missing online results and slow response times from nurses and doctors.

Synthesised finding 2 - preparing healthcare providers for a CCM

Factors which influenced whether healthcare providers embraced the implementation of a CCM also depended on whether sufficient information was provided in an appropriate manner and whether staff were convinced that a change to the way healthcare was delivered would be beneficial. This synthesised finding acknowledged that without staff who had the necessary skills and experience to take on new roles and responsibilities, implementing a new CCM would be particularly difficult. Also noted, was the importance of ensuring that healthcare staff are supported by strong leaders and champions who are able to provide both management and clinical support.

Category: Information about the change

Clearly articulated concepts and examples of how a CCM could work once implemented, were identified as an important facilitator to implementation [28]. Staff who were not provided with this information may be left wondering what the expected outcomes could or should be [32]. Structured learning sessions involving a whole of team approached that focused on collaborative and supportive learning environments, providing opportunities for staff to ask questions and raise concerns, were thought to prevent any resistance to change [26, 34].

Ensuring that individual staff members have the necessary knowledge and skills required to undertake their particular roles and manage any new responsibilities prior to implementing a new CCM was also shown to be important [59]. If, for example, the model included

community or family support, it could be particularly advantageous for staff to know about community resources including existing disease management group meetings, exercise facilities, mental health services, or discounted health programs [35]. It was also considered important for staff to feel comfortable and confident in taking on any new responsibilities; if necessary by being provided with opportunities for additional training and on the job support [61]. In order to facilitate fruitful working relationships, staff who needed to collaborate with people external to their immediate team or an external organisation were believed to have benefited from being provided with information about and even a chance to meet with these collaborating parties prior to implementation [54].

Category: A reason to change

One of the most important facilitators to implementing a CCM is a well thought out and articulated argument for change [60]. Without clearly defined benefits, healthcare providers may become dismissive and uncooperative. A groundswell of agreement for improvements needs to be carefully nurtured prior to beginning the implementation process [31]. Quality Improvement initiatives that clearly identify gaps in care [44], where the goal can be clearly recognised as improvements to patient care rather than change for the change sake of change were considered to be a useful strategy [56]. Goals and outcomes that appear unclear or fuzzy, and a process of change that were uncoordinated, were believed to result in healthcare providers disengaging from the implementation process [31]. Managers, therefore, played an important role in leading staff through the change process, which was further enhanced by ensuring that any success was measured and appropriately rewarded [41].

Category: Appropriately qualified and experienced chronic care staff

Unsuitable or insufficient staffing undermined the implementation and sustainability of a CCM [27]. While physicians were considered to be an essential component of the chronic care team particularly in regards to advising and supporting other healthcare providers [61], the lack of nurses dedicated to chronic disease programs [61], as well as management and administrative support staff [24, 31, 55], impeded the implementation and/or sustainability of a new CCM.

A high turnover of staff was noted as another barrier to both implementing and sustaining a new CCM [61]. In one instance [26] a general shortage of qualified healthcare providers meant that highly skilled staff were being replaced by less adept medical assistants which in turn put at risk the sustainability of the CCM. High staff turnover, in this instance, resulted in a complete derailing of the implementation process [33]. Irregular rotations of both doctors and nurses in another remote location created a lack of consistent chronic disease care, which was vital to the success of a given model [59]. Yet on a more positive note, the implementation of a new CCM in one study [41] was believed to be associated with a decrease in staff turnover.

Skills and experiences of chronic care staff were also important for the success of a new CCM. Although providing staff had a desire to learn, and sufficient time to devote to understanding new ways of working, shortfalls in any skills or experience could be overcome [28]. Another way of supporting staff through the change process was to form multi-disciplinary teams [42]. Yet, setting up a multidisciplinary team was not always easy. Respect for the role of each discipline and enhanced interdisciplinary communication were critical to the success of this initiative [54]. Furthermore, if existing staff had no prior history of working within an interdisciplinary team the sustainability of the model may be put at risk [54].

Category: Leaders and champions for success

A consistent theme within the papers reporting upon facilitators and barriers was the need for supportive leadership [24, 26, 31, 34, 35, 41, 42, 60]. As well as management staff who were committed to the implementation and sustainability of the new model [24, 42], strong clinical leaders and champions were needed to support healthcare providers through the change process [31]. In a primary care clinic within a teaching hospital physician leaders were found to be essential in helping a provider population of rotating residents and part-time physicians implement a CCM model. Indeed the educationally rich environment fostered by these leaders was felt to benefit temporary and permanent staff members alike [26]. Without this type of support, the implementation and sustainability of the model may be put at risk [31, 34].

Synthesized finding 3 - supporting patients

The third synthesised finding identified factors that were believed to influence whether patients were able and willing to engage with care delivered through a CCM. In particular, patients needed to be supported to fully engage with healthcare, particularly when a model incorporated aspects of self-management support. Providing understandable information about their health, as well as support groups that motivated them to reach their own goals, encouraged patients to take a greater interest in and responsibility for their health. This finding also identified that patients may not always be able to actively contribute to their care. Instead, it was important to acknowledge patients as unique individuals with different levels of capacity for engagement.

Category: Patients supported and encouraged to engage with care

Self-management support, which relied on patients taking some responsibility for their own healthcare, was one of the most common elements identified in this review (see Description of Studies). Educational services that provided clear and concise information to patients so that they were able to respond appropriately were generally viewed positively [45, 54]. Yet educating and empowering patients was a challenge given the breadth of clinical questions that may need to be covered, the nature of patients' concerns and anxieties, patients' varying cultural needs, and related difficulties of concordance and adherence [53]. Support groups were another way of encouraging patients to take on a degree of responsibility for their own care. Support groups were found to be mutually motivating and patients participating in such groups were found to monitor their condition more closely and respond to health promoting activities such as physical exercise, more positively [47]. Support groups were often seen as a particularly beneficial adjunct to general healthcare.

However, not all patients were ready or able to take on greater responsibility for their own healthcare [58]. In particular, poor psychological health (health beliefs, motivation and self-efficacy), lower levels of education (poor knowledge or awareness of education services), and other social determinants of health (finance, transport), as well as psychosocial factors (discrimination due to having diabetes, lack of support from family, friends or the community and inappropriate cultural messages), can all act as major barriers to diabetes care [40]. Other interventions including online systems that allowed patients to monitor their own records did not suit all patients, especially if many of the target group did not have the necessary skills to navigate these sometimes complex systems [56].

Category: Acknowledging patient differences

Another barrier to implementing self-management support was that advice provided in educational activities was not personalised to the individual patient [47]. A client- or patient-centred approach was considered to be far more effective in supporting patients to take responsibility for their own health [35, 57]. Individualised self-management plans with dedicated time to speak to clients in order to ensure they have all of the relevant information and ability to implement the plan is required [59]. However, not all healthcare facilities were set up to provide this level of care. Walk-in clinics may not have the time and solo family practices may not have the staff required to provide extensive patient-centred self-management support [46].

In addition to patient-centred care, there was also a need to ensure that programs were tailored to the needs of the community or region more generally [54]. In particular, language and literacy issues were a challenge to changing delivery system design. Strategies for addressing these included recruiting multilingual staff, adapting and translating materials, redesigning educational handouts towards a pictorial focus, and using interpreters [50].

Synthesised finding 4 - resources for implementation and sustainability

Features that supported implementation and sustainability more broadly included the time and effort required to implement a new CCM, as well as the need for sufficient resources, including information and communication systems and funding. Ongoing monitoring and evaluation to ensure continuous quality improvements was then needed to ensure the sustainability of CCMs.

Category: Time needed to implement and sustain chronic care models

Key to implementation was the need to maintain realistic expectations regarding the time required to implement a CCM [31]. While people may have wanted or wished that changes were quickly realised, in reality it took time for healthcare providers and patients to come to trust the new initiative [54]. Attempting to make too many simultaneous changes to existing delivery of care practices could also discourage staff from moving towards a new model of care [31]. Instead, introducing the model slowly and carefully, with sufficient time for the necessary cultural shifts as the healthcare team take on new roles and responsibilities, was believed to be important for success [58].

Even once implemented, new ways of delivering services appeared to require more, rather than less, staff time [24]. One study [57] found that the amount of time required to conduct patient-centred care planning was a serious barrier to implementing their CCM more widely. Even when supposedly time saving devises such as electronic medical information systems were implemented health providers found that such initiatives took a significant amount of effort to integrate these into their daily practice [45, 56]. Motivating patients to participate in education programs [54], developing patient treatment plans, encouraging self-management and meeting preventive and psychosocial needs of chronically ill patients [41], were all found to require additional healthcare provider time, which should be recognised and factored into daily work schedules.

Category: Information and communication

Appropriate information and communication systems were considered to be vital tools for the implementation and sustainability of a new CCM. These systems assisted

by identifying and keeping track of patients with chronic disease [42, 58], monitoring healthcare against service standards, identifying gaps in services, and documenting successes [29]. Information and communication systems also aided in self-management support, for example, by using a patient portal to connect with clients and providing up to date information on their health as well as tips for continuing to reduce their risk of further complications from their chronic disease [26, 56].

Nevertheless, information and communication systems that were inappropriately designed or did not function well were a barrier to the implementation and sustainability of CCMs. Healthcare providers were critical of, for example, systems that simply replicated existing manual systems, electronic health records that were limited in terms of not being able to provide reminders in real time, and electronic records that required a significant amount of time to enter or retrieve information [56, 53]. In addition, the simultaneous demands associated with the implementation of a electronic medical record system while at the same time changing the way in which care is delivered were thought to be overly onerous [31] . Intensive support was needed to ensure that information and communication systems facilitated rather than hindered the implementation and sustainability of a new CCM [44].

Category: Sufficient funding

The implementation and ongoing sustainability of CCMs was sometimes costly, and without sufficient funding, the process was likely to fail [54]. Unfortunately, healthcare services often found it difficult to find the funds to support clinical change, especially when there were other projects competing for the same pot of money [41]. In particular, specialised services such as support groups, which are generally seen as a facilitator to implementation, could require significant amounts of money to fund [47]. Funding some of the basic services such as case management and care planning meetings, important elements to many of the CCMs discussed in this review, were also beyond the budget of some organisations [57]. Yet, incentivising healthcare providers to improve healthcare practices, in combination with the implementing a CCM [27], and possibly even a separate reimbursement for follow-up care or performance-based pay, increased the use of CCMs in practice [32].

On the positive side one study [35] found that increased visits for patients as a direct result of the implementation of a CCM provided additional income to offset any initial loss of revenue. Likewise, another study [39] implemented new patient scheduling arrangements to ensure provider productivity and cost effectiveness for Shared Medical Appointments.

Category: Collaborations with other healthcare services

Partnering with other healthcare services such as hospitals and specialist services was considered to facilitate the implementation and sustainability of CCMs. In particular, collaboration was linked with cross institutional learning [42] and communication [53], joint decision making [54, 60], pooling of scarce resources [34, 62]. Other important features of collaborations was the access to healthcare services which otherwise may not have been available [45], and improved transitioning of patients between healthcare services [43].

Category: Monitoring and evaluating

Finally, CCMs required systems for ongoing monitoring and evaluation if they were to be effectively implemented and sustained [27, 59]. One of the primary barriers to the process of continuous quality improvements is the lack of useful data and poor collection of existing measures [26, 31]. Yet a system for monitoring and evaluation was a hindrance if providers perceived that it did not add particular value but instead was an additional burden [54].

Discussion

This systematic literature aimed to identify facilitators and barriers to implementing a CCM in a primary healthcare setting from the perspectives of healthcare providers and patients. The four synthesised findings – Acceptability of the CCM intervention, Preparing Healthcare Providers for the CCM, Supporting Patients, and Resourcing Implementation and Sustainability – spoke to a need to consider an holistic approach to CCM implementation and sustainability both from patients' and healthcare providers' perspectives. While it is important to consider whether the healthcare system will be able to support the implementation of a CCM, this review highlighted the importance of human factors to the success or otherwise of CCM interventions [62].

Facilitators and barriers

Whether or not the CCM was acceptable to both patients and providers was a factor for determining the success of the interventions included in this review. However, definitions of acceptability varied. One of the primary difficulties in measuring acceptability is that the term is often inclusive of a number of different constructs including whether the patient is willing to implement changes to their behaviour [63]. Early work in this field suggests that from a patient's perspective, these constructs can include social validity, which refers to the social desirability of an intervention [64]. In addition, concepts such as treatment integrity and treatment use [65] have also been used in to better understand whether individuals like a prescribed treatment or procedure

[66]. Adding to this complexity is the number of underlying issues that influence the degree to which any individual finds an intervention acceptable. For patients this may include the severity of their condition [67] and the quality and amount of information that is available to them [68]. The reputation of the service, the number of alternative healthcare options and previous experiences also influence patients' perceptions [69]. Very few studies, however, considered acceptability from a healthcare provider perspective. In addition, simply asking whether a patient or healthcare provider liked or was satisfied with a particular intervention may therefore not be a reliable method for measuring this construct.

The papers included this review also suggested that preparing healthcare providers for change was an important factor for success. If the information provided is not sufficient, or alternatively if healthcare providers do not see the benefits of implementing a CCM, it is more likely to fail. This highlights the importance of leaders and champions for guiding their healthcare staff through the change process. These are the people who not only sell the vision for the future but also legitimise the change and "call people to action" ([70] p. 366). Effective leaders will involve their staff from the very beginning of the change process to help embed a sense of ownership [71].

Patients must not be left to fend for themselves but instead should receive support as part of the intervention. Yet none of the studies described in this review utilised FS, and only nine of the papers utilised CS. However, the review did find that it was important to appreciate patients' individual capacity to respond to self-management support initiatives. Not only the degree of support, but also the type of support needed, may vary across time and therefore healthcare providers will need to continually monitor patient needs. Importantly, a team approach, whereby a range of healthcare providers are available to a patient at any one point in time, may best support patients' needs [72]. Other important factors that influence the success of self-management initiatives include ensuring that patients are able to access appropriate levels of information in a format that they are able to understand, identifying whether patients have the desire and resources to manage their own health, being able to help patients plan strategies that contribute to their particular goals and ensuring there is mutual investment, with both the healthcare provider and the patient working towards common goals [73].

This systematic literature review also identified the importance of ensuring appropriate resources are in place to support change. Many of the CCM elements including case management and self-management support require healthcare providers to spend more, not less, time with patients [74]. Yet insufficient funding for employing additional chronic care staff as well as issues pertaining to recruiting and retaining healthcare providers particularly in rural and remote areas [75] often means that time for patients is at a premium. The time needed to develop and use a clinical information system was also highlighted. The perceived ease of use is also an important acceptance criteria for whether a new technology will be accepted and used by healthcare providers [76].

A greater focus on the human factors

Three of the four synthesised findings in this systematic literature review highlighted the significant contribution that patients and providers can make in either facilitating or impeding the implementation of CCMs. However, even the crucial resources identified in the fourth synthesised finding such as time, underlined the importance of human factors for implementation and sustainability. Obstacles to implementation may therefore be as much about the people involved, as they are about resources, processes and systems. Yet, the two theories that are thought to inform the development and underpin the philosophy behind CCMs – Integrated Care and Quality Management – have tended to take a more structural or systems approach to the delivery of care [9].

Although not always clearly defined, the concept of Integrated Care grew from the notion that the development of "coherent set of methods and models on the funding, administrative, organisational, service delivery and clinical levels" ([77], p. 3) will lead to better connectivity between healthcare services. More recently, Integrated Care has evolved to become more synonymous with individual patients' needs [78]. Some researchers [79, 80] going so far as to call for the development of evaluation measures and techniques which capture broader and more nuanced understandings of patient perspectives. Generally, there is a move away from regarding patients as passive recipients of healthcare to one which acknowledges their active participation in making choices about the way in which their health is managed [81].

Quality management theory also started out by emphasising the organisational level perspective [82]. This theory originated from the manufacturing sector where quality was first assured through the inspection of products prior to despatch. Quality control which aimed to find defects during the production process, quality assurance which developed processes that prevented defects and finally total quality management which utilised a management approach to ensuring an entire quality system, have also been developed [10]. Within healthcare, quality management theory has tended to focus on the total quality management approach, seeking to design and control systems in order to minimise harm to patients [8]. Yet more recently there is a recognition

that commitment to improving services from healthcare providers is crucial to the success of quality initiatives [83]. Rather than thinking about quality at just the system level, "quality systems that give staff ongoing "ownership" and pride in a way that is akin to the era of the craftsmen" ([84], p. 367) has been called for. As was found in this review, commitment and support from leaders is particularly crucial for the successful implementation of quality management programs in healthcare settings.

This systematic literature review therefore mirrors the more recent progression in thinking behind both Integrated Care and Quality Management theories by re-emphasising the human factors which need to be considered when implementing complex interventions such as CCMs. While others have suggested that the implementation of complex intervention primarily depends on the behaviour of healthcare providers , this review suggests that patients can also act to facilitate or impede the implementation of CCMs.

Limitations

While no papers were excluded based on quality, of particular concern was the risk of bias, particularly in the case of one author (CD) being responsible for the data extraction. In addition, the quality of the case studies and case series included in this review was considered to be poor. Yet the findings from this systematic literature review are supported by more recent shifts in two of the primary theories – Integrated Care and Quality Management – which have informed the development of CCMs. It is important to acknowledged that the vast majority of included studies were conducted in the Americas. While US, Canadian and to some extent Mexican perspectives are well represented, the results may not thoroughly reflect facilitators and barriers to intervention implementation in the other countries. The authors also acknowledge that to be included in this review the paper had to have reported on an intervention which included at least two of the eight specified elements (CS, FS, CM, SMS, OC, DSD, DS, CS). It is probable that there will be other CCMs which do not include two of these elements. Finally, the authors also acknowledge that the key findings may be very different had papers reporting the perspectives of other stakeholders including, for example, policy makers been sought.

Conclusion

The successful implementation of complex interventions such as a CCM may depend not only on the provision of appropriate resources and the development of effective systems and processes, but also on a broad range of different stakeholders who will interpret and influence this implementation process. This systematic literature review has re-emphasised the need to consider the human factors, including the role of both patients and healthcare providers, who can either facilitate or impede successful implementation. In addition to ensuring appropriate resources, this review highlights the importance of ensuring that the intervention is acceptabile to both patients and healthcare providers. It was also emphasises the impotance of preparing healthcare providers for the change process and ensuring that patients are supported throughout the implementation of a CCM.

Additional files

Additional file 1: Medline Search Strategy. (DOCX 13 kb)

Additional file 2: Description of Chronic Care Models. (DOCX 19 kb)

Additional file 3 Quality appraisal of Case studies and Case series. (DOCX 44 kb)

Additional file 4: Non-Randomised Control Trials. (DOCX 14 kb)

Additional file 5: Appraisal for qualitative research. (DOCX 43 kb)

Additional file 6: Risk of bias in randomised controlled trials. (DOCX 15 kb)

Additional file 7: Retrospective Studies. (DOCX 15 kb)

Abbreviations

CCM: Chronic Care Model; CIS: Clinical information systems; CM: Case management; CS: Community support; DS: Decision support; DSD: Delivery system design; FS: Family support; OC: Health organisational change; SMS: Self-management support.

Competing Interests

The authors declare that they have no competing interests.

Authors Contributions

CD participated in the design of the study, the literature search, assessment of quality and bias, extraction of findings and drafting the manuscript. JB participated in the extraction of findings and drafting the manuscript. HL and MT participated in the literature search, assessment of quality and bias and extraction of findings. SP participated in the design of the study, the literature search, assessment of quality and bias and extraction of findings. AB participated in the design of the study. All authors read and approved the final manuscript.

Acknowledgements

This research and the researchers working on this study were supported by a Centre for Research Excellence Grant from the Australian Primary Health Care Research Institute. AB is supported by a post-doctoral fellowship from the National Heart Foundation (#PR 08 M 4207) and a senior medical research fellowship from the Viertel Charitable Foundation. This research was also supported by National Health and Medical Research Council (NHMRC) Grant No 1061242. The published material are solely the responsibility of the individual authors and do not reflect the views of NHMRC.

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Received: 12 March 2015 Accepted: 7 August 2015
Published online: 19 August 2015

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APPENDIX 3

Appendix Overview

This appendix comprises of 2 publications from the ATTEND Collaborative Group- the protocol of the RCT, and the findings of the RCT.

Authors' Contributions: JDP originally suggested the study. JDP, RIL, CSA, LB, AF, MLH, LAH, SJ, PL, PKM, GVSM, and MFW designed the study and obtained funding. QL and LB did the statistical analysis. HL led the process evaluation. RIL wrote the first draft of the manuscript, and all writing committee members contributed, edited, and approved the final version.

Publications details:

The ATTEND Collaborative Group. (Writing Group: Lindley R….Liu HM et al) Family-led rehabilitation after stroke in India (ATTEND): a randomised controlled trial. Lancet. 2017. doi:10.1016/S0140-6736(17)31447-2.

Alim M, Lindley R, Felix C, Gandhi DB, Verma SJ, Tugnawat DK…Liu H, et al. Family-led rehabilitation after stroke in India: the ATTEND trial, study protocol for a randomized controlled trial. Trials. 2016

Manuscripts:

Family-led rehabilitation after stroke in India (ATTEND): a randomised controlled trial

*The ATTEND Collaborative Group**

Summary

Background Most people with stroke in India have no access to organised rehabilitation services. The effectiveness of training family members to provide stroke rehabilitation is uncertain. Our primary objective was to determine whether family-led stroke rehabilitation, initiated in hospital and continued at home, would be superior to usual care in a low-resource setting.

Methods The Family-led Rehabilitation after Stroke in India (ATTEND) trial was a prospectively randomised open trial with blinded endpoint done across 14 hospitals in India. Patients aged 18 years or older who had had a stroke within the past month, had residual disability and reasonable expectation of survival, and who had an informal family-nominated caregiver were randomly assigned to intervention or usual care by site coordinators using a secure web-based system with minimisation by site and stroke severity. The family members of participants in the intervention group received additional structured rehabilitation training—including information provision, joint goal setting, carer training, and task-specific training—that was started in hospital and continued at home for up to 2 months. The primary outcome was death or dependency at 6 months, defined by scores 3–6 on the modified Rankin scale (range, 0 [no symptoms] to 6 [death]) as assessed by masked observers. Analyses were by intention to treat. This trial is registered with Clinical Trials Registry-India (CTRI/2013/04/003557), Australian New Zealand Clinical Trials Registry (ACTRN12613000078752), and Universal Trial Number (U1111-1138-6707).

Findings Between Jan 13, 2014, and Feb 12, 2016, 1250 patients were randomly assigned to intervention (n=623) or control (n=627) groups. 32 patients were lost to follow-up (14 intervention, 19 control) and five patients withdrew (two intervention, three control). At 6 months, 285 (47%) of 607 patients in the intervention group and 287 (47%) of 605 controls were dead or dependent (odds ratio 0·98, 95% CI 0·78–1·23, p=0·87). 72 (12%) patients in the intervention group and 86 (14%) in the control group died (p=0·27), and we observed no difference in rehospitalisation (89 [14%] patients in the intervention group *vs* 82 [13%] in the control group; p=0·56). We also found no difference in total non-fatal events (112 events in 82 [13%] intervention patients *vs* 110 events in 79 [13%] control patients; p=0·80).

Interpretation Although task shifting is an attractive solution for health-care sustainability, our results do not support investment in new stroke rehabilitation services that shift tasks to family caregivers, unless new evidence emerges. A future avenue of research should be to investigate the effects of task shifting to health-care assistants or team-based community care.

Funding The National Health and Medical Research Council of Australia.

Published Online
June 27, 2017
http://dx.doi.org/10.1016/S0140-6736(17)31447-2

See Online/Comment
http://dx.doi.org/10.1016/S0140-6736(17)31489-7

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Introduction

Stroke rates are rising in low-income and middle-income countries (LMICs) but services are scarce.[1] Task shifting rehabilitation activities to unpaid caregivers might offer a sustainable alternative to conventional rehabilitation, and provide an affordable strategy to meet the health demands both in high-income countries and LMICs.[2–5] India, with a sixth of the world's population, has only around 35 stroke units, located mainly in urban centres.[6,7] Consequently, most people have no access to specialised stroke care and little access to conventional rehabilitation programmes. Given that LMICs have only about 3% equivalent purchasing power to spend on health care compared with high-income countries, any new model of stroke rehabilitation should be both sustainable and effective.[8,9] Our hypothesis was that family caregiver-delivered rehabilitation would increase independence and survival after stroke unit admission. We report the results of the Family-led Rehabilitation after Stroke in India (ATTEND) trial, which assessed a rehabilitation training programme to deliver family-led rehabilitation after stroke.

Methods

Study design and participants

ATTEND was a prospectively randomised open trial with blinded endpoint (PROBE) done across 14 hospitals in India. Approvals were obtained from the ethics committees of the University of Sydney, Australia, and at each participating hospital. Permission was also obtained from the Health Ministry Screening Committee, New Delhi, India. The trial methods were piloted in Ludhiana (Punjab, India)[10] and the protocol was published before unblinding.[11]

Patients were eligible if they had a family-nominated caregiver (ie, an informal family caregiver or family-hired help or nurse) who was willing to deliver rehabilitation, were aged 18 years or older, had had a stroke within the

Research in context

Evidence before this study

In low-income and middle-income countries, community rehabilitation is seen as a high priority for health-care delivery to reduce disability. Systematic reviews of early supported discharge (ESD) stroke services have shown this model of care reduces death or dependency without adverse effects on family caregivers. We updated the search strategy (to Jan 6, 2017) for the Cochrane review of ESD services for people with acute stroke that categorises interventions into those with or without coordinated multidisciplinary team input. We identified two randomised controlled trials (n=289 in total) in the latter category that had tested a similar intervention: the ATTEND pilot study and an unpublished Chinese trial of nurse-delivered rehabilitation after stroke.

Added value of this study

This randomised controlled trial is the first large trial to our knowledge to test task shifting of stroke rehabilitation to family members. This approach did not improve outcome (compared with usual care) after stroke unit admission. The results were consistent with previous smaller trials of ESD services without multidisciplinary team coordination.

Implications of all the available evidence

Family-led rehabilitation did not improve outcomes, but did not increase harms such as increased burden of care for the family. These results do not support investment in new stroke rehabilitation services that shift tasks to family caregivers, unless new evidence emerges. Future models of low-cost stroke rehabilitation should investigate task shifting to non-family workers or team-based community care.

past month, were able to be randomised within 7 days of admission to hospital, had residual disability (defined by needing help from another person for everyday activities), had a reasonable expectation of survival (ie, not for palliative care, with no evidence of widespread cancer or similar terminal condition), would be available for follow-up for 6 months, and they and their caregiver provided consent. Site coordinators screened all admitted stroke patients and obtained written informed consent from patients and caregivers.

Overall management of the study was coordinated from The George Institute for Global Health (Sydney, Australia). Weekly teleconferences were undertaken between study personnel in Sydney and India during the preparation, conduct, and close-out of the trial. The national clinical coordination centre was based in Ludhiana and project management was based at The George Institute India (Hyderabad, Telangana, India). The Indian Institute of Public Health (Hyderabad, Telangana) provided independent trial monitoring. Additional logic checks and central monitoring of data were done.

Randomisation and masking

The trial funded full-time coordinators (physiotherapists) and masked assessors at each site. The coordinator assessed patients for eligibility, obtained consent from them, and gathered key baseline and demographic data before randomisation. Coordinators were also responsible for training the patients and caregivers. Patients were randomly assigned (1:1) to intervention or a usual care control group via a secure web-based central randomisation system with minimisation by site and stroke severity (National Institutes of Health Stroke Scale [NIHSS] scores <8 *vs* ≥8). To address potential unblinding, coordinators were not permitted to treat other non-trial stroke patients or share an office with the masked assessor. Additionally, they were instructed to undertake patient training sessions in a private room or behind curtains. Assessors were kept unaware of the details of the trial intervention, including having separate training sessions at annual collaborator meetings. Any inadvertent unblinding at an assessment was recorded.

Procedures

The family rehabilitation training intervention was delivered in addition to routine rehabilitation at each site. An international steering group developed the culturally specific intervention, piloted an early version,[10] and incorporated features to ensure it could be affordable when scaled up. The intervention was designed to be delivered by a rehabilitation professional (coordinator), started in hospital, and continued at home. It involved training family members to provide a simplified version of evidence-based rehabilitation,[12–14] and included comprehensive impairment and disability assessment by the coordinators; information provision; joint goal setting with the patient and caregiver for basic activities of daily living (ADL), extended ADL (EADL), and communication; caregiver training for limb positioning; encouragement of the practice of task-specific activities; and reminders to prepare the patient and carer for hospital discharge. The training was designed to take place for about 1 h a day in hospital for about 3 days, with the intention of expediting early supported discharge.[11] After hospital discharge, the coordinator made up to six home visits to assess progress, continue caregiver training activities, and reset goals, and was available for further support by telephone for up to 2 months after randomisation. No trial assessments were done by the coordinators during these home visits, which were purely for guidance and training. A written intervention guide was available for the coordinators and an intervention manual for the patient and caregiver. To

reduce potential contamination, the manual was given to participants on the first home visit to prevent access by control participants in hospital.[10] The coordinator ceased contact 1 month before the first follow-up (ie, at 2 months after randomisation) to reduce the risk of unblinding. Only the coordinators and members of the steering and management committees were aware of the details of the family rehabilitation training intervention (including the written guide). In our trial sites, usual care consisted of some therapy, in the form of assessment and treatment by a physiotherapist, during hospital stay, with post-discharge care varying from no therapy to some outpatient therapy sessions.

To ensure intervention fidelity across sites, coordinators were collectively trained at study initiation and annual collaborator meetings, supplemented by on-site training as required. Intervention training was led by physiotherapists from India and Australia. Day-to-day support was provided by a clinical coordination team that included a neurologist and physiotherapist. A log of trial interventions was kept by the coordinator for each participant for hospital and home visit activities. Intervention patients (with their caregivers) were encouraged by the coordinator to keep a daily log of rehabilitation activities for 30 days after discharge.

Baseline characteristics and events during the initial hospital stay were obtained by the unmasked coordinators: all other trial assessments were done at 3 months and 6 months after randomisation by trained masked assessors who assessed the patient and caregiver at home, or at the hospital, or by phone if a face-to-face visit was not possible. Patients were assessed with the modified Rankin scale (mRS), which is a global seven-level measure of functioning with scores of 0–2 representing good outcome and functional independence, 3–5 representing increasing levels of disability, and 6 death;[15] the simple validated recovery and dependency questions;[16] the Barthel Index of ADL (on a scale of 0–100 with lower scores representing fewer activities);[17] the Nottingham EADL scale (on a scale of 0–66 with lower scores representing fewer activities);[18] the WHO Quality of Life (WHOQOL-BREF, with domains scored from 0 to 100 with lower scores representing lower quality of life);[19] the EuroQol Group 5-Dimension Self-Report Questionnaire, which includes an overall health state (on a scale of 0–100, with lower scores representing lower quality of life);[20] and the Hospital Anxiety and Depression Scale subscales (HADS, with lower scores indicating fewer symptoms).[21] Caregivers were assessed with the Caregiver Burden Scale (on a scale from 21 to 84, with lower scores representing less burden) and the HADS subscales.[22]

Outcomes

The primary outcome was the proportion of patients who were dead or dependent at 6 months as defined by scores of 3–6 on the mRS, with an ordinal shift analysis of the full range of categories of the mRS as a secondary outcome. Other secondary outcomes were the simple validated recovery and dependency questions, length of hospital stay, place of residence (whether the same as before stroke [yes/no]), the Barthel Index, the Nottingham EADL scale, quality of life (WHOQOL-BREF and the EuroQol Group 5-Dimension Self-Report

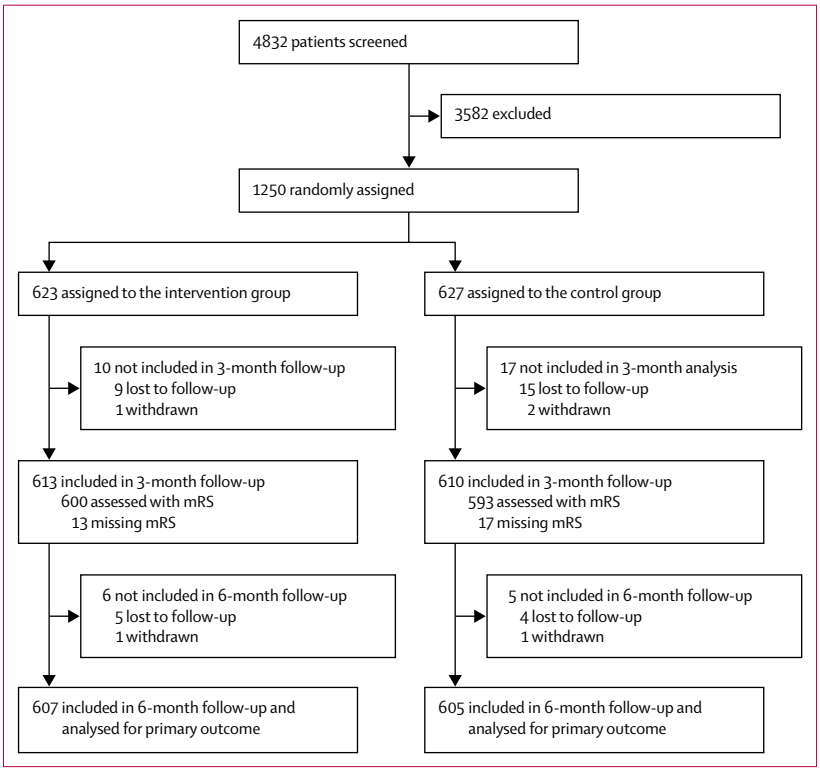

Figure 1: **Trial profile**

	Intervention (n=623)*	Control (n=627)	Total (N=1250)
Sex			
Male	421 (68%)	416 (66%)	837 (67%)
Female	202 (32%)	211 (34%)	413 (33%)
Age (years)			
n, mean (SD)	623, 57·5 (12·92)	627, 58·0 (14·21)	1250, 57·7 (13·58)
Median (IQR)	58 (50–66)	59 (49–67)	59 (50–66)
Range	18–95	19–95	18–95
18 to <40	58 (9%)	63 (10%)	121 (10%)
40 to <50	89 (14%)	97 (15%)	186 (15%)
50 to <60	189 (30%)	159 (25%)	348 (28%)
60 to <70	175 (28%)	176 (28%)	351 (28%)
70 to <80	89 (14%)	89 (14%)	178 (14%)
≥80	23 (4%)	43 (7%)	66 (5%)
Marital status			
Married	563 (91%)	557 (89%)	1120 (90%)
Unmarried	16 (3%)	18 (3%)	34 (3%)
Separated	2 (<1%)	1 (<%)	3 (<1%)
Widowed	41 (7%)	51 (8%)	92 (7%)

(Table 1 continues on next page)

	Intervention (n=623)*	Control (n=627)	Total (N=1250)
(Continued from previous page)			
Main caregiver			
Spouse	257 (41%)	261 (42%)	518 (41%)
Mother	14 (2%)	11 (2%)	25 (2%)
Father	3 (<1%)	6 (1%)	9 (1%)
Grandparents and others	2 (<1%)	2 (<1%)	4 (<1%)
Daughter or daughter-in-law	151 (24%)	125 (20%)	276 (22%)
Son or son-in-law	171 (27%)	192 (31%)	363 (29%)
Sister	3 (<1%)	8 (1%)	11 (1%)
Brother	17 (3%)	19 (3%)	36 (3%)
Hired help or nurse	4 (1%)	3 (<1%)	7 (1%)
Highest level of education completed (patient)			
No schooling	88 (14%)	96 (15%)	184 (15%)
Less than primary school	58 (9%)	65 (10%)	123 (10%)
Primary school	113 (18%)	106 (17%)	219 (18%)
Secondary school	68 (11%)	57 (9%)	125 (10%)
High school	123 (20%)	142 (23%)	265 (21%)
College/university	142 (23%)	140 (22%)	282 (23%)
Postgraduate degree	29 (5%)	21 (3%)	50 (4%)
Unknown	1 (<1%)	0	1 (<1%)
Field of work (patient)			
Management	4 (1%)	7 (1%)	11 (1%)
Professional and related	22 (4%)	19 (3%)	41 (3%)
Service	85 (14%)	75 (12%)	160 (13%)
Sales/commercial	64 (10%)	57 (9%)	121 (10%)
Construction	27 (4%)	29 (5%)	56 (4%)
Armed forces	7 (1%)	9 (1%)	16 (1%)
Farming/forestry/fishing and related	60 (10%)	65 (10%)	125 (10%)
Clerical/administrative support	21 (3%)	14 (2%)	35 (3%)
Installation and related	8 (1%)	4 (1%)	12 (1%)
Manufacture/production	16 (3%)	21 (3%)	37 (3%)
Transportation/driver	25 (4%)	27 (4%)	52 (4%)
Housewife	181 (29%)	186 (30%)	367 (29%)
Not applicable	102 (16%)	114 (18%)	216 (17%)
Work situation (patient)			
Full-time paid work	224 (36%)	186 (30%)	410 (33%)
Part-time paid work	46 (7%)	50 (8%)	96 (8%)
Retired	96 (15%)	111 (18%)	207 (17%)
Unemployed	47 (8%)	31 (5%)	78 (6%)
Home duties	171 (27%)	203 (32%)	374 (30%)
Student	3 (<1%)	3 (<1%)	6 (<1%)
Other	35 (6%)	43 (7%)	78 (6%)
Accommodation details			
Own house	501 (81%)	498 (79%)	999 (80%)
Own apartment/flat	19 (3%)	26 (4%)	45 (4%)
Rented flat	37 (6%)	36 (6%)	73 (6%)
Rented accommodation in a house	42 (7%)	47 (7%)	89 (7%)
Government/company-provided house	22 (4%)	17 (3%)	39 (3%)
Jhuggi (slum)	0	1 (<1%)	1 (<1%)
Other	1 (<1%)	2 (<1%)	3 (<1%)

(Table 1 continues on next page)

Questionnaire), patient and caregiver anxiety and depression according to the HADS subscales, and the Caregiver Burden Scale. We also assessed the following health economic outcomes, which will be reported elsewhere: health-care resource use (visits to health professionals, hospitalisation, and medication use), indirect costs to the family (eg, a family member giving up employment to act as a caregiver), direct medical costs (eg, private treatment, admission charges, drug treatments), and non-medical direct costs (eg, travelling costs). Adverse events, including a prespecified list of those most frequent after stroke, were sought. The prespecified list was comprised of deaths due to the initial stroke, myocardial infarction, pneumonia or other vascular or non-vascular causes, and hospitalisation due to recurrent stroke, myocardial infarction, bony fracture, infection, or other causes. Patients and caregivers were given a health diary to record details of any re-hospitalisation, with details obtained at each assessment.

Statistical analysis

On the basis of the Early Supported Discharge Stroke trials,[13] in which death or dependency was 50% in controls, we estimated that a sample size of 1200 patients (600 per group) was needed to provide 90% power (α=0·05) to detect a 21% relative risk reduction (10·5% absolute reduction) in death or dependency in the intervention group with a 20% loss to follow-up.

All analyses were by intention to treat, and all tests were two-sided with a nominal level of significance of 5%. The primary analysis compared the proportion of patients who were dead or dependent (mRS 3–6) at 6 months between the intervention and usual care groups in an unadjusted logistic regression model. Sensitivity analyses were adjustment for study site, stroke severity (NIHSS score <8 or ≥8), age (as a continuous variable), sex, household income (<5000 INR, 5000 to <15 000 INR, 15 000 to <30 000 INR, 30 000 INR and more, no answer or missing data), and patient level of education (completed college [diploma or certificate], university [degree], or postgraduate studies; completed high school [up to grade 12]; completed primary school or secondary school [up to grade –10]; did not complete primary school; no schooling or data missing); and a so-called leave one out analysis whereby the effect on the primary outcome was be calculated with all the participants from a single site removed one at a time.[23] We did nine prespecified subgroup analyses (age, sex, stroke severity, stroke pathology, stroke Oxfordshire Community Stroke Project Classification, carer type, education level, household income, and type of accommodation) by adding the subgroup variable as well as its interaction term, with the intervention as fixed effects to the logistic regression model used for the primary analysis. Sex had been inadvertently omitted (due to author error) in the published statistical analysis plan but was prespecified in our internal analysis and is included for

completeness.[23] Other analyses included all seven categories of the mRS with ordinal logistic regression and a permutation test proposed by Howard and colleagues.[24,25] Analyses of secondary outcomes at 3 and 6 months used *t* tests to compare means (eg, mean scores) and χ^2 tests to compare proportions (eg, place of residence). We analysed length of hospital stay using a log-rank test and serious adverse events using Fisher's exact test. Further details are available in the Statistical Analysis Plan,[23] which was finalised and submitted for publication before unblinding. All analyses were done with SAS Enterprise Guide version 7.1 (SAS/Stat version 9.4). An independent Data and Safety Management Committee monitored the unblinded accumulating results and adverse events according to a written charter.

The trial was registered at the Clinical Trials Registry-India (CTRI/2013/04/003557) and the Australian New Zealand Clinical Trials Registry (ACTRN12613000078752), and has a Universal Trial Number (U1111-1138-6707).

Role of the funding source

The National Health and Medical Research Council had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 13, 2014, and Feb 12, 2016, 4832 patients were screened, of which 1250 were randomly assigned to the intervention group (n=623) or the control group (n=627; figure 1). Baseline characteristics are shown in table 1. At hospital discharge, we found no between-group differences in mRS scores (562 [90%] of 622 patients in the intervention group *vs* 567 [90%] of 627 controls, p=0·96) nor in the Barthel Index scores (mean 43·0 [SD 23·17] in the intervention group *vs* 43·2 [23·39] in controls, p=0·88; appendix).

The training programme was delivered as planned with a mean time of 3·0 h (SD 1·6; median 2·9 [IQR 2·0–3·3]) in hospital. An additional 3·1 h (SD 1·7; median 2·8 [1·9–4·2]) of training were delivered during home visits. Intervention patients and caregivers reported 17·8 h (SD 21·6) of rehabilitation given in the first 30 days after hospital discharge (data available from 574 participants). Details of the rehabilitation provided to both groups as part of routine care and the intervention are shown in the appendix. We found no evidence of a difference in total routine hospital rehabilitation time (2·0 h for intervention patients *vs* 2·1 h for controls, p=0·23), although intervention participants practised fewer mobility activities than did controls (521 [84%] of patients in the intervention group practised at least one activity *vs* 553 [88%] in the controls, p=0·023). We showed no statistical differences between groups in other non-trial routine rehabilitation activities (appendix).

At 6 months, roughly the same number of participants were dead or dependent in the intervention group and in the control group (table 2). The neutral results were

See Online for appendix

	Intervention (n=623)*	Control (n=627)	Total (N=1250)
(Continued from previous page)			
Living situation pre-stroke			
Independent at home	616 (99%)	610 (97%)	1226 (98%)
Dependent at home	6 (1%)	12 (2%)	18 (1%)
Other	0	5 (1%)	5 (<1%)
Financial situation			
Patient or his close family owns the house	507 (82%)	508 (81%)	1015 (81%)
Patient or his close family owns the flat	18 (3%)	20 (3%)	38 (3%)
Rented from landlord	77 (12%)	83 (13%)	160 (13%)
Government-owned or allocated housing	20 (3%)	16 (3%)	36 (3%)
Monthly household income (INR)†			
<5000	93 (15%)	101 (16%)	194 (16%)
5000–14 999	178 (29%)	196 (31%)	374 (30%)
15 000–29 999	166 (27%)	151 (24%)	317 (25%)
30 000–59 999	99 (16%)	74 (12%)	173 (14%)
60 000–100 000	18 (3%)	20 (3%)	38 (3%)
>100 000	8 (1%)	12 (2%)	20 (2%)
Decline to answer	39 (6%)	43 (7%)	82 (7%)
Do not know	21 (3%)	30 (5%)	51 (4%)
Days from stroke onset to randomisation			
n, mean (SD)	623, 4·9 (3·8)	627, 5·1 (4·1)	1250, 5·0 (4·1)
Median (IQR)	4 (3–6)	4 (2–6)	4 (3–6)
Range	0–28	0–29	0–29
Stroke type			
Ischaemic	478 (77%)	478 (76%)	956 (76%)
Large artery atherosclerosis	214/478 (45%)	213/478 (45%)	427/956 (45%)
Cardioembolism	75/478 (16%)	54/478 (11%)	129/956 (13%)
Small artery occlusion	113/478 (24%)	131/478 (27%)	244/956 (26%)
Determined, other aetiology	16/478 (3%)	21/478 (4%)	37/956 (4%)
Undetermined	60/478 (13%)	58/478 (12%)	118/956 (12%)
Intracerebral haemorrhage	143 (23%)	148 (24%)	291 (23%)
Unspecified	1 (<1%)	1 (<1%)	2 (<1%)
OCSP classification‡			
Total anterior circulation syndrome	67/478 (14%)	51/478 (11%)	118/956 (12%)
Partial anterior circulation syndrome	263/478 (55%)	269/478 (56%)	532/956 (56%)
Posterior circulation syndrome	72/478 (15%)	76/478 (16%)	148/956 (15%)
Lacunar syndromes	76/478 (16%)	81/478 (17%)	157/956 (16%)
NIHSS score			
n, mean (SD)	622, 10·1 (4·9)	627, 9·6 (4·8)	1249, 9·9 (4·9)
Median (IQR)	9 (6–13)	9 (6–12)	9 (6–13)
Range	1–29	1–28	1–29
0 to <5	72 (11·6)	103 (16·4)	175 (14·0)
5 to <10	247 (39·7)	241 (38·4)	488 (39·1)
10 to <15	188 (30·2)	182 (29·0)	370 (29·6)
≥15	115 (18·5)	101 (16·1)	216 (17·3)

(Table 1 continues on next page)

	Intervention (n=623)*	Control (n=627)	Total (N=1250)
(Continued from previous page)			
Medical history			
Hypertension	455/618 (74%)	460/620 (74%)	915/1238 (74%)
Diabetes mellitus	273/611 (45%)	265/614 (43%)	538/1225 (44%)
Dyslipidaemia	120/540 (22%)	132/536 (25%)	252/1076 (23%)
Atrial fibrillation	46/579 (8%)	44/589 (7%)	90/1168 (8%)
Coronary artery disease	93/595 (16%)	98/605(16%)	191/1200 (16%)
Obesity	95/621 (15%)	97/620 (16%)	192/1241 (15%)
Smoking	158/618 (26%)	143/622 (23%)	301/1240 (24%)
Alcohol use	164/619 (26%)	169/622 (27%)	333/1241 (27%)
Drug addiction	4/620 (1%)	1/621 (<1%)	5/1241 (<1%)
Carotid stenosis	112/562 (20%)	105/568 (18%)	217/1130 (19%)
Previous stroke/TIA	110/615 (18%)	112/617 (18%)	222/1232 (18%)
Rheumatic heart disease	21/611 (3%)	22/617 (4%)	43/1228 (4%)
Neoplastic disease	3/615 (<1%)	4/617 (1%)	7/1232 (1%)
Pregnancy	0/618	2/621 (<1%)	2/1239 (<1%)

Data are n (%) unless indicated otherwise. INR=Indian rupees. OCSP=Oxfordshire Community Stroke Project. NIHSS=National Institutes of Health Stroke Scale. TIA=transient ischaemic attack. *Data complete for sex and age. One patient withdrew from the intervention group after randomisation and the denominator is 622 for other baseline variables.†US$1=68 INR. ‡Classification for patients with ischaemic stroke.

Table 1: **Baseline characteristics**

similar in adjusted analyses, leave-one-out sensitivity analyses, and across all secondary outcomes (tables 2, 3, figure 2, appendix). The mean number of days from randomisation to hospital discharge was 6·0 (SD 6·8) in the intervention group and 6·3 (7·5) in the controls (p=0·65). The intervention did not reduce total length of stay (mean stay of 9·3 [SD 7·4] days in the intervention group *vs* 9·5 [7·9] days in the controls, p=0·58; appendix). We found no significant differences in non-fatal or fatal adverse events: 72 (12%) deaths occurred in the intervention group compared with 86 (14%) in the control group (p=0·27); 112 non-fatal events occurred in 82 (13%) patients in the intervention group compared with 110 events in 79 (13%) patients in the control group (p=0·80); and 89 (14%) patients in the intervention group were rehospitalised after discharge compared with 82 (13%) patients in the control group (p=0·56; appendix). In the intervention group, deaths due to the initial stroke occurred in nine (1%) patients and 18 (3%) controls (p=0·12). We showed no between-group difference in caregiver strain, nor in anxiety or depression on the HADS. We documented unblinding in 33 (5%) intervention patients and 21 (3%) control patients (p=0·09).

	Intervention (n=623)	Usual care (n=627)	Total (n=1250)	Odds ratio (95% CI)	p value*
Death or dependency (mRS score 3–6)					
Month 3 (unadjusted)	336/600 (56%)	337/593 (57%)	673/1193 (56%)	0·97 (0·77–1·22)	0·77
Month 3 (adjusted)†	335/599 (56%)	337/593 (57%)	672/1192 (56%)	1·00 (0·77–1·29)	0·99
Month 6 (unadjusted; primary outcome)	285/607 (47%)	287/605 (47%)	572/1212 (47%)	0·98 (0·78–1·23)	0·87
Month 6 (adjusted)†	284/606 (47%)	287/605 (47%)	571/1211 (47%)	1·02 (0·80–1·31)	0·87
Ordinal analysis of mRS scores‡					
Month 3 (unadjusted)					
0	23/600 (4%)	27/593 (5%)	50/1193 (4%)	0·92 (0·75–1·12)	0·42
1	147/600 (25%)	130/593 (22%)	277/1193 (23%)	..	..
2	94/600 (16%)	99/593 (17%)	193/1193 (16%)	..	..
3	141/600 (24%)	133/593 (22%)	274/1193 (23%)	..	..
4	116/600 (19%)	107/593 (18%)	223/1193 (19%)	..	..
5	22/600 (4%)	30/593 (5%)	52/1193 (4%)	..	..
6	57/600 (10%)	67/593 (11%)	124/1193 (10%)	..	..
Month 3 (adjusted)				0·94 (0·76–1·15)	0·52
Month 6 (unadjusted)					
0	56/607 (9%)	55/605 (9%)	111/1212 (9%)	1·00 (0·82–1·22)	1·00
1	170/607 (28%)	183/605 (30%)	353/1212 (29%)	..	..
2	96/607 (16%)	80/605 (13%)	176/1212 (15%)	..	..
3	120/607 (20%)	123/605 (20%)	243/1212 (20%)	..	..
4	82/607 (14%)	65/605 (11%)	147/1212 (12%)	..	..
5	11/607 (2%)	13/605 (2%)	24/1212 (2%)	..	..
6	72/607 (12%)	86/605 (14%)	158/1212 (13%)	..	..
Month 6 (adjusted)	..	..	..	1·03 (0·84–1·27)	0·75

Data are n/N (%). mRS=modified Rankin scale. *p value calculated from the likelihood ratio of the logistic regression. †Adjusted analysis includes the following covariates: study site, stroke severity, age, sex, income, and education. ‡Ordinal analysis using proportional odds logistic regression.

Table 2: **Analysis of mRS**

We found one significant interaction on the pre-specified subgroup analysis, by sex, in which men had reduced odds of death or dependency at 6 months compared with women (figure 3).

Discussion

Our study showed that the addition of family-led rehabilitation training to usual stroke unit care did not decrease death or dependency at 6 months, nor was there any benefit noted at the 3-month assessment. Additionally, the training did not influence any of the other physical, emotional, or quality-of-life outcomes. The intervention was safe, with an observed non-significant reduction in deaths, and no increase in caregiver burden. The training was delivered as planned with a mean of 3·0 h (median 2·9) of hospital training and a mean of 3·1 h (median 2·8) of community-based training, with components consistent with the trial intervention guide. In the context of these Indian stroke units, in which patients received a total of only 2 h of therapy, the intervention more than doubled the amount of hospital rehabilitation and provided additional community caregiver and patient training. In the intervention group, 30 min of daily rehabilitation activities were reported by the patient and caregivers in the month after discharge (17 h over 30 days).

The ATTEND intervention failed to reduce length of hospital stay. When our results are viewed in the context of the systematic review of early supported discharge after stroke,[13] it can be seen that interventions without coordination from a dedicated multidisciplinary team currently do not have evidence of benefit. We also note that the smaller RECOVER trial of nurse-delivered rehabilitation after stroke in China was negative (R Lindley, personal communication).

Our results are also consistent with the absence of benefit seen in a systematic review[26] of trials of caregiver-mediated exercises to improve activities of daily living. In this overview, the authors noted that the data were insufficient (only 333 patients were included in the six trials analysed) and that the quality of evidence was low to moderate. Although the ATTEND intervention emphasised caregiver-mediated exercises, these were not the only component of the intervention.

The absence of benefit of the family-rehabilitation intervention has important implications for stroke recovery research, behavioural change, and task shifting in general. Our training programme might not have

	Month 3			Month 6		
	Intervention	Control	p value	Intervention	Control	p value
Recovery, dependency, and place of residence						
Complete recovery from stroke*	72/546 (13%)	78/530 (15%)	0·55	133/534 (25%)	142/514 (28%)	0·28
Need help for everyday activities*	332/543 (61%)	320/528 (61%)	0·60	266/533 (50%)	245/514 (48%)	0·17
Place of residence†			0·81			0·92
Same as before stroke	516/543 (95%)	500/528 (95%)		502/533 (94%)	483/512 (94%)	
Other	27/543 (5%)	28/528 (5%)		31/533 (6%)	29/512 (6%)	
In another hospital since admission for stroke	1/27 (4%)	1/28 (4%)		1/31 (3%)	0	
In family or friends' home	17/27 (63%)	14/28 (50%)		16/31 (52%)	11/29 (38%)	
In same hospital since admission for stroke	0	0		0	1/29 (3%)	
Other dwelling place	9/27 (33%)	13/28 (46%)		14/31 (45%)	17/29 (59%)	
Barthel Index						
Total score‡			0·41			0·74
n, mean (SD)	543, 76·1 (25·24)	525, 74·8 (26·05)		533, 82·1 (23·09)	512, 82·6 (23·19)	
Median (IQR)	85 (60–100)	85 (60–100)		95 (70–100)	95 (70–100)	
Range	0–100	0–100		0–100	0–100	
Caregiver burden						
Total score‡			0·21			0·52
n, mean (SD)	543, 30·9 (10·70)	524, 31·7 (11·38)		532, 28·9 (10·01)	511, 29·3 (10·85)	
Median (IQR)	27 (22–35)	29 (22–37)		25 (21–33)	25 (21–33)	
Range	21–73	21–80		21–77	21–81	
Nottingham Extended ADL Scale						
Total score†			0·43			0·86
n, mean (SD)	537, 27·1 (17·21)	523, 26·3 (17·31)		527, 31·0 (17·67)	509, 31·2 (17·52)	
Median (IQR)	27 (12–40)	25 (11–40)		31 (16–45)	32 (17–44)	
Range	0–66	0–66		0–66	0–66	

(Table 3 continues on next page)

	Month 3			Month 6		
	Intervention	Control	p value	Intervention	Control	p value
(Continued from previous page)						
WHO Quality of Life						
Physical health‡			0·96			0·63
n, mean (SD)	534, 51·2 (12·65)	521, 51·3 (12·28)		525, 54·3 (12·06)	509, 54·7 (12·11)	
Median (IQR)	56 (44–63)	56 (44–63)		56 (44–63)	56 (44–63)	
Range	13–81	6–81		13–94	19–100	
Psychological‡			0·99			0·17
n, mean (SD)	534, 49·2 (15·16)	521, 49·3 (14·99)		525, 52·1 (15·09)	509, 53·4 (14·63)	
Median (IQR)	50 (38–56)	50 (38–63)		56 (44–63)	56 (44–63)	
Range	6–100	6–94		0–94	6–88	
Social relationship‡			0·42			0·45
n, mean (SD)	529, 60·8 (17·21)	519, 60·0 (16·89)		523, 63·0 (17·41)	509, 62·2 (18·43)	
Median (IQR)	69 (50–75)	56 (50–69)		69 (50–75)	69 (50–75)	
Range	0–100	0–100		0–100	0–100	
Environment‡			0·61			0·76
n, mean (SD)	534, 65·3 (14·70)	521, 64·8 (15·78)		525, 67·8 (15·69)	509, 68·1 (15·95)	
Median (IQR)	69 (56–75)	63 (56–75)		69 (56–75)	69 (56–81)	
Range	19–100	13–100		19–100	19–100	
Quality of life*			0·41			0·52
Very poor	21/535 (4%)	34/521 (7%)		17/526 (3%)	17/509 (3%)	
Poor	97/535 (18%)	86/521 (17%)		77/526 (15%)	72/509 (14%)	
Neither poor nor good	176/535 (33%)	167/521 (32%)		115/526 (22%)	105/509 (21%)	
Good	225/535 (42%)	217/521 (42%)		284/526 (54%)	268/509 (53%)	
Very good	16/535 (3%)	17/521 (3%)		33/526 (6%)	47/509 (9%)	
Satisfaction with health*			0·31			0·65
Very dissatisfied	24/535 (4%)	17/521 (3%)		18/526 (3%)	16/509 (3%)	
Dissatisfied	142/535 (27%)	123/521 (24%)		111/526 (21%)	92/509 (18%)	
Neither satisfied nor dissatisfied	152/535 (28%)	156/521 (30%)		105/526 (20%)	104/509 (20%)	
Satisfied	204/535 (38%)	203/521 (39%)		257/526 (49%)	254/509 (50%)	
Very satisfied	13/535 (2%)	22/521 (4%)		35/526 (7%)	43/509 (8%)	
EuroQol Group 5-Dimension Self-Report Questionnaire						
Mobility*			0·37			0·32
I have no problems in walking	256/539 (47%)	226/523 (43%)		292/529 (55%)	282/510 (55%)	
I have some problems in walking	235/539 (44%)	247/523 (47%)		201/529 (38%)	204/510 (40%)	
I am confined to bed	48/539 (9%)	50/523 (10%)		36/529 (7%)	24/510 (5%)	
Self-care*			0·52			0·75
I have no problems with self-care	235/539 (44%)	212/523 (41%)		278/529 (53%)	280/510 (55%)	
I have some problems bathing or dressing myself	199/539 (37%)	197/523 (38%)		176/529 (33%)	162/510 (32%)	
I am unable to bathe or dress myself	105/539 (19%)	114/523 (22%)		75/529 (14%)	68/510 (13%)	
Usual activities*			0·95			0·59
I have no problems in performing my usual activities	185/538 (34%)	175/523 (33%)		227/529 (43%)	232/510 (45%)	
I have some problems in performing my usual activities	210/538 (39%)	206/523 (39%)		211/529 (40%)	188/510 (37%)	
I am unable to perform my usual activities	143/538 (27%)	142/523 (27%)		91/529 (17%)	90/510 (18%)	
Pain/discomfort*			0·70			0·64
I have no pain or discomfort	228/538 (42%)	210/523 (40%)		270/529 (51%)	273/510 (54%)	
I have moderate pain or discomfort	270/538 (50%)	269/523 (51%)		231/529 (44%)	208/510 (41%)	
I have extreme pain or discomfort	40/538 (7%)	44/523 (8%)		28/529 (5%)	29/510 (6%)	

(Table 3 continues on next page)

	Month 3			Month 6		
	Intervention	Control	p value	Intervention	Control	p value
(Continued from previous page)						
Anxiety/depression*			0·70			0·44
I am not anxious or depressed	229/538 (43%)	212/523 (41%)		265/529 (50%)	257/510 (50%)	
I am moderately anxious or depressed	266/538 (49%)	272/523 (52%)		238/529 (45%)	219/510 (43%)	
I am extremely anxious or depressed	43/538 (8%)	39/523 (7%)		26/529 (5%)	34/510 (7%)	
Overall health state‡			0·68			0·18
n, mean (SD)	539, 63·2 (21·21)	523, 63·8 (20·82)		529, 70·1 (20·36)	510, 71·8 (20·40)	
Median (IQR)	65 (50–80)	65 (50–80)		70 (55–90)	75 (60–90)	
Range	3–100	0–100		0–100	0–100	
Hospital Anxiety and Depression Scale						
Patient						
Total score‡			0·67			0·90
n, mean (SD)	536, 11·3 (8·35)	520, 11·5 (8·72)		527, 9·0 (7·81)	509, 9·1 (8·64)	
Median (IQR)	10 (5–17)	10 (4–18)		7 (3–14)	7 (2–13)	
Range	0–39	0–39		0–38	0–42	
Anxiety score‡			0·57			0·91
n, mean (SD)	536, 4·8 (4·01)	520, 4·9 (4·36)		527, 3·7 (3·74)	509, 3·7 (4·19)	
Median (IQR)	4 (1–7)	4 (1–8)		3 (0–6)	2 (0–6)	
Range	0–18	0–18		0–18	0–21	
Score ≥8*	122/536 (23%)	138/520 (27%)	0·15	84/527 (16%)	83/509 (16%)	0·87
Depression score‡			0·79			0·91
n, mean (SD)	536, 6·5 (4·94)	520, 6·6 (4·99)		527, 5·3 (4·64)	509, 5·3 (4·96)	
Median (IQR)	6 (2–10)	6 (2–10)		4 (2–8)	4 (1–8)	
Range	0–21	0–21		0–21	0–21	
Score ≥8*	197/536 (37%)	198/520 (38%)	0·66	145/527 (28%)	141/509 (28%)	0·95
Caregiver						
Total score‡			0·62			0·86
n, mean (SD)	546, 7·5 (7·52)	527, 7·7 (7·88)		532, 5·5 (6·68)	511, 5·5 (6·80)	
Median (IQR)	5 (2–12)	5 (1–12)		3 (0–9)	3 (0–8)	
Range	0–42	0–39		0–36	0–42	
Anxiety score‡			0·67			0·91
n, mean (SD)	546, 3·7 (3·86)	527, 3·8 (4·17)		532, 2·7 (3·40)	511, 2·6 (3·51)	
Median (IQR)	2 (0–6)	2 (0–6)		1 (0–4)	1 (0–4)	
Range	0–21	0–20		0–16	0–21	
Score ≥8*	83/546 (15%)	96/527 (18%)	0·19	55/532 (10%)	50/511 (10%)	0·77
Depression score‡			0·61			0·82
n, mean (SD)	546, 3·8 (4·17)	527, 3·9 (4·16)		532, 2·9 (3·69)	511, 2·8 (3·60)	
Median (IQR)	3 (0–6)	3 (0–6)		1 (0–5)	2 (0–5)	
Range	0–21	0–21		0–21	0–21	
Score ≥8*	100/546 (18%)	100/527 (19%)	0·78	68/532 (13%)	56/511 (11%)	0·36

ADL=activities of daily living. *p value by χ^2 test. †p value by χ^2 test only performed on "same as before stroke" versus "other". ‡p value by *t* test.

Table 3: **Analysis of secondary outcomes at months 3 and 6**

been sufficient (in time and content) to deliver effective family rehabilitation, as we observed only about 30 min of daily activities in the intervention group. Conventional western rehabilitation is usually associated with greater daily therapy time (1–2 h).[27] Training of family members was designed to be sustainable, and if family members required more training to meet the needs of their family patient, then the aspiration of routinely providing rehabilitation through task shifting to family caregivers might not be feasible. Family dynamics might also limit the effectiveness of this strategy, and task shifting to a non-family generic health worker, such as the established Indian Accredited Social Health Activist (ASHA), might have been a more effective strategy, although probably more expensive. Technology-assisted rehabilitation might also be another option of task shifting that is the subject of current trials.[28]

The absence of benefit might also have been due to individual training components being ineffective in changing behaviour. This possibility was raised by another trial, undertaken in the UK, in which caregiver training (part of our intervention) was ineffective in the acute setting.[29] Because we were aware of these results before beginning our study, we also placed emphasis on the importance of continuation of caregiver training after hospital discharge. The comprehensive nature of our intervention might have diluted the effect of individual components, and this less specified approach—eg, too much time spent on information provision—might have been at the expense of training task-specific mobility exercises.

Although our primary outcome was not significant, the sample size might still have been insufficient to detect a more modest treatment effect. However, the consistency of results across all health dimensions provides support for the overall neutral effect. The main qualitative differences between conventional rehabilitation in high-income countries, compared with our family rehabilitation intervention, are in the professional multidisciplinary

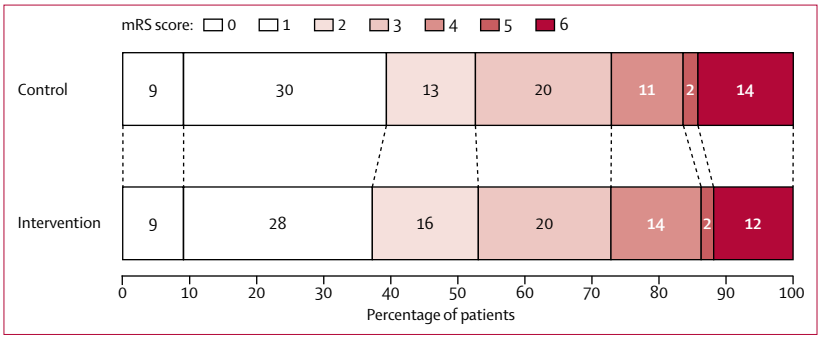

Figure 2: **Patients achieving each mRS score at 6 months**
mRS=modified Rankin Scale.

	Events/patients		Odds ratio (95% CI)	p value for interaction
	Intervention	Control		
Age (years)				
0 to <40	11/56 (20%)	18/56 (32%)	0·52 (0·22–1·23)	0·2265
40 to <50	34/87 (39%)	36/96 (38%)	1·07 (0·59–1·94)	
50 to <60	72/186 (39%)	69/154 (45%)	0·78 (0·50–1·20)	
60 to <70	95/168 (57%)	86/171 (5%)	1·29 (0·84–1·97)	
≥70	73/110 (66%)	78/128 (61%)	1·26 (0·74–2·15)	
Sex				
Female	115/198 (58%)	102/204 (50%)	1·39 (0·93–2·05)	0·0374
Male	170/409 (42%)	185/401 (46%)	0·83 (0·63–1·10)	
Stroke severity (NIHSS)				
0 to <5	18/71 (25%)	15/98 (15%)	1·88 (0·87–4·05)	0·1353
5 to <10	84/242 (35%)	85/237 (36%)	0·95 (0·65–1·38)	
10 to <15	101/185 (55%)	106/173 (61%)	0·76 (0·50–1·16)	
≥15	82/109 (75%)	81/97 (84%)	0·60 (0·30–1·20)	
Stroke type				
Intracerebral haemorrhage	69/139 (50%)	78/142 (55%)	0·81 (0·51–1·29)	0·3544
Ischaemic	216/467 (46%)	209/462 (45%)	1·04 (0·80–1·35)	
OCSP subtype				
Lacunar syndromes	22/76 (29%)	19/79 (24%)	1·29 (0·63–2·63)	0·5097
Partial anterior circulation syndrome	126/253 (50%)	124/260 (48%)	1·09 (0·77–1·54)	
Posterior circulation syndrome	29/71 (41%)	37/72 (51%)	0·65 (0·34–1·27)	
Total anterior circulation syndrome	39/67 (58%)	28/50 (56%)	1·09 (0·52–2·29)	
Caregiver type				
Daughter or daughter-in-law	89/148 (60%)	65/123 (53%)	1·35 (0·83–2·18)	0·4292
Son or son-in-law	84/166 (51%)	102/184 (55%)	0·82 (0·54–1·25)	
Spouse	97/252 (38%)	105/253 (42%)	0·88 (0·62–1·26)	
Other	15/41 (37%)	15/45 (33%)	1·15 (0·47–2·80)	
Patient's education level				
College, university, or postgraduate	66/165 (40%)	58/154 (38%)	1·10 (0·70–1·73)	0·1660
High school completed	50/123 (41%)	73/137 (53%)	0·60 (0·37–0·98)	
Secondary, primary, or less than primary school	114/231 (49%)	104/223 (47%)	1·11 (0·77–1·61)	
No schooling	54/87 (62%)	52/91 (57%)	1·23 (0·67–2·24)	
Household income				
<5000	57/93 (61%)	53/97 (55%)	1·31 (0·74–2·34)	0·4821
5000–14 999	72/173 (42%)	94/190 (49%)	0·73 (0·48–1·10)	
15 000–29 999	69/163 (42%)	59/146 (40%)	1·08 (0·69–1·70)	
≥30 000	55/121 (45%)	44/103 (43%)	1·12 (0·66–1·90)	
No answer or missing	32/57 (56%)	37/69 (54%)	1·11 (0·55–2·24)	
Type of accommodation				
Own house	234/489 (48%)	233/482 (48%)	0·98 (0·76–1·26)	0·9774
Other	51/118 (43%)	54/123 (44%)	0·97 (0·58–1·62)	

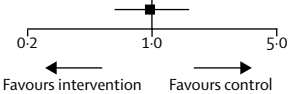

Figure 3: **Main subgroup analyses on the primary outcome (dead or dependent)**
NIHSS=US National Institutes of Health Stroke Scale. OCSP=Oxfordshire, UK, Community Stroke Project Stroke Classification. *Household income in Indian rupees (INR) per month (US$1=68 INR).

structure and frequent review meetings. Our results suggest that the lower dose of family rehabilitation training, delivered by one professional, although based on evidence-based components across multiple disciplines, is an ineffective model of care. Since our trial was done at stroke units around India, our findings have not ruled out the possibility that the intervention could offer benefits in non-specialised hospitals, especially in rural and remote settings.

The unexpected interaction with sex, with the observed improved outcome in men compared with women, might be due to the play of chance and requires further analysis. However, in Indian society, important sex differences might exist in the receipt and provision of a complex intervention such as ours. Our process evaluation aims to explore this, and other, aspects of the trial, in more detail.[30]

Strengths of our study include the piloting and development of a structured intervention supported by written materials and use of robust trial methods to address priorities set out in the WHO and World Bank World Report on Disability.[9] Our funding provided sufficient resources to address the research question comprehensively and has contributed to building stroke research capacity across India. Our trial data are consistent with epidemiological evidence that stroke is affecting people in India about 15 years younger than those in high-income countries, highlighting the public health importance of improving global rehabilitation services, especially since many of our participants were still in paid work.[31] However, generalisability of our results to other areas of the country without rehabilitation might be limited, given that our participants were generally from urban centres with higher-than-average education and income.

Task shifting is an attractive solution for health-care sustainability.[4,32,33] However, none of 22 recommendations of the WHO Task Shifting Guidelines referenced evidence generation on effectiveness, despite acknowledgment that implementation of these recommendations and guidelines should be accompanied by rigorous evaluation.[4] Our assessment of training the patient and family caregiver showed that this particular model of rehabilitation was ineffective. Our results illustrate that task shifting away from conventional rehabilitation, without rigorous evaluation, could waste limited resources. Our neutral results will be further interrogated through a process assessment that will examine the social and economic influences on the behaviour of carers and patients. ATTEND was developed from the evidence base current at the time and focused on pragmatic solutions. Future research in this area could incorporate more behavioural change theory and evidence when developing a new intervention.

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Contributors

JDP originally suggested the study. JDP, RIL, CSA, LB, AF, MLH, LAH, SJ, PL, PKM, GVSM, and MFW designed the study and obtained funding. QL and LB did the statistical analysis. HL led the process evaluation. RIL wrote the first draft of the manuscript, and all writing committee members contributed, edited, and approved the final version.

Declaration of interests

MLH reports grants from National Health and Medical Research Council (NHMRC) of Australia and from National Heart Foundation (NHF), Australia, during the conduct of the study, and reports other support from Boehringer Ingelheim, outside the submitted work. LB, RIL, CSA, PKM, PL, GVSM, and JDP report grants from NHMRC, during the conduct of the study. CSA reports personal fees from Boehringer Ingelheim, Takeda, AstraZeneca, and Medtronic, outside the submitted work. AF reports grants from The George Institute for Global Health, Sydney, during the conduct of the study, and was lead investigator of similar work undertaken in the UK (*Lancet* 2013; **382:** 2069–76). RIL reports personal fees from Covidien and Pfizer, outside the submitted work. QL, LAH, MFW, HL, and SJ have nothing to declare.

Acknowledgments

The trial was funded by Project Grant APP1045391 from the National Health and Medical Research Council of Australia. PKM is a recipient of an Intermediate Career Fellowship of Wellcome Trust—Department of Biotechnology India Alliance. MLH is a recipient of a National Heart Foundation Future Leader Fellowship, Level 2 (100034, 2014–2017). SJ is the recipient of an NHMRC Senior Research Fellowship. CSA holds an NHMRC Senior Principal Research Fellowship. HL is the recipient of an NHMRC APP1114897 scholarship to undertake her doctorate.
The steering committee designed the study, gathered the data (in collaboration with the hospital sites), made the decision to submit the manuscript for publication, and vouched for the fidelity of the study to the protocol. The George Institute for Global Health was responsible for analysis of the data.

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Alim et al. Trials (2016) 17:13
DOI 10.1186/s13063-015-1129-8

Trials

STUDY PROTOCOL Open Access

Family-led rehabilitation after stroke in India: the ATTEND trial, study protocol for a randomized controlled trial

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Abstract

Background: Globally, most strokes occur in low- and middle-income countries, such as India, with many affected people having no or limited access to rehabilitation services. Western models of stroke rehabilitation are often unaffordable in many populations but evidence from systematic reviews of stroke unit care and early supported discharge rehabilitation trials suggest that some components might form the basis of affordable interventions in low-resource settings. We describe the background, history and design of the ATTEND trial, a complex intervention centred on family-led stroke rehabilitation in India.

Methods/design: The ATTEND trial aims to test the hypothesis that a family-led caregiver-delivered home-based rehabilitation intervention, designed for the Indian context, will reduce the composite poor outcome of death or dependency at 6 months after stroke, in a multicentre, individually randomized controlled trial with blinded outcome assessment, involving 1200 patients across 14 hospital sites in India.

Discussion: The ATTEND trial is testing the effectiveness of a low-cost rehabilitation intervention that could be widely generalizable to other low- and middle-income countries.

Trial registration: Clinical Trials Registry-India CTRI/2013/04/003557. Australian New Zealand Clinical Trials Registry ACTRN12613000078752. Universal Trial Number U1111-1138-6707.

Keywords: Caregivers, Costs, Disability, Rehabilitation, Stroke

Background

Stroke causes 6 million deaths each year among 17 million affected people, with the greatest burden experienced in populations of low- and middle-income countries [1]. In these countries, the burden of stroke is increasing, owing to lifestyle changes and rapid ageing of populations. Furthermore, stroke tends to affect people at relatively younger ages where there is poor control of established risk factors, in particular high blood pressure [2], with significant social and financial consequences for families, owing to limited financial protection from the costs of care and minimal social safety nets [3]. Stroke usually affects at least two people in a family, the patient and at least one family caregiver, with epidemic proportions of premature loss of productive lives in developing countries, such as India [4–6].

Like many developing countries, India is experiencing an epidemiologic transition, in which the burdens of infectious disease, maternal and child health problems are decreasing, while the burden of non-communicable chronic diseases, such as stroke and injury, is increasing [7]. In India, based upon an annual incidence of stroke of 135 to 145 per 100,000, and early case fatality of

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between 27 % and 41 % [7–10], it has been estimated that 1.5 million people experience stroke each year, and a further 500,000 people live with stroke-related disability. The long-term consequences of stroke on families in India, particularly in rural areas, are likely to be significant.

The most important treatment for patients with stroke is well-organized specialist care [11], which allows rapid and well-coordinated assessment and diagnosis [12, 13], early recognition and management of complications, early rehabilitation, education, and appropriate long-term support and secondary preventative therapy. Stroke unit care has greater public health impact than treatment with thrombolysis (alteplase) alone, even with the most optimal thrombolysis rates [11], because thrombolysis rates are rarely greater than 20 % (with a 5–10 % absolute benefit), yet stroke unit care is applicable to all (with a 5 % absolute benefit). Organized stroke care should be a public health priority in low- and middle-income countries, to ameliorate the increasing burden of stroke.

Although appropriate stroke unit care and rehabilitation may meet important clinical, physical and psychosocial needs during the early post-stroke phase, the needs of patients and families in the long term cannot solely be addressed in hospital [14, 15]. Advocates for early supported discharge and home-based stroke rehabilitation, which is based upon a coordinated stroke unit model of care, argue that it offers several advantages: satisfying patient choice; reducing risks (and costs) associated with inpatient care through reductions in length of hospital stay; a better rehabilitation setting, as the home setting is more focused towards realistic goals, social inclusion and a supportive environment; and leading to savings in direct and indirect costs [16, 17]. Early supported discharge provides a continuous process of rehabilitation that spans the in-hospital period and the weeks of resettlement and readjustment at home. A meta-analysis of 11 trials (mainly conducted in developed countries, where fully funded community rehabilitation teams are available) shows that early supported discharge services significantly reduced the odds of death or dependency by 21 % (odds ratio 0.79; 95 % confidence interval 0.64–0.97), without major adverse effects, either on patients or caregivers [17].

Although acute stroke units are increasing as resources improve in India, they meet the needs of only a tiny fraction of the country's vast population, and the majority of Indians do not have access to rehabilitation services, either in hospital or following discharge. The development of effective low-cost community rehabilitation services for emerging major chronic diseases, such as stroke in India, has the potential for significant public health impact. Such interventions, if shown to be effective and affordable, could be widely scaled up or generalizable. Indeed, the research question of how to create sustainable and multiprofessional rehabilitation systems in low- and middle-income countries, including the provision of services to the rural population, was considered the second most important research priority (after equality of healthcare access) for disabled people in a recent *Lancet* expert panel [18]. Currently, most Indian stroke units are situated in the private sector [19, 20]. Clear evidence that low-cost interventions are cost-effective in India would facilitate their expansion within the public hospital system, where rehabilitation has some important features that differ from those in high-income countries: therapy is driven largely by physiotherapists, with limited input from other health professionals, such as occupational therapists; it is often poorly coordinated; and most people receive care within a large family unit ('a joint family', often called an extended family) after discharge [21].

A modified version of the Western model of early supported discharge, together with a development of the Indian-suggested solution based on rehabilitation delivered by a trained family caregiver, appears to be the most promising hybrid model of stroke care that could be widely implemented, if shown to be successful. Similar models have been shown to be cost-effective in the UK [22, 23]. To develop appropriate health policy, though, effectiveness and cost-effectiveness of any new model of care including rehabilitation needs rigorous evaluation in the relevant setting.

Methods

The ATTEND study is a multicentre, prospective, individually randomized, blinded outcome assessed, controlled trial (prospective, randomized, open, blinded, endpoint design) of early supported discharge with a trained family-led caregiver.

The intervention is a stroke rehabilitation package of care that starts in hospital and continues at home, compared with usual care, in at least 1200 patients with mild to moderate disability recruited from 14 hospital sites across India.

The inclusion criteria are:

- Adults (≥18 years);
- Recent (<1 month) acute ischaemic, haemorrhagic or undifferentiated stroke;
- Residual disability (requiring help from another person for everyday activities);
- Expected to survive to discharge from hospital, with a reasonable expectation of 6 month survival (i.e. not palliative, no evidence of widespread cancer etc.);
- Able (or by proxy) to provide informed consent.

Exclusion criteria are:

- Unable to identify a suitable family-nominated caregiver for training and subsequent delivery of care;
- Unwilling or unable to adhere to follow-up.

Randomization

Eligible patients are identified by the trial stroke coordinator (usually a physiotherapist) and medical coordinator. A patient information sheet (Additional file 1) is shared with the patient and nominated caregiver, and outlines the study objectives and risks and benefits to the patient or caregiver. Informed consent from each participant and his or her caregiver is obtained based on the International Conference on Harmonisation Good Clinical Practices guidelines (ICH/GCP) and ethical guidelines for biomedical research on human participants published by the Indian Council of Medical Research, New Delhi (Fig. 1). If the caregiver changes by the time of the 3- or 6-month follow-up periods, the new caregiver will be asked to provide consent for the caregiver aspects of follow-up after reading the patient information sheet. Stroke patients often do not have the capacity to consent, owing to the acute effects of stroke. Capacity for informed consent is assessed by the medically qualified principal investigator at each site. The ethics committee have approved ATTEND to obtain consent from a legally acceptable representative in such cases. Once consented, patients are randomized by the trial stroke coordinator to the intervention or control arm in a 1:1 ratio within 7 days of hospital admission, using a secure, central, password-protected, web-based system, stratified by centre and stroke severity.

Intervention arm

Patients allocated to the intervention arm have their family-nominated caregiver trained by a specially trained trial stroke coordinator health professional (e.g., nurse, therapist) using a trial-specific structured assessment (cognition, language, function and mobility) and recommended rehabilitation package. The rehabilitation package includes a structured checklist and culturally appropriate manual (adapted to local Indian contemporaneous stroke practice) covering key activities relevant to daily living (e.g., positioning, transfers, mobilization, feeding, dressing, activity and motor practice, and monitoring of mood). Detailed instructions for selected training exercises are used from http://www.physiotherapyexercises.com. Training begins in hospital immediately after randomization for those allocated to the intervention, with a goal of approximately 60 min training per day for about 3 days, with the intention of accelerating the patient's hospital discharge, when it is safe to do so, in addition to usual hospital care. The trial stroke coordinator visits the patient and caregiver's home, if they are allocated to the intervention arm, on up to six occasions over the next 2 months, to provide guidance and to monitor progress after discharge, and is available by telephone for further support and guidance as the patient progresses.

A detailed written intervention guide, adapted from previous work [24], instructs all trial stroke coordinators in delivering the structured intervention in a standardized manner; this is reinforced at training sessions during the annual collaborators' meetings.

The intervention components are:

- Information on stroke recovery trajectory, risk, identification and management of low mood, importance of repeated practice of specific activities.
- Positioning, transfers and mobility.
- Discharge planning.
- Joint goal setting with patient, nominated family caregiver and therapist (reviewed with coordinator as patient progresses and new goals set).
- Task-orientated training (particularly walking, upper limb and self-care tasks) with personalized copy of culturally appropriate manual.

The detailed intervention guide and manual are kept confidential and will only be published after the last patient follow-up has been completed, to avoid contamination of the control patients during the conduct of the trial.

Control arm

These patients will receive usual hospital care in terms of access to rehabilitation, timeliness of discharge and follow-up, without any explicit provision of accelerated discharge or caregiver training.

Outcome measurement

The primary outcome measure is the effect of treatment allocation on death or dependency (a score of 0–2 on the modified Rankin scale [25]) at 6 months after randomization [26]. Patients will be seen after 3 and 6 months by an independent blinded assessor who will collect the primary and secondary outcome data.

Secondary outcome measures are:

- Effect of treatment on shift in disability, as measured by the modified Rankin scale, and analyzed with shift (ordinal) analysis;
- Answers to the simple validated recovery (Have you made a complete recovery from your stroke?) and dependency (Do you need help from another person for everyday activities?) questions [27];
- Hospital length of stay;
- Place of residence;

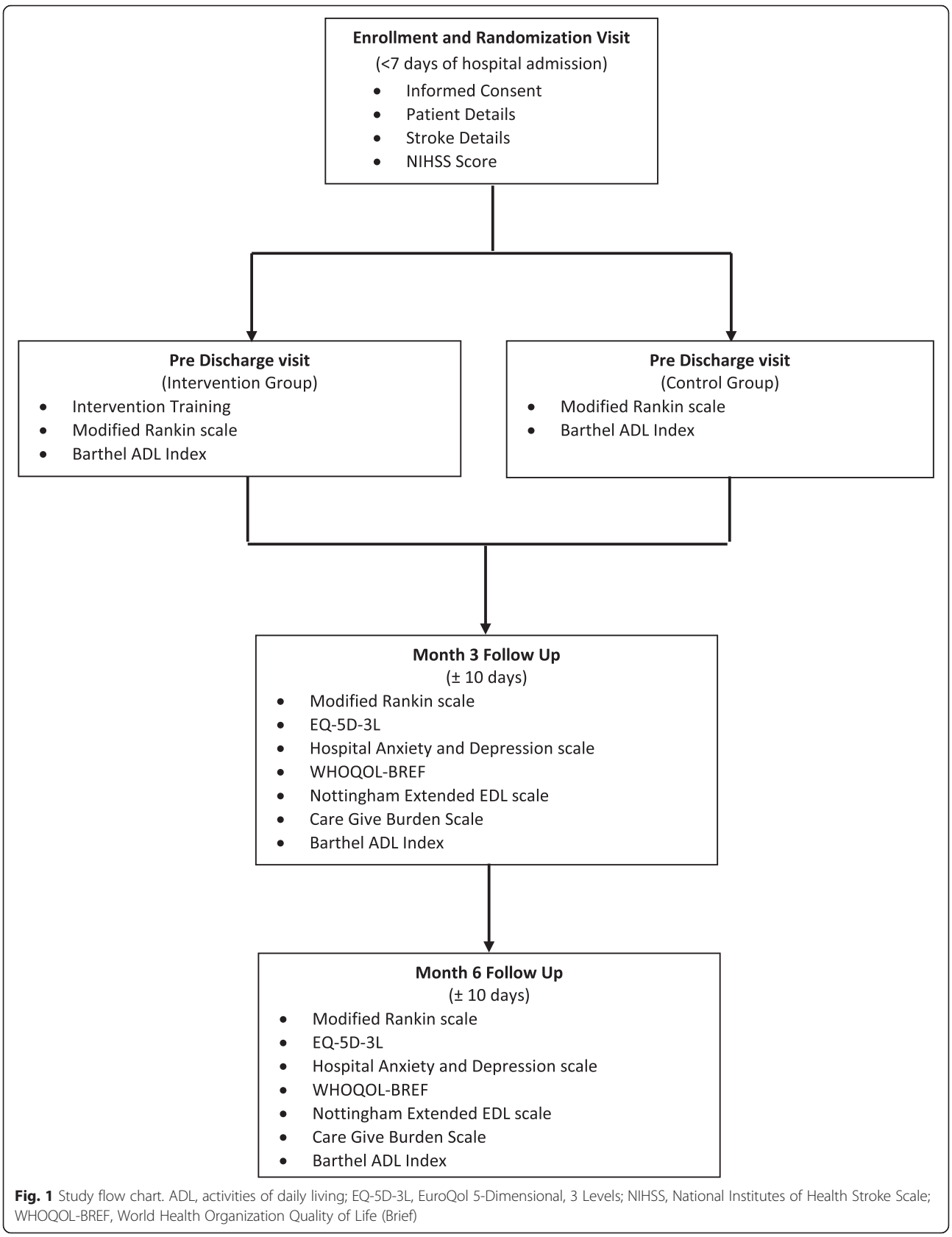

Fig. 1 Study flow chart. ADL, activities of daily living; EQ-5D-3L, EuroQol 5-Dimensional, 3 Levels; NIHSS, National Institutes of Health Stroke Scale; WHOQOL-BREF, World Health Organization Quality of Life (Brief)

- Scores on the Barthel Index [26];
- Score on the Caregiver Burden Scale [28];
- Health-related quality of life (World Health Organization Quality of Life Assessment and EuroQol 5-Dimensional scores) [29, 30];
- Patient and caregiver mood (Hospital Anxiety and Depression Scale) [31];
- Extended activities of daily living (Nottingham Extended Activities of Daily Living Scale) [32];
- Health care resource use (visits to health professionals, hospitalization, and medication use) and direct costs for the patient (e.g. payment to the caregiver to act as carer for this patient, total direct costs of healthcare paid by the family since time of stroke);
- Indirect costs (e.g. family member giving up paid employment to act as caregiver) of the family;
- Direct medical costs (e.g. total expenditure during hospital admission, including first place where patient was taken, general or private admission, length of hospital stay, admission charges, investigation charges and drug treatment);
- Non-medical direct costs (e.g. travelling costs).

Clinic or telephone follow-up will be offered if home visits are not possible.

Data are collected on paper forms with an English translation on one side and the appropriate local Indian language on the other side. Each patient is identified by a unique identifier with only local sites holding the master log of names. The trial database is held and maintained by The George Institute for Global Health, with access for analysis determined by the steering committee. Future access to participant level data and statistical code will depend on additional funding to safeguard and prepare the data and is contingent upon compliance with data management guidelines in India and Australia.

Adverse events

Given that patients with stroke are expected to experience frequent adverse events, we defined our 'expected' events *a priori*. These are listed in a checklist at each follow-up. Any other adverse event is also recorded. Our expected serious events are: (1) deaths categorized as vascular (stroke, myocardial infarction, other vascular), infection, fracture, other and (2) Hospitalizations (stroke, myocardial infarction, other vascular, infection, fracture, other).

Risks to internal validity

The main risks to the internal validity of the trial are 'contamination' between treatment groups, threats to the fidelity of the intervention and unblinding. To prevent 'contamination' between intervention and control patients in the ward during the hospital stay, we advise that the stroke coordinators delivering the intervention interview patients and carers in a private consulting or treatment room or use curtains around the patient's bed. The time spent by the routine ward physiotherapist with control and intervention patients is monitored and recorded, to check that there is no systematic bias in routine physiotherapy. To help prevent control patients from viewing the trial manual, the manuals are given to intervention patients at the time of the first home visit and a general stroke booklet (placebo) is given to both groups. The topic of 'contamination' forms part of the regular training at site initiation, site visits and annual collaborators' meetings.

Fidelity of the trial intervention is monitored during site initiation and subsequent site training visits by the clinical coordination team and a consultant physiotherapist contracted to help with training. Logs of all intervention activities are collected and analyzed to summarize the duration of each intervention and the main activities within the intervention. In addition, we will document whether the trial participants were assessed or treated by the usual routine care physiotherapists, and measure the total time spent per patient, to ensure that both intervention and control patients have the same background rehabilitation care.

Blinding is maintained by employing a dedicated blinded outcome assessor for each site. It is a requirement that the blinded outcome assessor not share the same office as the stroke coordinator and has separate computer and scanning equipment. The detailed written intervention guide has been kept confidential from the site principal investigators and blinded outcome assessors at each site. At the annual collaborators' meetings, there are separate training sessions for the stroke coordinators and blinded outcome assessors, to maintain confidentiality of the intervention details. Patients are asked not to disclose details of home visits to the blinded outcome assessor, and intervention patients are asked to hide the trial manual when the blinded outcome assessors visit. The trial intervention is stopped one month before the first follow-up at 3 months to help reduce unblinding. Any inadvertent unblinding is recorded by the blinded assessor. Examples of unblinding are discussed at the plenary sessions at the collaborators' meetings to share experiences, and to implement strategies to prevent future occurrences.

Sample size and statistical consideration

In the meta-analysis of early supported discharge trials, the proportion of people dead or dependent at the end of follow-up was 50 % and the likely beneficial effect of early supported discharge treatment was an odds reduction of 21 % (95 % confidence interval 3–26 %). Therefore, the proposed minimum sample size of 1200 (600 per group) provides at least 90 % power (two-tailed α,

0.05) to detect plausible modest 10.5 % reductions in death or dependency in the intervention group with inflation by 20 % to account for patients dropping out of the trial. Ideally, a higher recruitment will allow a greater precision for treatment estimates, and could permit more detailed subgroup analysis; thus, when 1200 patients have been recruited, and if funding and time permits, the data and safety monitoring committee will advise on whether it is safe to continue recruitment. Experience during 2014 and early 2015 has allowed prediction that the trial will complete recruitment in early 2016, based on current strategies.

The intention to treat principle will be applied in all analysis. The primary endpoint measure is the proportion of those dead or dependent (modified Rankin scale score 0–2) at 6 months. This will be analyzed using an unadjusted logistic regression model. Binary secondary outcomes will be analyzed similarly, using analysis of variance (t tests) for continuous variables. For the shift analysis of modified Rankin scale using all seven categories (including 6 for death), ordinal logistic regression will be used, after verifying the proportional odds assumption. A statistical analysis plan will be completed prior to analysis and unblinding of the trial data.

Ethics

Ethical approval has been obtained from Research Integrity, the Human Research Ethics Committee at the University of Sydney and at each local site (Table 1). Protocol amendments will be first approved by the University of Sydney ethics committee and then by local ethics committees before implementation. The current approved protocol is version 1.3, dated 9 December 2013.

Data collection and study management

Data will be collected for all patients randomized in the trial. Baseline data will be collected by the stroke coordinator and the follow-up data by the blinded outcome assessor on paper forms with appropriate local translation and are scanned and directly sent to the data management team for entry into the electronic database. The investigators and institution will allow monitors to verify the data collected on case report forms with respect to all pertinent medical records, according to ICH/GCP guidelines [33].

A data and safety monitoring committee, composed of five experts in the fields of stroke medicine, rehabilitation, statistics and clinical trials, with appropriate Indian representation, is monitoring the study, guided by a written charter with appropriate stopping rules.

The trial is governed by a steering committee formed by the applicants of the National Health and Medical Research Council (NHMRC) grant, and supplemented as agreed by the committee. The steering committee is co-chaired by Richard Lindley and GV Murthy. Other members include Jeyaraj Pandian, Pallab Maulik, Peter Langhorne, Lisa Harvey, Maree Hackett, Marion Walker, Anne Forster, BR Shamanna, Craig Anderson and Stephen

Table 1 Trial sites

Collaborator	Centre	City	Name of ethics committee
Dr Jeyaraj D Pandian	Christian Medical College and Hospital	Ludhiana, Punjab	Institutional Ethics Committee
Dr MV Padma	All India Institute for Medical Sciences and Technology	New Delhi	Institute Ethics Committee
Dr PN Sylaja	Sree Chitra Tirunal Institute for Medical Sciences and Technology	Trivandrum, Kerala	Institutional Ethics Committee
Dr P Vijaya	Lalitha Super Specialty Hospital	Guntur, Andhra Pradesh	Lalitha Super Specialities Hospital Ethics Committee
Dr Sanjith Aaron	Christian Medical College	Vellore, Tamil Nadu	Office of Research Institutional Review Board
Dr Jayanta Roy	Apollo Gleneagles	Kolkata	Institutional Ethics Committee
Dr Lydia John	Baptist Christian Hospital	Tezpur, Assam	Research Ethics Committee
Dr Subhash Kaul	Nizam Institute for Medical Sciences	Hyderabad	Nizam's Institute of Medical Sciences Institutional Ethics Committee
Dr Dheeraj Khurana	Postgraduate Institute for Medical Sciences and Research	Chandigarh	Institute Ethics Committee
Dr NC Borah	Guwahati Neurological Research Centre Hospitals	Assam	Institute of Neurological Sciences Trust Ethics Committee
Dr DS Halprashanth	Global Hospitals	Chennai	Institutional Ethics Committee
Dr B Lokesh	BGS Global Hospital	Bangalore	Institutional Ethics Committee
Dr Vivek Nambiar	Amrita Institute of Medical Sciences	Kochi	Institutional Ethics Committee
Dr Sachin Sureshbabu	St Stephen's Hospital	New Delhi	Ethics Committee of St. Stephen's Hospital

Jan. The steering committee is responsible for all major decisions regarding the running of the trial, the appointment of trial staff and financial reconciliation for the NHMRC funding.

The day-to-day management of the trial is undertaken by a management committee comprised of co-principal investigators Professors Pandian and Lindley, together with Mr Mohammed Alim, the trial senior project manager (based at The George Institute, India), the trial clinical coordinator (based at the Christian Medical College Ludhiana), and representatives from the Indian Institute of Public Health, Hyderabad, together with appropriate trial administrative staff. These meetings are conducted weekly by teleconference. Trial monitoring is performed according to the monitoring plan and as per ICH/GCP, by the monitors from Indian Institute of Public Health.

The main results of the trial will be published in the name of the 'ATTEND Collaborative Group' with all contributions named in the primary trial manuscript. According to new NHMRC policy, this primary publication must be free to access. All publications must be approved by the steering committee with appropriate authorship determined by the steering committee and journal regulations. The NHMRC funding will be acknowledged in all publications.

Discussion

The beneficial effects of early supported hospital discharge and home-based rehabilitation on a patient's recovery from stroke are probably due to improved focusing of therapy around functioning and activities that are most relevant and familiar within the home environment with family support. Yet, as most of this research has been undertaken in urban settings of high-income countries, the impact in low- and middle-income countries is unclear. Moreover, uncertainty over the essential staffing and organizational requirements of such services (i.e. a complex intervention and organizational transfer) has hampered their wider implementation and development in different settings, even in the UK [34].

ATTEND is testing the effectiveness of a low-cost rehabilitation intervention that could be widely generalizable to other low- and middle-income countries. If the trial provides evidence of safety, efficacy and cost-effectiveness, it is likely that adaptations of the intervention could then be considered to augment routine care in high-income countries, with culturally appropriate adaptations to other low-income, marginalized or disadvantaged populations.

The ATTEND intervention was developed during 2010–2012 based on emerging new Indian stroke services, modified by accumulating evidence from the stroke unit and early supported discharge trials, as advised by an expert panel of stroke researchers and trial organizers. The intervention was a pragmatic culturally adapted package piloted in Ludhiana, Punjab, India [35] and was further modified based on this experience. After the main trial was funded, the clinical coordination team developed the final intervention guide with further advice from the steering committee, and a trial manual for the intervention patients was produced.

Careful thought was given to the time and cost implications for the interventions, while keeping in mind the number and quality of interventions included in the package; the stroke coordinator is trained to deliver a tailor-made package for patient-specific functional needs. The efficacy and safety of health interventions are best evaluated in randomized controlled trials and our prospective, randomized, open, blinded, endpoint study design helps ensure avoidance of bias in the follow-up of patients, a recurrent problem in previous rehabilitation trials. Extensive measures were taken to ensure that assessment was blinded in ATTEND, e.g., keeping the details of the intervention confidential to the stroke coordinators, ensuring separate training of the blinded outcome assessors, and employing dedicated research staff for the blinded assessment.

India launched its National Programme for Prevention and Control of Diabetes, Cardiovascular Diseases and Stroke in January 2008. The programme aims to strengthen infrastructure at all levels of care at the community level with the help of caregivers, who are important in the delivery of this programme, and are thus clearly aligned with a family-led rehabilitation model [36].

If ATTEND does not show efficacy or results in an unexpected hazard, data from the trial will inform the reasons why and what modifications could be made while balancing the additional costs against the infrastructure and human resource needs.

Trial status

The first patient was randomized on 13 January 2014 and the recruitment is expected to complete by February 2016. The study recruitment is continuing as planned.

Additional file

Additional file 1: Model informed consent form. (PDF 237 kb)

Abbreviations

GCP: Good Clinical Practice; ICH: International Conference on Harmonisation; NHMRC: National Health and Medical Research Council of Australia.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions
JDP suggested the original trial idea and over a period of years the steering committee (RL, GVSM, PKM, PL, LAH, MLH, MW, AF, BRS, CSA and SJ) designed the trial through a series of grant applications, workshops and meetings held during international stroke conferences. The trial management group contributed to the design of the trial intervention, study set-up and operations, and include MA, CF, DBCG, SJV, DKT, HL, AS, RKR. All authors read and approved the manuscript.

Acknowledgements
We thank Shailaja Chilappagari and Laurent Billot, the trial statisticians.
This work is sponsored by The George Institute for Global Health Sydney, Australia.
This study is funded by the National Health and Medical Research Council of Australia (Project grant no APP1045391).
Pallab K Maulik is a recipient of an Intermediate Career Fellowship of Wellcome Trust-Department of Biotechnology India Alliance.
Maree L Hackett is a recipient of a National Heart Foundation Future Leader Fellowship, Level 2 (100034, 2014–2017).
Stephen Jan is the recipient of an NHMRC Senior Research Fellowship.
Craig Anderson holds an NHMRC Senior Principal Research Fellowship.

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Received: 21 August 2015 Accepted: 17 December 2015
Published online: 07 January 2016

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APPENDIX 4

Appendix Overview

This appendix comprises of a publication titled "The need for theory-based evaluation of care coordination initiatives: Considerations from the 2017 International Conference on Realist Research, Evaluation and Synthesis."

This is a publication arising from a serendipitous and engaging discussion with 3 other researchers, at an international conference in 2017. We had come to present our work which was informed by realist evaluation, and found that the conference stimulated debate in advancing the methodology of evaluating complex interventions across different fields (e.g. environmental health, public health and education). We noted the call for manuscripts on the use of realist evaluation by the International Journal of Care Coordination, and decided to combine our reflections to inform other researchers interested in applying Realist evaluation to their research. This paper provides an overview of our reflections of the topical debates about the application of realist methodology to health services research and potential implications for care coordination initiatives.

Authors' contributions: MV conceived the original idea for the paper. MV and HL developed the structure of the manuscript, and synthesised the individual contributions from all authors. MV drafted the initial manuscript, and all authors helped revise the manuscript and respond to reviewer's comments.

Manuscript details: Vugts M, Liu H, Boumans J, Boydell E. The need for Theory-based evaluation of care coordination initiatives: Considerations from the 2017 International Conference on Realist Research, Evaluation and Synthesis. International Journal of Care Coordination. 2018

Discussion & Opinion Paper

International Journal of Care Coordination

International Journal of Care Coordination
0(0) 1–7

DOI: 10.1177/2053434518779751
journals.sagepub.com/home/icp
SAGE

The need for theory-based evaluation of care coordination initiatives: Considerations from the 2017 International Conference on Realist Research, Evaluation and Synthesis

Miel Vugts[1], Hueiming Liu[2], Joge Boumans[1] and Edward Boydell[3]

Abstract

Research in the field of care coordination faces the challenge of providing transferable explanatory insights regarding what principles and initiatives work in practice and why. Such insights are crucial in developing effective solutions for global disease burdens. Realist research approaches have demonstrated potential to deliver stronger theoretical contributions of evaluation studies across fields of research. These were discussed at the International Conference for Realist Research, Evaluation and Synthesis in Brisbane (from 24 to 26 October 2017). This paper provides an overview and reflection on the conference by four participants. It focuses on (1) topical debates and challenges for the application of realistic methodology in health services research, as presented at the conference and (2) implied opportunities and challenges for (realist) evaluation of care coordination initiatives. Based on the reflections, future realist evaluation on evaluating complex care coordination initiatives is recommended.

Keywords

Program evaluation, health services research, evaluation studies, research design, delivery of health care, integrated

Introduction

Uses of care coordination principles aim to help patient navigation through health care systems and improve their experiences and outcomes.[1] Care coordination researchers could potentially benefit from progress in realist evaluation (RE) methodology, as they are in need of adequate strategies for accumulating explanatory knowledge about how initiatives work under complex conditions. The theme of the International Conference for Realist Research, Evaluation and Synthesis in Brisbane (from 24 to 26 October 2017) was the ability of RE to deliver on its promises. Authors participated at the conference as PhD students (MV, HL, and JB) or evaluation consultant (EB) coming from different research fields and sharing (hands-on) experiences of benefiting from the opportunities and dealing with challenges in applying realistic principles in their evaluation work. Topical insights were accessed into general methodological developments and ongoing projects across various fields of research. This facilitated reflection about implied methodological and practical opportunities and challenges for applying RE worth sharing with fellow evaluators (researchers, commissioners, and policy makers) from the field of care coordination.

The need for theory-based methodology in empirical evaluation of care coordination initiatives

Systematic reviews on the effectiveness of various care coordination initiatives are able to show a rich variety

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of initiatives with study outcomes that are heterogeneous and mostly promising.[2–4] However, scant reporting of initiatives' characteristics (e.g. their logics) and the contexts in which they were implemented generally hinders synthesis and transfer to similar future circumstances.[7,8] Improved reporting of primary studies will help accumulating yields of evaluation projects, but may not suffice to improve understanding how care coordination initiatives work under complicated or complex conditions.[9,10] Care coordination initiatives get complicated when targeting multiple outcomes (e.g. reductions of both economic costs and effort for patient transitions as perceived by patients, families, professionals, organizations), and/or involve multiple interventions (e.g. facilities for inter-professional flows of information as well as for patient self-management).[11] Complex individual patient health needs, agency of local stakeholders, social determinants of health, and differences in culture and organization of health care systems are sources of complexity determining the needs for—and circumstances of—care coordination.[12,13] Qualitative evaluations provide complementary in-depth insight into complexity but, even when synthesized, acknowledged limited transferability (e.g. between different geographic regions or health jurisdictions).[14,15] Some studies adjudicated or integrated existing theoretical frameworks of care coordination.[1,5,6] Synthesis between trials, qualitative, and theoretical work could be improved.

Key concepts of realistic evaluation

> Black swans lurk in prey of the "law" based on the million observations that swans are white. (Ray Pawson)

RE is an increasingly popular approach, not a set of technical procedures, for building and testing program theories about why mechanisms (M) are triggered in certain contexts (C + M) to produce certain outcomes (O).[16] Mechanisms exist in the domain of the real. They are not directly observable (not in the empirical domain). The question is what works, in what respect, over what duration, how, for whom, under what circumstances, and why.[17] The realist view implies that (social) realities of policies or programs cannot be reduced to directly observable outcome patterns (e.g. correlations) or meanings constructed by subjects.[16] The "swan analogy" (quoted), used by Pawson, may illustrate this key point:[7] mere observations of the color of swans in a certain area, regardless how many, leads to the conclusion that swans are white. However, this is not as adequate as conceiving "reality" as a set of simple rules (i.e. of evolution) generating the particularities of the species of swans, including them being observed as black in some places. This "generative" view of causation agrees with complex adaptive systems theory in the sense that minor contextual changes can cause substantial (non-linear) influences on outcome patterns.[16] Therefore, realists stress that evaluating outcomes independent of context makes no sense, criticize "hierarchies of evidence" and prioritization of particular sets of methods, do not determine the use of specific ones but hold ideas for how they could be applied to inform program theories.[18]

Objectives

The objectives of this paper are to (1) focus on topical challenges and debates in realist methodology in general and illustrations from projects in health services/policy research discussed at the conference and thereupon to (2) reflect on their implications, especially for future realist (inspired) theory-based evaluation of care coordination initiatives under complexity. In contributing to the objectives (1 and 2), authors covered four conference themes based on their backgrounds (see initials of authors included in the headings of next sections). Ideally, critical reflection is elicited in evaluators (scientists, policy makers, and health professionals) supportive in overcoming challenges for future (realistic) work on transferable explanations of outcome heterogeneity in care coordination initiatives.

Conference themes and their implications

General challenges in the application of RE on research methods (MV and HL)

The conference showcased the continuing impact of RE upon research methods with relevance to health services/policy research along with its challenges (see Box 1). RE seems well accepted for program theory building and testing on an initiative (e.g. an element of a larger policy) at early (piloting) stages to understand how and why (mixed) outcome patterns are produced across contexts before scaling up to different social, political, cultural, or environmental contexts.[19] In the face of increasing profile of realist approaches in research and evaluation, Tilley and Pawson cautioned against "mechanistic" use of methods.[19,20] Instead, they highlighted that realist evaluators need to combine high-quality interaction with research subjects and subject matter knowledge, with a level of intellectual craft (i.e. being able to find and compare plausible explanations), and creativity in the analysis and presentation of realist findings. Pawson also argued that evaluators need to shift the unit of analysis from the "program" itself to the "program theory" (the ideas behind it), to do more RE on policy (i.e. big ideas), and explore policy histories.[20] Immersion in realistic argument

Box 1. Additional details on general challenges of RE.

General sessions about the implications for evaluation methods

Several sessions elaborated on details of qualitative RE, including data collection[40,41] and analysis methods with details of choosing and using software packages.[42,43] Maxwell's plea for realist mixed-methods designs, with research questions at its center, seemed generally well accepted.[44] Quantitative analysis methods in the context of RE, that is, for testing hypothetical patterns indicating elements of program theories (e.g. using propensity scores and latent constructs), are at an exploratory stage.[24,45] Realistic economic evaluation methods developing as well.[46]

Examples of methods used by ongoing realist (inspired) studies from the field of health services/policy research selected from the book of oral abstracts:[47]

Qualitative or mixed-methods:

- Patient-centered decision-making in indigenous cancer
- Oral health promotion for schoolchildren in rural Andean communities (Peru)
- Medical patient journeys in Tasmania
- Preventing sexual violence and abuse in (Australian) Indigenous communities
- Technical assistance to support local innovation of sustainable funding for population health initiatives in the United States
- Lean' health system reform in Saskatchewan and Tasmania
- Coordinators for enhancing access to telehealth for children in rural and remote Australia

Realist reviews:

- Optimal perinatal surgical services for rural women
- Early years interventions to improve child health and well-being
- Comprehensive geriatric assessment in primary care
- Technology-supported intervention for engaging hospitalized patients in their care

Tension between realist principles and MRC guidelines

Despite its reference to realistic work,[9] the MRC contains from this perspective: (1) a limited conception of complexity, (2) acceptance of pragmatic divergence from "ideal" RCT designs (which, however, remain to be prioritized at all stages), and 3) recommendation for theory-based process evaluation alongside outcomes assessment in trials (but does not recommend shifting the unit of analysis from programs to program theories).

Debate about the role of RCTs in RE

In previous literature, it was suggested that the "realist RCT" (i.e. using "normal" RCT methods for the aims of RE) may be an oxymoron because realistic conceptions on generative causation and complexity contradict the assumption that control groups are necessary in experimentation, that random allocation results in equal group conditions in all relevant aspects, and that quantitative data can suffice for explanatory purposes.[16,18] Discussion seemed tamed when Hawkins argued that the most useful information an RCT could provide for the aims of RE is a "final" assessment to confirm previous explanatory work: when there are clear hypotheses on outcome pattern changes as the result of a single mechanism (well-framed and "cut-off" from any other) "firing" in a context bounded through experimental control.[24]

elicited attendants to reflect about its older philosophical roots,[21] which may have already been influencing interpretations of evaluation findings in researchers, clinicians, and policy makers more implicitly for longer. Evaluators' topical outputs, including work in adapting methods to realistic principles, and empirical evaluations from the field of health services/policy research (using qualitative methods and realist syntheses) are summarized in Box 1. It also describes tension we recognize of realist approaches with Medical Research Council (MRC) guidelines for evaluating (processes of) complex interventions hinted at by Gill Westhorp (in a pre-conference workshop), and on a debate about whether (and when) a randomized controlled trial (RCT) is usefully performed within an RE. This debate was continued in response to presentations sequel to previously published work[12,22,23] by Marchal,[18] Hawkins,[24] and Porter.[25]

Implications

Potential implications for choosing methods and fitting them to purpose in RE seem infinite, which could simultaneously feed a sense of opportunity and uncertainty. Therefore, it is expected that besides specific guidance for applying RE (e.g. reporting guidelines and course materials), a (broad) background and experience of various social and/or clinical (evaluation) research methods will be of general help to evaluators. Given the biomedical evidence paradigm omnipresent in medicine and public health (enacted by funding bodies and journals), realist arguments against the RCT as "golden standard" challenges re-thinking about what rigorous research methods are. In time, the realistic position may evolve as an opposing force to the legitimacy of context and theory "ignorant" evaluation, favoring the practical value of

scientific evaluation: a better ability to show that nothing is as practical as a good (program) theory. For realistic evaluation of care coordination, with its likely dependency on factors related to time and multiple levels of systems, one could think of using (mixed-) methods,[26] involving characteristics of action research and (comparative) case studies (qualitative), as well as techniques for structuring large amounts of data, and multi-level, longitudinal, and path analytic modeling (quantitative). A "big idea" lending itself for a realistic approach is the strategic agenda of the World Health Organization for people-centered integrated health services, as it explicitly includes a crucial responsibility for adaptation to local circumstances for which policy makers could use complementary understanding.[27]

Collaboration and co-creation of evidence are needed in dynamic contexts (JB and HL)

Hawkins gave four main recommendations for evaluators and commissioners for RE in the real world based on her experience in international development evaluation and public policy:[28] (1) *Innovative initiatives in dynamic context require creative evaluative thinking* and; 2) *Decisions and changes need to be informed by insights*. Realist evaluators must be aware of a dynamic context to which a uniquely designed evaluation plan is needed. Such design requires creative thinking. Changes in the environment taking place must be acknowledged during an evaluation. To such changes, evaluation plans are possibly to be adaptation. Therefore, rapid feedback loops based on ongoing data analysis are and integration of learning into decisions are necessary. Furthermore, (3) *a practical approach is needed and it should be context and system sensitive*. Due to the complexity, it is impossible to evaluate all parts of the all systems involved. Decisions are to be made about which part is of most interest. (4) *Collaboration and co-creation are key elements*. In working from a realist approach, evaluators and commissioners benefit from a flexible attitude and a collaborative relationship of sharing evaluative insights. The same points are illustrated by JB's plan for a collaborative and co-creative RE on care concepts for people with dementia living in residential care facilities[29] (Box 2). However, how difficult such approaches can be was saliently illustrated by a representative from an Indigenous working group observing the suitability for Indigenous peoples. RE seemed overall acceptable if Indigenous communities are being actively and continuously involved for a real-world impact. Otherwise, it was cautioned, research can seem like a form of "colonialism," for which researchers would only advance in their careers.

Implications

Taken into account the above and our own experiences, evaluating initiatives in care coordination using RE would be a good fit. First, one of the principals of care coordination is patient centeredness, that is, focusing on patients' needs, engagement, and participation.[1] In RE, collaboration and co-creation of the researcher with the key stakeholders, patients foremost, are highly encouraged. Thus, following an RE approach of patient participation preserves patient centeredness and focuses evaluation outcomes more on patients' needs. Second, RE would stimulate iterative development of care coordination initiatives involving key stakeholders from the first until final step to implementation. In doing so, implementation may be more likely to succeed and/or be understood.Third, RE using participatory action research embodying an iterative co-creation cycle in the collection and analysis of data, enabling action, and involving communities in an ongoing, respective, and accountable manner, may be accepted by and be suitable for empowering communities (e.g. Indigenous Australians).[30,31] To the knowledge of the authors, REs including community member participation were not published yet.

Box 2. Example (by JB) of planning a participatory RE approach.

In a PhD research on evaluating care concepts for people with dementia living in residential care facilities,[31] JB shows what realistic evaluation research in a real health care setting implies in concrete. In planning a "pathway" of realist research in time, the decision was made to facilitate an iterative development process by performing several successive short studies that build upon the knowledge gained through the previous one(s). Thereby, creating opportunity for creative evaluative thinking processes in response to new insights and information. Detailed plans about which parts of the system are investigated are made before the start of every study. This is one of many kinds of decisions that are taken collaboratively and in co-creation at each step within a mentoring team of key stakeholders (employees) from the two participating care organizations: coaches, managers, and members from the board of directors. Meetings are held every couple of months, discussing the results of previous studies and designs of upcoming studies. In this way, system or context-sensitive knowledge brought in by the stakeholders and scientific knowledge can be synthesized for arriving at explanations for outcome patterns that stakeholders need in practice.

Challenges in informing practice and policy (EB)

A major focus of the conference was the application of RE to inform better policy and practice.[20] Several participants presented findings of impact evaluations commissioned by Government and non-government agencies across a range of sectors including healthcare. However, a key challenge explored was how to better communicate about complexity; in a way that supports relevance to, and uptake by, intended audiences.[19] This implies avoiding formulaic or particularly wordy descriptions of findings (as Context-Mechanism-Outcome configurations).[19] A realist lens could also assist in understanding this issue of uptake and the mechanisms through which our research and evaluations might be adopted. Presentations examined visual representations of realist program theories for better communication and stronger methodological uptake.[32,33] Another avenue for relevance was a call for closer relationships in co-creation between commissioners, researchers/evaluators, implementers, and people affected by a particular intervention.[34] This offers both substantive (see previous section on collaboration and co-creation of evidence are needed in dynamic contexts) and communicative advantages. One presentation dealt specifically about how realist findings on integrated care initiatives were differently received at various organizational levels.[35]

Implications

For the time being, the above-described experienced challenges within wider domains of (health services) research offer starting points for high-quality applications of realistic principles to care coordination research. "High quality" thus implies that the standards of RE are met and that stakeholders take over their findings at all relevant organizational levels. Recommendable for achieving this is to balance subject matter knowledge with a solid grounding in realist methodology within an evaluation team. RAMESES protocols, which provide guidance and reporting standards for RE and synthesis,[17,36] may serve as practical artifacts in ongoing dialogue between program implementers, evaluation commissioners, and the evaluation team.

Conclusion

Care coordination efforts often constitute dynamic contexts suited to realist approaches. A realist research approach is compatible with several care coordination "principles," including patient centeredness and governance structures representing stakeholder groups.[1] There are no restrictions on methods that can be applied for "signifying" elements of realistic program theories on care coordination. It is, however, generally recommendable to collaborate with crucial stakeholders in a process of iterative co-production and creative evaluation and to strategically convey complexities to policy makers and practitioners. Program theories could, for example, come to complement larger strategic policy frameworks and facilitate their adoption for better health services integration, which is needed globally in a timely manner.[1,27] For better supporting to the accumulation of explanatory knowledge about how care coordination works under complexity, following up on early realist work in the field is recommended (5,37,38,39).

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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APPENDIX 5

Appendix Overview

This appendix comprises of the supplementary files of Chapter 2.

Systematic review protocol- Additional files 5

1) PRISMA-P checklist
2) Example of Search strategy
3) Eligibility forms
4) Data extraction forms comprising of four tables
5) Form of appraisal for risk of bias

A systematic review of primary care interventions addressing chronic disease- 5

Supplementary Files

1) PRISMA Checklist
2) Table 1
3) Table 2
4) Table 3
5) Table 4

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Yes/ No/ Not applicable
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Y
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	NA
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Y
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Y
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Y
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	NA
Support:			
Sources	5a	Indicate sources of financial or other support for the review	Y
Sponsor	5b	Provide name for the review funder and/or sponsor	NA
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	NA
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Y
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Y
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Y
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Y
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	Y

Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Y
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Y
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Y
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Y
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Y
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	Y
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Y
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	NA
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Y
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Y
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	NA
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	NA

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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

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	2	Program Evaluation/ or process evaluation.mp. or "Outcome and Process Assessment (Health Care)"/ ►	722945	Advanced	Display More ≫
	3	Qualitative research.mp. or Qualitative Research/ ►	90806	Advanced	Display More ≫
	4	qualitative.mp. ►	477736	Advanced	Display More ≫
	5	Clinical trials.mp. or Clinical Trial/ ►	1848296	Advanced	Display More ≫
	6	Randomized Controlled Trials as Topic/ or Clinical Trials as Topic/ or randomised controlled trials.mp. ►	401314	Advanced	Display More ≫
	7	complex interventions.mp. ►	2533	Advanced	Display More ≫
	8	Mental Disorders/ or Primary Health Care/ or Chronic Disease/ or Diabetes Mellitus/ or chronic care model.mp. or Pulmonary Disease, Chronic Obstructive/ or Disease Management/ ►	1449344	Advanced	Display More ≫
	9	Primary health care.mp. or Primary Health Care/ ►	158339	Advanced	Display More ≫
	10	cardiovascular diseases.mp. or exp Cardiovascular Diseases/ ►	5530823	Advanced	Display More ≫
	11	chronic kidney disease.mp. or exp Renal Insufficiency, Chronic/ ►	215546	Advanced	Display More ≫
	12	exp Pulmonary Disease, Chronic Obstructive/ or Lung Diseases, Obstructive/ or Respiratory Tract Diseases/ or Chronic respiratory disease.mp. or Chronic Disease/ ►	594762	Advanced	Display More ≫
	13	Obesity/ or Blood Glucose/ or Diabetes Mellitus, Type 2/ or Diabetes Mellitus/ or type 2 diabetes.mp. or Insulin/ or Hypoglycemic Agents/ ►	1698732	Advanced	Display More ≫
	14	exp Depression/ or depression.mp. ►	1119824	Advanced	Display More ≫
	15	general practice.mp. or Family Practice/ or General Practice/ ►	183431	Advanced	Display More ≫
	16	family physician.mp. or Physicians, Family/ ►	89336	Advanced	Display More ≫
	17	Social Support/ or Community Health Services/ or Community Mental Health Services/ or community support.mp. ►	294906	Advanced	Display More ≫
	18	Social Environment/ or Adolescent/ or Social Support/ or Mental Disorders/ or Family Relations/ or family support.mp. or Family/ ►	3761942	Advanced	Display More ≫
	19	case management.mp. or Community Mental Health Services/ or "Quality of Health Care"/ or "Delivery of Health Care"/ or Mental Disorders/ or Case Management/ or Chronic Disease/ or Patient Care Team/ ►	1303857	Advanced	Display Delete More ≫
	20	self management.mp. or Self Care/ ►	89895	Advanced	Display More ≫
	21	Primary Health Care/ or "Delivery of Health Care"/ or Organizational Innovation/ or organisational change.mp. ►	426297	Advanced	Display More ≫
	22	Primary Health Care/ or Quality Assurance, Health Care/ or Chronic Disease/ or delivery system design.mp. or Diabetes Mellitus/ or "Delivery of Health Care"/ ►	1432354	Advanced	Display More ≫
	23	Decision Making/ or Decision Support Techniques/ or Decision Making, Computer-Assisted/ or Decision Support Systems, Clinical/ or decision support.mp. ►	347732	Advanced	Display More ≫
	24	Information Systems/ or Medical Records Systems, Computerized/ or clinical information systems.mp. or Electronic Health Records/ ►	120031	Advanced	Display More ≫
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☐	30	8 or 10 or 11 or 12 or 13 or 14 ►	8720590	Advanced	Display More ≫
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☐	36	limit 35 to ("review articles" and "topic reviews (cochrane)") [Limit not valid in CCTR; records were retained , Limit not valid in Embase,PsycINFO,Global Health; records were eliminated] ►	8	Advanced	Display More ≫
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☐	38	limit 37 to humans [Limit not valid in CCTR,PsycINFO,Global Health; records were retained] ►	1498	Advanced	Display More ≫
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3. ☐ Psychiatric consultation in somatization disorder. A randomized controlled study.

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Additional Files 3-5

Additional file 3: Eligibility Criteria Forms

Inclusion Criteria	**Study**
Type of study: Process evaluation Qualitative study within RCT	
Design: RCT Complex intervention	
Setting: primary health care	
Exclusion criteria	
Not a journal article, not a specific trial, not a report based on empirical research (e.g. protocol, editorial), not reported in English, and not human research. Other	

Additional file 4: Data extraction tables

Table 1: Details of the RCTs and its complex intervention

Article	Summary of trial being evaluated	Causal assumptions clarified (hypothesis of how the intervention would work) (Y/N)	Setting (Rural, Urban, Countries	Disease (eg mental health, diabetes) Mental health	Main trial outcomes positive/ negative/equivalent	Cost analysis (Y/N/NA)

Table 2: Details about the process evaluation

Article	Labelled as a process evaluation (Y/N)	Stated purpose (Y/N)	Pre-specified protocol (Y/N)	Processes examined at which stage a) Feasibility and piloting- Acceptability, Testing of processes, Feasibility b) Evaluation of effectiveness- are the main trial designs and findings reported (Y/N/NA), Fidelity, mechanism, contextual influences c)Post-evaluation implementation- integrating of intervention into new context, long term maintenance	Specified theory (Y/N) (Theory e.g. Realist)	Methods used (eg stakeholder interviews, routine monitoring data, documentary analysis, observations) .	Analysis (if applicable -quantitative data on fidelity dose, reach -detailed modelling across sites -integration of quantitative process data and outcome datasets -qualitative and quantitative analysis building on each other -analysing process data prior to trial outcomes -generating hypothesis or post hoc explanation)

Table 3: to learn what the strengths and limitations of the PE in these contexts and to discuss what can be used to overcome it eg. Sampling, resources

Study	Strengths of process evaluation	Limitations of the process evaluation
For example: Boase 2011	Insights provided by the SAMS researchers of the trial may have enhanced data quality.	Interviews conducted by the researchers and thus known by the practice nurses, and different data may have been collected otherwise. Conducted at the end of the trial, and if interviewed at the start may have provided data to address the findings of competing time and demands during the implementation of the trial.

Table 4: to provide information so as to learn from previous process evaluations in implementing future trials in these contexts

Study	Implementation Issues (stated themes)	Implementation barriers	Implementation facilitators
For example: Boase 2011	Organisation of research	Recruitment into the study and whether it included the practice nurse's opinion at the start. Time issues- not having it compensated adequately to deliver the intervention and to do the administrative tasks associated with the study. This at times led to resentment from other team members who perceived that clinical time was taken up by research time resulting in increased work pressure overall.	Having the buy in of the practice nurse from the start of the study The intervention and the allocated time provided an opportunity to do things differently, and to allow for patient empowerment and patient centred care. Thus for most of them, positively changed their practice. Having time set aside for the practice nurse was perceived positively.
	Delivering the intervention	Competing demands- from GP, patients, research Standardised script to have it the same across the sites meant that at times it was not patient centred, and at times made the interactions with established patients awkward.	

Additional file 5: Appraisal form for the Risk of Bias

Criteria	**Study**
Planning:	
Degree of separation between outcome and process evaluation teams stated and described.	
Design and conduct:	
Process evaluations should clearly state their purpose.	
The intervention should be clearly described and causal assumptions clarified	
Process evaluations should state the choice of methods and justify them in terms of the stated aims of the evaluation, and the selected timing (eg retrospective data collection, was it planned initially)	
If the process evaluation is done at the evaluation stage: Transparently report of the process data are analysed blind to trial outcomes or for post- hoc explanation	
If qualitative methods used, the study was appraised with the use of COREQ (Domain 1: research team and reflexivity, Domain 2: study design, Domain 3: analysis and reporting)	
Reporting:	
Process evaluations should be clearly labeled	
Publish a full report of evaluation components or a protocol paper	
Risk of Bias Low, Unclear, High	

Author	Title	Year	Setting	Disease Condition	RCT Outcomes	Cost Considerations (Y/N/NA)
1. Gask L, Ludman E, Scaefer J.	Qualitative study of an intervention for depression among patients with diabetes: how can we optimise patient-professional interaction	2006	Primary health care, Manchester UK	Depression and Diabetes	Positive	N
2. Chew-Graham CA, Lovell K, Roberts C, Baldwin R, Morley M, Burns A, et al	A randomised controlled trial test the feasibility of a collaborative care model for the management of depression in older people	2007	Primary Care trust, Manchester	Depression	Positive	N
3. Lovell K, Bower P, Richards D, Barkham M, Sibbald B, Roberts C, et al	Developing guided self-help for depression using the Medical Research Council complex interventions framework: A description of the modelling phase and results of an exploratory randomised controlled trial	2008	Primary care Units England. United Kingdom	Depression	Negative	N
4. Slade M, Gask L, Leese M, McCrone P, Montana C, Powell R, Stewart M, Graham-Chew C	Failure to improve appropriateness of referrals to adult community mental health services—lessons from a multi-site cluster randomized controlled trial	2008	General Practice, Community Services. London & Manchester, United Kingdom	Depression (Mental Health)	negative	Y
5. Gask L, Bower P, Lovell K, Escott D, Archer J, Gilbody S, Lankshear A, Simpson AE, Richards DA.	What work has to be done to implement collaborative care for depression? Process evaluation of a trial utilizing the Normalisational Process Model	2010	Primary health care, UK	Depression	NA	N
6. Chalder M, Wiles NJ, Campbell J, Hollinghurst SP, Searle A, Haase AM, et al	A pragmatic randomised controlled trial to evaluate the cost-effectiveness of a physical activity intervention as a treatment for depression: The treating depression with physical activity (TREAD) trial	2012	General practices in the Bristol and Exeter areas, United Kingdom	Depression	Negative	Y
7. Bennett M, Walters K, Drennan V, Buszewicz M	Structured Pro-Active Care for Chronic Depression by Practice Nurses in Primary Care: A Qualitative Evaluation	2013	General Practice. United Kingdom	Depression	Positive	N
8. Stallard P, Phillips R, Montgomery AA, Spears M, Anderson R, Taylor J, et al	A cluster randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of classroom-based cognitive-behavioural therapy (CBT) in reducing symptoms of depression in high-risk adolescents	2013	Schools. United Kingdom	Depression	Negative	Y
9. Coupe N, Anderson E, Gask L, Sykes P, Richards DA, Chew-Graham C	Facilitating professional liaison in collaborative care for depression in UK primary care; A qualitative study utilising normalisation process theory	2014	Primary care GP. Bristol, London, and greater Manchester. United Kingdom	Depression	Positive	N

Synthesis (depression in UK)	Types of intervention: collaborative care models, introducing CBT in schools, introduction of physical activity,	9 studies in UK looking at depression between 2006-2014)			4 positive RCTs, 4 negative and 1 NA.	3/9 studies for costs analysis.
10. Oishi SM, Shoai R, Katon W, Callahan C, Unutzer J, Arean P, et al	Impacting late life depression: Integrating a depression intervention into primary care	2003	Primary care Practices. United States	Depression	NA (not complete)	N
11. Dietrich AJ, Oxman TE, Williams JW, Kroenke K, Schulberg HC, Bruce M, et al	Going to scale: Re-engineering systems for primary care treatment of depression	2004	5 Medical groups and health plans in the USA, with 60 practices participating	Depression	Positive	NA
12. Gask L, Dixon C, May C, Dowrick C	Qualitative study of an educational intervention for GPs in the assessment and management of depression	2005	Group Health Clinics. Western Washington. USA	Depression	Negative	N
13. Lee PW, Dietrich AJ, Oxman TE, Williams Jr JW, Barry SL	Sustainable impact of a primary care depression intervention	2007	Health care organisations. USA	Depression	Positive	N
14. Chung B, Jones L, Dixon EL, Miranda J, Wells K, Community Partners in Care Steering Council	Using a Community Partner Participatory Research Approach to Implement a Randomised Controlled Trial: Planning Community Partners in Care	2010	USA (community multi agencies for minority groups)	Depression	NA	N
15. Chaney EF, Rubenstein LV, Liu CF, Yano EM, Bolkan C, Lee M, et al	Implementing collaborative care for depression treatment in primary care: A cluster randomized evaluation of a quality improvement practice redesign	2011	Primary care settings, Veteran affairs in several states USA	Depression	Positive	Y
16. Rapp AM, Chavira DA, Sugar CA, Asarnow JR	Integrated Primary Medical-Behavioral Health Care for Adoolescent and Young Adult Depression: Predictors of Service Use in Youth Partners in Care Trial.	2017	Primary Health Care USA	Depression	Positive	N
Synthesis (depression in USA)	All 7 studies were a version of collaborative care models either between primary and tertiary care, or increasing the outreach through settings outside of health.	7 studies in USA looking at depression.			4 positive, 2 NA and 1 negative	1Y, 4 N, 1 NA
17. Thornett AM, Mynors-Wallis LM	Credibility of problem-solving therapy and medication for the treatment of depression among primary care patients	2002	Primary Care setting, South Australia	Depression	Positive	NA
18. Gensichen J, Guethlin C, Sarmand N, Sivakumaran D,	Patients' perspectives on depression case management in general practice - A qualitative study	2012	General Practices. Germany	Depression	Positive	N

Jager C, Mergenthal K, et al						
19. Chatterjee S, Chowdhary N, Pednekar S, Cohen A, Andrew G, Araya R, et al	Integrating evidence-based treatments for common mental disorders in routine primary care: Feasibility and acceptability of the MANAS intervention in Goa, India	2008	Primary Health care, Goa, India	Depression	Positive	N
20. Richter-Sundberg L, Nystrom ME, Krakau I, Sandahl C	Improving treatment of depression in primary health care: A case study of obstacles to perform a clinical trial designed to implement practice guidelines	2015	Primary Health care Units. Sweden	Depression	NA	N
Synthesis (depression)	**Interventions mostly around collaborative care through increasing expertise of different roles (e.g. lay worker, nurse for pro-active care, GP for PHC) (15 studies), at times to implement practice guidelines (4 studies), and trialling specific interventions such as physical exercise and CBT (2 studies).**	**2003-2015**	**9 were in UK, 6 in USA, and 1 Sweden, 1 Germany, 1 Australia and 1 in India.**	**Overall 19 studies in depression.**	**10 positive RCTs, 5 Negative, 4 NA**	**4/19 Y, 13 N, 2 NA**
1. Tai SS, Nazareth I, Donegan C, Haines A	Evaluation of general practice computer templates. Lessons from a pilot randomised controlled trial	1999	North London. United Kingdom	Diabetes (and asthma)	Positive	N
2. Hetlevik I, Holmen J, Kruger O, Kristebsen P, Iversen H, Furuseth K	Implementing Clinical guidelines in the treatment of Diabetes Mellitus in General Practice	2000	Norway	Diabetes Mellitus	Negative	N
3. Ilag LL, Martin CL, Tabaei BP, Isaman DJ, Burke R, Greene DA, et al	Improving diabetes processes of care in managed care	2003	United States, nine university- affiliated primary care internal medicine practices affiliated with a managed care organisation.	Diabetes	Negative on main outcome measures but positive on process outcomes	N
4. Smith S, Bury G, O'Leary M, Shannon W, Tynan A, Staines A, Thompson C	The North Dublin randomized controlled trial of structured diabetes shared care	2004	Ireland	Diabetes	Neutral	N
5. Jackie Sturt, Hafrun Taylor, Andrea Docherty, Jeremy Dale, Taylor Louise	A psychological approach to providing self-management education for people with type 2 diabetes: the Diabetes Manual	2006	Primary health care UK	Diabetes	NA	NA
6. Pylypchuk G, Vincent L, Wentworth J, Kiss A, Perkins N, Hartman S, et al	Diabetes risk evaluation and microalbuminuria (DREAM) studies: Ten years of participatory research with a First Nation's home and community model for type 2 diabetes care in northern Saskatchewan	2008	First Nations, Northern Saskatchewan, Canada	Diabetes type 2	not significantly positive	N

7. Smith S, Paul G, Kelly A, Whitford D, O'Shea E, O'Dowd T	Peer support for patients with type 2 diabetes: Cluster randomised controlled trial	2011	General Practice. Ireland	Type 2 Diabetes mellitus	Equivalent	Y
8. Ratanawongsa N, Bhandari VK, Handley M, Rundall T, Hammer H, Schillinger D	Primary care provider perceptions of the effectiveness of two self-management support programs for vulnerable patients with diabetes	2012	Community health network. San Francisco	Type 2 Diabetes mellitus	Positive	N
9. Lakerveld J, Bot S, Chinapaw M, van Tulder M, Kingo L, Nijpels G	Process evaluation of a lifestyle intervention to prevent diabetes and cardiovascular diseases in primary care	2012	Semi-rural region of West Friesland	Type 2 diabetes mellitus	Negative	Y(economic evaluations done separately)
10. Paul G, Keogh K, D'Eath M, Smith SM	Implementing a peer-support intervention for people with type 2 diabetes: A qualitative study	2013	General Practices, Ireland	Type 2 Diabetes mellitus	positive	N
11. Carlisle K, Warren R	A qualitative case study of tele-health for in-home monitoring to support the management of type 2 diabetes	2013	Queensland. Australia	type 2 diabetes	Positive	N
12. Grimshaw JM, Presseau J, Tetreo Jm , Eccles MP, Francis JJ, Godin G, Graham ID, Hux, JE, Johnston M, Legare F, Lemyre L, Robinson N, Zwarenstein M.	Looking inside the black box: results of a theory-based process evaluation exploring the results of a randomized controlled trial of printed educational messages to increase primary care physicians' diabetic retinopathy referrals	2014	Primary care setting, Ontario, Canada	Diabetes (leading to retinopathy)	Negative	N
13. Burridge LH, Foster MM, Donald M, Zhang J, Russell AW, Jackson CL	Making sense of change: patients' views of diabetes and GP-led integrated diabetes care	2014	Primary Care, Brisbane. Australia	Type 2 Diabetes	NA	N
14. Naik AD, Lawrence B, Kiefer L, Ramos K, Utech A, Masozera N, et al	Building a primary care/research partnership: lessons learned from a tele-health intervention for diabetes and depression	2015	Primary care teams Veterans affair Medical centre in Southern USA	Depression & Uncontrolled diabetes	not stated in paper	N
15. Eborall HC, Dallosso HM, McNicol S, Speight J, Khunti K, Davies MJ, et al	Explaining engagement in self-monitoring among participants of the DESMOND self-monitoring trial: A qualitative interview study	2015	Primary care trust, United Kingdom	type 2 diabetes mellitus	Positive	N
16. Ramadas A, Chan C, Oldenburg B, Hussien Z, Quek K	A Web-Based Dietary Intervention for People with Type 2 Diabetes: Development, Implementation, and Evaluation	2015	In the community, recruited from outpatient medical clinics of public hospitals Kuala Lumpur. Malaysia	Type 2 Diabetes Mellitus	Positive	N

17. Kenealy TW, Parsons MJG, Rouse PB, Doughty RN, Sheridan NF, Hindmarsh JKH, Masson SC, Rea HH.	Tele-care for Diabetes, CHF or COPD; Effect on Quality of Life, Hospital Use and Costs. A Randomised Controlled Trial and Qualitative Evaluation	2015	New Zealand	Diabetes, Chronic Heart Failure, COPD	Neutral	Y
Synthesis (diabetes)	**The interventions included improving guidelines referral and treatment (7 studies), patient self-management and community support (7 studies) and tele-health (3 studies).**	**1999-2016**	**3 Ireland, 1 Norway, 2 USA, 2 Canada (1 of the First Nations), 3 UK, 2 Australia, 1 New Zealand, 1 Malaysia**	**17 studies on diabetes (2 included other chronic disease)**	**6 Positive, 10 Negative/Neutral, 1 N/A**	**3/16 Y, 13/16 N, 1/16 NA**
1. Pearl A, Wright S, Gamble G, Doughty R, Sharpe N	Randomised trials in general practice--a New Zealand experience in recruitment	2003	General Practices .New Zealand	Heart failure	Positive	NA
2. Lobo CM, Euser L, Kamp J, Frijling BD, Severens JL, Hulscher MEJL, et al	Process evaluation of a multifaceted intervention to improve cardiovascular disease prevention in general practice	2003	General Practices, Netherlands	Cardiovascular Disease	Positive	Y
3. Weiss MC, Montgomery AA, Fahey T, Peters TJ	Decision analysis for newly diagnosed hypertensive patients: a qualitative investigation	2004	General Practice. South West-England. United Kingdom	Hypertension	Positive	N
4. Murchie P, Campbell NC, Ritchie LD, Thain J	Running nurse-led secondary prevention clinics for coronary heart disease in primary care: Qualitative study of health professionals' perspectives	2005	North East Scotland, UK	Cardiovascular Disease (Coronary Heart Disease)	Positive	N
5. Byrne M, Cupples ME, Smith SM, Leathem C, Corrigan M, Byrne MC, et al	Development of a complex intervention for secondary prevention of coronary heart disease in primary care using the UK Medical Research Council framework	2006	General Practices Urban & Rural Settings The island of Ireland, where 2 different healthcare systems exist. In the north, in line with Britain, the National Health Service allows everyone free access to general practice and hospital services. In the south, a mixed public and private healthcare system operates, with less than 30% of the population qualifying for free general practice and hospital services.	Cardiovascular disease	Positive	N

6.	Heaven, B, Murtagh, M. Rapley, T.May, C., raham, R. Kaner, E., Thomson, R.	Patients or research subjects? A qualitative study of participation in a randomised controlled trial of a complex intervention	2006	GP clinics in UK	CVD (AF patients at risk for a stroke)	NA	NA
7.	Clark RA, Yallop JJ, Piterman L, Croucher J, Tonkin A, Stewart S, et al	Adherence, adaptation and acceptance of elderly chronic heart failure patients to receiving healthcare via telephone-monitoring	2007	General Physicians, Rural Australia	Cardiovascular disease	Positive	N
8.	Fakiri FE, Hows MW, Uitewaal PJM, Frenken RA, Bruijnzeels MA.	Process evaluation of an intensified preventive intervention to reduce cardiovascular risk in general practices in deprived neighbourhoods	2008	General practices in deprived neighbourhoods, United Kingdom	Cardiovascular disease	Negative	N
9.	Wentzlaff DM, Carter BL, Ardery G, Franciscus CL, Doucette WR, Chrischilles EA, et al	Sustained Blood Pressure Control Following Discontinuation of a Pharmacist Intervention	2011	Iowa. United States of America	Hypertension	positive	N
10.	Passey ME, Laws RA, Jayasinghe UW, Fanaian M, McKenzie S, Powell-Davies G, et al	Predictors of primary care referrals to a vascular disease prevention lifestyle program among participants in a cluster randomised trial	2012	2 Rural 3 urban Division of General practice in New South Wales. Australia	Cardiovascular disease	Positive	N
11.	Nelson P, Cox H, Furze G, Lewin RJP, Morton V, Norris H, et al	Participants' experiences of care during a randomized controlled trial comparing a lay-facilitated angina management programme with usual care: a qualitative study using focus groups	2013	District General Hospital, North England. United Kingdom	Cardiovascular disease (Angina)	Positive	NA
12.	Fairbrother, Peter McCloughan, Lucy Adam, Geraldine Brand, Richard Brown, Cecil Watson, Mary Cotter, Nicola Mackellaig, Juliet McKinstry, Brian	Involving patients in clinical research: The Telescot patient panel	2013	Primary health care Scotland, UK	CVD (Stroke)	NA	N

13. Hanley, J.Ure, J.Pagliari, C. Sheikh, A.McKinstry, B.	Experiences of patients and professionals participating in the HITS home blood pressure tele-monitoring trial: A qualitative study	2013	Primary health care in Edinburgh, UK	CVD with Hypertension as the major risk factor	Positive	N
14. Laws, R. A, Fanaian, M, Jayasinghe, U. W.McKenzie, S. Passey, M.Davies, G. P.Lyle, D. Harris, M. F	Factors influencing participation in a vascular disease prevention lifestyle program among participants in a cluster randomized trial	2013	Urban and rural PHC in Australia	CVD prevention	positive (changes in self- reported physical behaviours, but only those referred to life style modification program achieved improvement in diet or weight.	N
15. Manca DP, Greiver M, Carroll JC, Salvalaggio G, Cave A, Rogers J, et al	Finding a BETTER way: A qualitative study exploring the prevention practitioner intervention to improve chronic disease prevention and screening in family practice	2014	Primary care, Canada (urban setting)	Chronic disease- diabetes and heart disease (among others)	positive	N
16. Liu H, Massi L, Laba TL, Peiris D, Usherwood T, Patel A, Cass A, Eades AM, Redfern J, Hayman N, Howard K, Brien JA, Jan S.	Patients' and Providers' Perspectives of a Polypill Strategy to Improve Cardiovascular Prevention in Australian Primary Health Care: A Qualitative Study Set Within a Pragmatic Randomized, Controlled Trial.	2015	Australia PHC	CVD	Positive	Y
17. Liu H, Laba T, Massi L, Jan S, Usherwood T, Patel A, Hayman N, Cass A, Eades A, Peiris D.	Facilitators and barriers to implementation of a pragmatic clinical trial in Aboriginal health services.	2015	Australia PHC	CVD	NA	NA
18. Liu H, Massi L, Eades AM, Howard K, Peiris D, Redfern J, Usherwood T, Cass A, Patel A, Jan S, Laba T.	Implementing a pragmatic randomised controlled trial in Australia: lessons learnt from the Kanyini Guidelines Adherence with the Polypill study (Kanyini GAP)	2015	Australia PHC	CVD	NA	NA
19. Huntink E, Wensing M, Timmers IM, Lieshout JV	Process evaluation of a tailored intervention programme of cardiovascular risk management in general practices	2016	Netherlands	Cardiovascular risk management (high cardiovascular risk, and depressive symptoms)	Negative	N
20. Parsons, J. A. Yu, C. H. Y. Baker, N. A.	Practice doesn't always make perfect: A qualitative study explaining why a trial of an educational toolkit did not improve quality of care	2016	General Practices in Ontario, Canada	CVD prevention	Negative (possible harms)	N

	Mamdani, M. M. Bhattacharyya, O. Zwarenstein, M. Shah, B. R.						
21.	Presseau J, Grimshaw J, Tetroe JM, Eccles MP, Francis JJ, Godin G, Graham ID, Hux JE, Johnston M, Legare F, Lemyre L, Robinson N, Zwarenstein M.	A theory-based process evaluation alongside a randomised controlled trial of printed educational messages to increase primary care physician's prescription of thiazide diuretics for hypertension	2016	Ontario, Canada	Cardiovascular disease management(prescription of thiazide for hypertension)	Negative	N
22.	Yan LD, Chirwa C, Chi BH, Bosomprah S, Sindano N, Mwanza M, Musatwe D, Mulenga M, Chilengi R.	Hypertension management in rural primary care facilities in Zambia: a mixed methods study	2017	Rural Zambian clinics	Hypertension	NA (ongoing trial)	NA
23.	Wells S, Rafter N, Kenealy T, Herd, Geoff, Eggleton K, Lightfoot R, Arcus K, Wadham A, Jiang Y, Bullen C.	The impact of a point of care testing device on CVD risk assessment completion in New Zealand primary-care practice: A cluster randomised controlled trial and qualitative investigation	2017	General practices in Northland region, New Zealand,	CVD risk assessment	Negative	Y
24.	Grant A, Dreischulte T, Guthrie B	Process evaluation of the data-driven quality improvement in primary care (DQIP) trial: active and less active ingredients of a multi-component complex intervention to reduce high-risk primary care prescribing	2017	Primary Health care in UK. 33 practices from one Scottish health board	Cardiovascular and renal adverse events	Positive	N
25.	Grant A, Dreischulte T, Guthrie B	Process evaluation of the Data-driven Quality Improvement in Primary Care (DQIP) trial: case study evaluation of adoption and maintenance of a complex intervention to reduce high-risk primary care prescribing	2017	Primary Health care in UK. 33 practices from one Scottish health board	Cardiovascular and renal adverse events	Positive	N

Synthesis (CVD)	**Ten of the studies were about improving the screening and management of CVD using best-practice guidelines. (e.g. educational materials to improve referral, or decision analysis). Ten of the studies were about organisational change with models of care that incorporated new roles such as a nurse-led clinic, or the use of a lay worker for angina management, and technology (e.g. tele-monitoring, point of care testing). 5 of the studies explored trial implementation such as recruitment of patients and providers, and were less about the intervention.**	**2013-2017**	**2 New Zealand, 2 Netherlands, 9 UK, 1 Ireland, 6 Australia, 1 USA, 3 Canada, 1 Zambia (interesting that is so international, which I assume has to do with the recognition of CVD)**	**25 studies in CVD. (1 for chronic diseases, in which CVD is mentioned)**	**15 Positive, 5 Negative, and 5 N/A**	**3 Y, 15 N, 6 NA**
1. Van Den Bemt L, Schermer TRJ, Smeele IJM, Boonman-de Winter LJM, Van Boxem T, Denis J, et al	An expert-supported monitoring system for patients with chronic obstructive pulmonary disease in general practice: Results of a cluster randomised controlled trial	2009	General Practice. Netherlands	COPD	Negative	N
2. Casey D, Murphy K, Cooney A, Mee L, Dowling M.	Developing a structured education programme for clients with COPD	2011	Primary care, Ireland	COPD	NA	N
3. Julia A. E. Walters,E, Helen Courtney-Pratt , Helen Cameron-Tucker, Mark Nelson, Andrew Robinson, Jenn Scott, Paul Turner, E. Haydn Walters and Richard Wood-Baker	Engaging general practice nurses in chronic disease self-management support in Australia: Insights from a controlled trial in chronic obstructive pulmonary disease	2012	Australia PHC	COPD	NA	N
4. Fairbrother P, Pinnock H, Hanley J, McCloughan L, Sheikh A, Pagliari C, et al	Exploring tele-monitoring and self-management by patients with chronic obstructive pulmonary disease: A qualitative study embedded in a randomized controlled trial	2013	Lothian. Scotland, UK	Chronic Obstructive Pulmonary Disease	NA	N
5. Van der Weegen S, Verwey R et al	The Development of a Mobile Monitoring and Feedback Tool to Stimulate Physical Activity of People with a Chronic Disease in Primary Care: A User-Centred Design	2013	Netherlands PHC	Chronic Obstructive Pulmonary Disease or Type 2 diabetes	NA	NA

6. Vest BM, York TRM, Sand J, Fox CH, Kahn LS	Chronic kidney disease guideline implementation in primary care: A qualitative report from the TRANSLATE CKD study	2015	Primary Care Practices, New York. United States	Chronic Kidney Disease	Positive	N
7. Verwey R, van der Weegen S, Spreeuwenberg M, Tange H, van der Weijden T, de Witte L	Process evaluation of physical activity counselling with and without the use of mobile technology: A mixed methods study	2016	Netherlands	Chronic Obstructive Pulmonary Disease or Type 2 diabetes	Positive	NA
Synthesis (COPD, and CKD)	**4 of the studies were about improving self-management of patients through educational materials, or use of monitoring, with support from health providers. 2 of the studies were about stimulating physical activity through the use of technology. 1 study was about implementing management guidelines in CKD in PHC.**	**2009-2016**	**3 Netherlands, I Ireland, 1 UK (Scotland), 1 USA, 1 Australia**	**6 addressing COPD (2 including other chronic disease), and 1 addressing CKD.**	**2 Positive, 1 Negative, 4 N/A**	**0 Y, 5 N, 2 N/A.**
Overall Synthesis of 69 studies in total	**Overall, the complex primary care interventions fit within the general categories of facilitating patient self-management (13 studies), organisational change to include collaborative care (16 studies), facilitating better case management using clinical information systems (e.g. tele-health) (15 studies), and the use of decision support and guideline implementation (e.g. referral systems) (22 studies). In addition, 5 studies were exploring the conduct of trials in primary health care e.g. the recruitment of patients.**	**1999-2017**	**22 UK, 9 USA, 1 Sweden, 1 Germany, 10 Australia, 1 India, 3 Canada, 5 Ireland, 1 Norway, 3 New Zealand, 1 Malaysia, 5 Netherlands, 1 Zambia In addition, 2 studies focused on First Nations peoples in Australia and in Canada. 3 studies (Chung, Fakiri, Ratangawonsa) were focused on the populations living in disadvantage.**	**20 Depression, 17 Diabetes, 25 CVD, 6 COPD and 1 CKD.**	**33 Positive, 21 Negative and 14 Not applicable.**	**10 Y, 47 N, 11 Not applicable.**

Author	Title	Year	Labelled as Process Evaluation (Y/N)	Stated Purpose (Y/N)	Protocol (Y/N)	Processes examined at which stage	Use of Theory (Y/N)	Methods	Analysis
Tai SS, Nazareth I, Donegan C, Haines A	Evaluation of general practice computer templates. Lessons from a pilot randomised controlled trial	1999	N	Y	N	Feasibility and Piloting	N	qualitative (semi-structured interviews designed to assess the users' views) and quantitative (change in use of the template during the study period)	NA
Weiss MC, Montgomery AA, Fahey T, Peters TJ	Decision analysis for newly diagnosed hypertensive patients: a qualitative investigation	2004	Qualitative study	Y	N	Feasibility and Piloting	N	Semi-structured Interviews	Decision Analysis
Jackie Sturt, Hafrun Taylor, Andrea Docherty, Jeremy Dale, Taylor Louise	A psychological approach to providing self-management education for people with type 2 diabetes: the Diabetes Manual	2006	N	Y	N	Feasibility	Y	Using the MRC complex intervention framework the intervention was developed. Theory driven, needs assessment through focus group, and the use of a feasibility survey	Use of a survey to determine the feasibility of the developed intervention to be further tested in a definitive RCT
Byrne M, Cupples ME, Smith SM, Leathem C, Corrigan M, Byrne MC, et al	Development of a complex intervention for secondary prevention of coronary heart disease in primary care using the UK Medical Research Council framework	2006	N	Y	N	Feasibility and Piloting	Y	Semi structured Interviews	NR
Chew-Graham CA, Lovell K, Roberts C, Baldwin R, Morley M, Burns A, et al	A randomised controlled trial test the feasibility of a collaborative care model for the management of depression in older people	2007	N	Y	N	Feasibility and Piloting	N	Semi-structured Interviews and questionnaires	Thematic analysis
Clark RA, Yallop JJ, Piterman L, Croucher J, Tonkin A, Stewart S, et al	Adherence, adaptation and acceptance of elderly chronic heart failure patients to receiving healthcare via telephone-monitoring	2007	N	Y	Y	Feasibility and piloting	N	Triangulation of descriptive statistics, feedback surveys and qualitative analysis of clinical notes.	Thematic analysis of the clinical notes and open ended comments from survey and triangulated with the satisfaction survey.
Lovell K, Bower P, Richards D, Barkham M, Sibbald B, Roberts C, et al	Developing guided self-help for depression using the Medical Research Council complex interventions framework: A description of the modelling phase and results of an exploratory randomised controlled trial	2008	N	Y	N	Feasibility and piloting	yes- use of MRC	Interviews, systematic review and modelling.	Framework analysis

Chatterjee S, Chowdhary N, Pednekar S, Cohen A, Andrew G, Araya R, et al	Integrating evidence-based treatments for common mental disorders in routine primary care: Feasibility and acceptability of the MANAS intervention in Goa, India	2008	N	Y	N	Feasibility and Piloting & post evaluation	N	Stakeholder semi structured interviews	Thematic analysis
van Steenkiste B, van der Weijden TM, Stoffers JH, Grol RP	Patients' responsiveness to a decision support tool for primary prevention of cardiovascular diseases in primary care	2008	Y	Y	N	Feasibility and Piloting	N	routine monitoring data, observations (e.g. Patients' actually having read the booklet and returning for the second consultation; comprehension and perceived relevance of the information; perceived reassurance.)	Descriptive statistics, and logistic regression to dependent variables and independent variables.
Chung B, Jones L, Dixon EL, Miranda J, Wells K, Community Partners in Care Steering Council	Using a Community Partner Participatory Research Approach to Implement a Randomised Controlled Trial: Planning Commnunity Partners in Care	2010	N	Y	N	Feasibility	Y	Baseline survey, community dialogue to obtain community feedback	NA
Gask L, Bower P, Lovell K, Escott D, Archer J, Gilbody S, Lankshear A, Simpson AE, Richards DA.	What work has to be done to implement collaborative care for depression? Process evaluation of a trial utilizing the Normalisational Process Model	2010	Y	Y	N	Feasibility and piloting (exploratory trial)	Normalisation Process Model	Pre study data collection of focus group and interviews, and post study data collection of interviews	Used a template or apriori coding manual from normalisation process model.
Casey D, Murphy K, Cooney A, Mee L, Dowling M.	Developing a structured education programme for clients with COPD	2011	N, Development of programme	Y	N	Feasibility and Piloting	N	Content analysis and concept analysis and 2 qualitative studies	Constant Comparative approach
Chalder M, Wiles NJ, Campbell J, Hollinghurst SP, Searle A, Haase AM, et al	A pragmatic randomised controlled trial to evaluate the cost-effectiveness of a physical activity intervention as a treatment for depression: The treating depression with physical activity (TREAD) trial	2012	N, Qualitative study	Y	Y	Feasibility and Piloting	Y (Self Determination Theory)	Interviews	NA
Bennett M, Walters K, Drennan V, Buszewicz M	Structured Pro-Active Care for Chronic Depression by Practice Nurses in Primary Care: A Qualitative Evaluation	2013	N	Y	Y	Feasibility and Piloting	N	In depth interviews	Thematic analysis

Carlisle K, Warren R	A qualitative case study of telehealth for in-home monitoring to support the management of type 2 diabetes	2013	N	Y	Y	Feasibility and Piloting	N	Semi structured Interviews	Not described.
Van der Weegen S, Verwey R et al	The Development of a Mobile Monitoring and Feedback Tool to Stimulate Physical Activity of People with a Chronic Disease in Primary Care: A User-Centered Design	2013	N	Y	N	Feasibility	Y	Qualitative individual interviews and focus group. Literature search re behaviour change and self-management	Three staged iterative process. Literature review to identify end users and context, stage 2, the literature, experts and patient representatives consulted to set up a use case. Stage 3 where individual interviews and focus groups based on the use case helped to identify end user requirements, and build a prototype.
Fairbrother, Peter McCloughan, Lucy Adam, Geraldine Brand, Richard Brown, Cecil Watson, Mary Cotter, Nicola Mackellaig, Juliet McKinstry, Brian	Involving patients in clinical research: The Telescot patient panel	2013	N	Y	Y	Feasibility	N	Patient' panel and Focus groups	Thematic
Ramadas A, Chan C, Oldenburg B, Hussien Z, Quek K	A Web-Based Dietary Intervention for People with Type 2 Diabetes: Development, Implementation, and Evaluation	2015	Y	Y	Y	Feasibility and Piloting	N	Self-administered questionnaire (to determine program reception)	Descriptive statistics of the process evaluation measures.

Naik AD, Lawrence B, Kiefer L, Ramos K, Utech A, Masozera N, et al	Building a primary care/research partnership: lessons learned from a telehealth intervention for diabetes and depression	2015	Formative evaluation	Y	N	Feasibility and Piloting, and Evaluation of effectiveness	Y	Qualitative data from the research/clinical partnership meetings that was recorded and coded. Triangulated with other information such as research staff personal communication, field notes and minutes of meetings.	Qualitative Framework analysis
Vest BM, York TRM, Sand J, Fox CH, Kahn LS	Chronic kidney disease guideline implementation in primary care: A qualitative report from the TRANSLATE CKD study	2015	Y	Y	Y	Feasibility and Piloting	Y	Semi-structured Interviews	Thematic Content Analysis
Synthesis	**The quality data items do not fit these studies as they seem to be more applicable to the effectiveness stage. Though the COREQ ones still matter for the qualitative study/methods. The methods (literature search, consensus process, focus group interviews) can inform the intervention development and subsequent evaluation (e.g. testing of change in determinants). Use of classic theory especially psychological/behavioural ones seem relevant for chronic diseases given the emphasis on self-management as reflected in Box 1.**	**1999 - 2016**	**5 labelled as process evaluations**	**20 to stated purpose.**	**8 Y**	**20 Studies**	**9**	**18 used interviews. 3 used focus group discussions, 4 used questionnaires or surveys, 2 studies used routine monitoring data, field notes, minutes of meetings and observations.**	**Thematic analysis, constant comparative approach most commonly used, with some using framework analysis.**
Hetlevik I, Holmen J, Kruger O, Kristensen P, Iversen H, Furuseth K	Implementing clinical guidelines in the treatment of diabetes mellitus in general practice: Evaluation of effort, process, and patient outcome related to implementation of a computer-based decision support system	2000	Y	Y	N	Effectiveness	N	Use of number of patient registrations (fraction as the process evaluation) and a questionnaire to determine user friendliness, perceived benefit and feedback about implementation strategies	Quantitative analysis according to variables and across two time points.
Thornett AM, Mynors-Wallis LM	Credibility of problem-solving therapy and medication for the treatment of depression among primary care patients	2002	N	Y	N	Evaluation of effectiveness	N	Credibility scale questionnaires, Kruskall-Wallis rank test of relationships.	Statistical analysis
Ilag LL, Martin CL, Tabaei BP, Isaman DJ, Burke R, Greene DA, et al	Improving diabetes processes of care in managed care	2003	N	Y	N	Evaluation of effectiveness	N	Quantitative measures of processes of care (e.g. measuring HbA1c), and a Likert scale acceptability survey given to the health providers	Quantitative analysis between groups, with hierarchical liner mixed models for continuous models for categorical variables to control for random subject effects and random practice-site effects.

Lobo CM, Euser L, Kamp J, Frijling BD, Severens JL, Hulscher MEJL, et al	Process evaluation of a multifaceted intervention to improve cardiovascular disease prevention in general practice	2003	Y	Y	N	Evaluation of effectiveness	N	Implementer reports and questionnaires to health providers	Descriptive statistical analysis.
Pearl A, Wright S, Gamble G, Doughty R, Sharpe N	Randomised trials in general practice--a New Zealand experience in recruitment	2003	N	Y	N	effectiveness	N	Evaluation questionnaire	Descriptive
Smith S, Bury G, O'Leary M, Shannon W, Tynan A, Staines A, Thompson C	The North Dublin randomized controlled trial of structured diabetes shared care	2004	N	Y	N	Evaluation of effectiveness	N	processes of care and qualitative study, (and outcome study reported together)	Triangulation of mixed methods
Gask L, Dixon C, May C, Dowrick C	Qualitative study of an educational intervention for GPs in the assessment and management of depression	2005	N	Y	Y	Evaluation of effectiveness (Y)	N	Interviews	Qualitative Content Analysis
Gask L, Ludman E, Scaheffer J.	Qualitative Study of an intervention for depression among patients with diabetes: how can we optimise patient-professional interaction?	2006	N	Y	N	Evaluation of effectiveness	N	Qualitative semi structured interviews and content analysis of recorded case management (i.e. the intervention itself)	Constant Comparative approach
Heaven, B. Murtagh, M. Rapley, T. May, C. Graham, R. Kaner, E. Thomson, R.	Patients or research subjects? A qualitative study of participation in a randomised controlled trial of a complex intervention	2006	N	Y	N	Post hoc effectiveness ?	Y (informed by ideas of symbolic interactionism, phenomenology and critical psychology.	Mixed Methods: Part of an observational study alongside a RCT (comprising of video of consultation) and participant interview post clinic and 3 months post clinic (* this study only reports on the 3-5 days post clinic interviews.	Constant Comparative approach to the qualitative data, and informed by ideas from symbolic interactionism, phenomenology and critical psychology.
Fakiri FE, Hows MW, Uitewaal PJM, Frenken RA, Bruijnzeels MA.	Process evaluation of an intensified preventive intervention to reduce cardiovascular risk in general practices in deprived neighbourhoods	2008	Y	Y	N	Evaluation of effectiveness-fidelity and reach	N	Fidelity data e.g. ranking of the intervention as delivered by the protocol, and the Reach data through the number of consultations completed	Descriptive analysis

Slade M, Gask L, Leese M, McCrone P, Montana C, Powell R, Stewart M, Graham-Chew C	Failure to improve appropriateness of referrals to adult community mental health services—lessons from a multi-site cluster randomized controlled trial	2008	N	Y	Y	Evaluation of effectiveness	N	Outcomes, process data was presented and implementation was explored through the nested qualitative data.	Logistics analysis and thematic analysis of the qualitative data.
Van Den Bemt L, Schermer TRJ, Smeele IJM, Boonman-de Winter LJM, Van Boxem T, Denis J, et al	An expert-supported monitoring system for patients with chronic obstructive pulmonary disease in general practice: Results of a cluster randomised controlled trial	2009	Y	Y	N	Evaluation of effectiveness	N	For the process evaluation, the respiratory experts' database was examined to collect data on their recommendations. The nurse consultant collected data on GPs' implementation of recommendations. Patient questionnaires comprised questions about disease management. (i.e. documentary analysis and questionnaires)	Compared the implementation across control and intervention groups. Process evaluation and outcome evaluation was presented together.
Smith S, Paul G, Kelly A, Whitford D, O'Shea E, O'Dowd T	Peer support for patients with type 2 diabetes: Cluster randomised controlled trial	2011	Y	Y	Y	Evaluation of effectiveness	N	Interviews and FGD's. Routine monitoring data	Descriptive parallel qualitative analysis based on descriptive phenomenology
Passey ME, Laws RA, Jayasinghe UW, Fanaian M, McKenzie S, Powell-Davies G, et al	Predictors of primary care referrals to a vascular disease prevention lifestyle program among participants in a cluster randomised trial	2012	N	Y	Y	Evaluation of effectiveness	N	Routine monitoring data	Univariate analysis
Gensichen J, Guethlin C, Sarmand N, Sivakumaran D, Jager C, Mergenthal K, et al	Patients' perspectives on depression case management in general practice - A qualitative study	2012	N	Y	Y	Evaluation of effectiveness	N	Interviews	Content Analysis

Julia A. E. Walters,E, Helen Courtney-Pratt , Helen Cameron-Tucker, Mark Nelson, Andrew Robinson, Jenn Scott, Paul Turner, E. Haydn Walters and Richard Wood-Baker	Engaging general practice nurses in chronic disease self-management support in Australia: insights from a controlled trial in chronic obstructive pulmonary disease	2012	N	Y	N	Effectiveness	N	Mixed methods (quant survey and interviews)	Iterative thematic analysis with triangulation of quant data
Ratanawongsa N, Bhandari VK, Handley M, Rundall T, Hammer H, Schillinger D	Primary care provider perceptions of the effectiveness of two self-management support programs for vulnerable patients with diabetes	2012	N	Y	Y	Evaluation of effectiveness	N	self-administered questionnaire	Descriptive analysis
Lakerveld J, Bot S, Chinapaw M, van Tulder M, Kingo L, Nijpels G	Process evaluation of a lifestyle intervention to prevent diabetes and cardiovascular diseases in primary care	2012	Y	Y	Y	Evaluation of Effectiveness	Re-AIM	Questionnaires	Confirmatory factor analysis
Paul G, Keogh K, D'Eath M, Smith SM	Implementing a peer-support intervention for people with type 2 diabetes: A qualitative study	2013	N	Y	Y	Evaluation of effectiveness	N	Stakeholder interviews and FGD	Framework analysis and a matrix based method of analysing qualitative data.
Nelson P, Cox H, Furze G, Lewin RJP, Morton V, Norris H, et al	Participants' experiences of care during a randomized controlled trial comparing a lay-facilitated angina management programme with usual care: a qualitative study using focus groups	2013	N	Y	Y	Evaluation of Effectiveness	N	Focus group discussions	Thematic analysis
Fairbrother P, Pinnock H, Hanley J, McCloughan L, Sheikh A, Pagliari C, et al	Exploring tele monitoring and self-management by patients with chronic obstructive pulmonary disease: A qualitative study embedded in a randomized controlled trial	2013	N	Y	Y	Evaluation of effectiveness-views of the intervention	Schermer three degress of telemetric self management	Semi structured Interviews	Framework analysis

Stallard P, Phillips R, Montgomery AA, Spears M, Anderson R, Taylor J, et al	A cluster randomised controlled trial to determine the clinical effectiveness and cost-effectiveness of classroom-based cognitive-behavioural therapy (CBT) in reducing symptoms of depression in high-risk adolescents	2013	Y	Y	Y	Evaluation of effectiveness	REAIM	Questionnaires and Qualitative Interviews	Thematic analysis
Hanley, J. Ure, J. Pagliari, C. Sheikh, A. McKinstry, B.	Experiences of patients and professionals participating in the HITS home blood pressure tele-monitoring trial: A qualitative study	2013	N	Y	Y	Effectiveness (though informed by interviews at the pilot and feasibility stage, and there was a protocol-evolution allowed)	Y (Normalisation process theory)	Semi-structured qualitative interviews and a focus group to validate the findings and discuss implementation	Ongoing iterative analysis "*The trial context permitted triangulation with quantitative data. Owing to the protocolpermitted evolution in practice, it gives an indication of some of the issues which would need to be addressed for BP telemonitoring to be used in routine practice*."
Laws, R. A. Fanaian, M. Jayasinghe, U. W. McKenzie, S. Passey, M. Davies, G. P. Lyle, D. Harris, M. F	Factors influencing participation in a vascular disease prevention lifestyle program among participants in a cluster randomized trial	2013	N	y	y	effectiveness	N	Mixed methods of quantitative analysis of survey, clinical audit data, practice questionnaire on capacity for preventive care, and referral and attendance records, interviews with implementers of the program	Quantitative data analysis (to find the characteristics and the factors influencing attendance) and qualitative thematic analysis.
Manca DP, Greiver M, Carroll JC, Salvalaggio G, Cave A, Rogers J, et al	Finding a BETTER way: A qualitative study exploring the prevention practitioner intervention to improve chronic disease prevention and screening in family practice	2014	N	Y	N	Evaluation of effectiveness	Y (Grounded theory)	semi-structured interviews and focus groups	Constant Comparative approach
Richter-Sundberg L, Nystrom ME, Krakau I, Sandahl C	Improving treatment of depression in primary health care: A case study of obstacles to perform a clinical trial designed to implement practice guidelines	2015	N	Y	N	Evaluation of effectiveness	N	Semi-structured Interviews	qualitative analysis

Eborall HC, Dallosso HM, McNicol S, Speight J, Khunti K, Davies MJ, et al	Explaining engagement in self-monitoring among participants of the DESMOND self-monitoring trial: A qualitative interview study	2015	N	Y	N	Evaluation of effectiveness	N	Qualitative semi structured interviews	Constant Comparative approach
Grimshaw JM, Presseau J, Tetreo Jm , Eccles MP, Francis JJ, Godin G, Graham ID, Hux, JE, Johnston M, Legare F, emyre L, et al..	Looking inside the black box: results of a theory-based process evaluation exploring the results of a randomized controlled trial of printed educational messages to increase primary care physicians' diabteic retinopathy referrals	2014	Y	Y	Y	Evaluation of effectiveness	Y (Theory of planned behaviour)	Surveys at two time points	Compared groups factorially on changes at the two time points pre and post intervention. Thematic analysis of the open comment section
Burridge, L. H. Foster, M. M. Donald, M. Zhang, J. Russell, A. W. Jackson, C. L.	Making sense of change: patients' views of diabetes and GP-led integrated diabetes care	2014	N	Y	N	Evaluation of effectiveness	Y, Normalisation Process Theory	Qualitative study (as part of a mixed methods evaluation)	Thematic Analysis with a modified framework based on NPT.
Coupe N, Anderson E, Gask L, Sykes P, Richards DA, Chew-Graham C	Facilitating professional liaison in collaborative care for depression in UK primary care; A qualitative study utilising normalisation process theory	2014	N	Y	Y	Evaluation of effectiveness	Normalization process theory (NPT)	Interviews	Thematic analysis
Kenealy TW, Parsons MJG, Rouse PB, Doughty RN, Sheridan NF, Hindmarsh JKH, Masson SC, Rea HH.	Telecare for Diabetes, CHF or COPD; Effect on Quality of Life, Hospital Use and Costs. A Randomised ControlledTrial and Qualitative Evaluation	2015	N	Y	N	Evaluation of effectiveness	N	Individual and focus group interviews and questionnaire. (note that other process measures such as the nurse keeping a log of their activities for calculation of health care use was also collected)	Thematic analysis

Liu H, Massi L, Laba TL, Peiris D, Usherwood T, Patel A, Cass A, Eades AM, Redfern J, Hayman N, Howard K, Brien JA, Jan S.	Patients' and Providers' Perspectives of a Polypill Strategy to Improve Cardiovascular Prevention in Australian Primary Health Care: A Qualitative Study Set Within a Pragmatic Randomized, Controlled Trial.	2015	Y	Y	Y	Effectiveness	Y	Qualitative interviews and triangulation with outcomes, and knowledge of trial implementation	Iterative thematic analysis, with the use of the Realist framework to guide the development of the themes.
Liu H, Laba T, Massi L, Jan S, Usherwood T, Patel A, Hayman N, Cass A, Eades A, Peiris D.	Facilitators and barriers to implementation of a pragmatic clinical trial in Aboriginal health services.	2015	Y	Y	Y	Effectiveness	N	Qualitative interviews and triangulation with outcomes, and knowledge of trial implementation	Iterative thematic analysis
Liu H, Massi L, Eades AM, Howard K, Peiris D, Redfern J, Usherwood T, Cass A, Patel A, Jan S, Laba T.	Implementing a pragmatic randomised controlled trial in Australia: lessons learnt from the Kanyini Guidelines Adherence with the Polypill study (Kanyini GAP)	2015	Y	Y	Y	Effectiveness	N	Qualitative interviews and triangulation with outcomes, and knowledge of trial implementation	Iterative thematic analysis
Huntink E, Wensing M, Timmers IM, Lieshout JV	Process evaluation of a tailored intervention programme of cardiovascular risk management in general practices	2016	Y	Y	N	Evaluation of effectiveness	N	Mixed methods- quantitative measures (survey results and scoring of recorded motivational interviews) and qualitative data of interviews conducted.	Quantitative analysis of the scores, and qualitative analysis using the pre-specified tailored intervention for chronic diseases
Presseau J, Grimshaw J, Tetroe JM, Eccles MP, Francis JJ, Godin G, Graham ID, Hux JE, Johnston M, Legare F, Lemyre L, Robinson N, Zwarenstein M.	A theory-based process evaluation alongside a randomised controlled trial of printed educational messages to increase primary care physician's prescription of thiazide diuretics for hypertension	2016	Y	Y	Y	Evaluation of effectiveness	Y (Theory of planned behaviour)	Pre, post postal questionnaire to a random sub-sample of family physicians in each trial arm	Analysis of co-variance to test for group differences using a 2X3 factorial design and content analysis of the open ended question about perceived barriers to thiazide prescription. Tested whether baseline measures of TPB constructs predicted self-reported thiazide prescribing

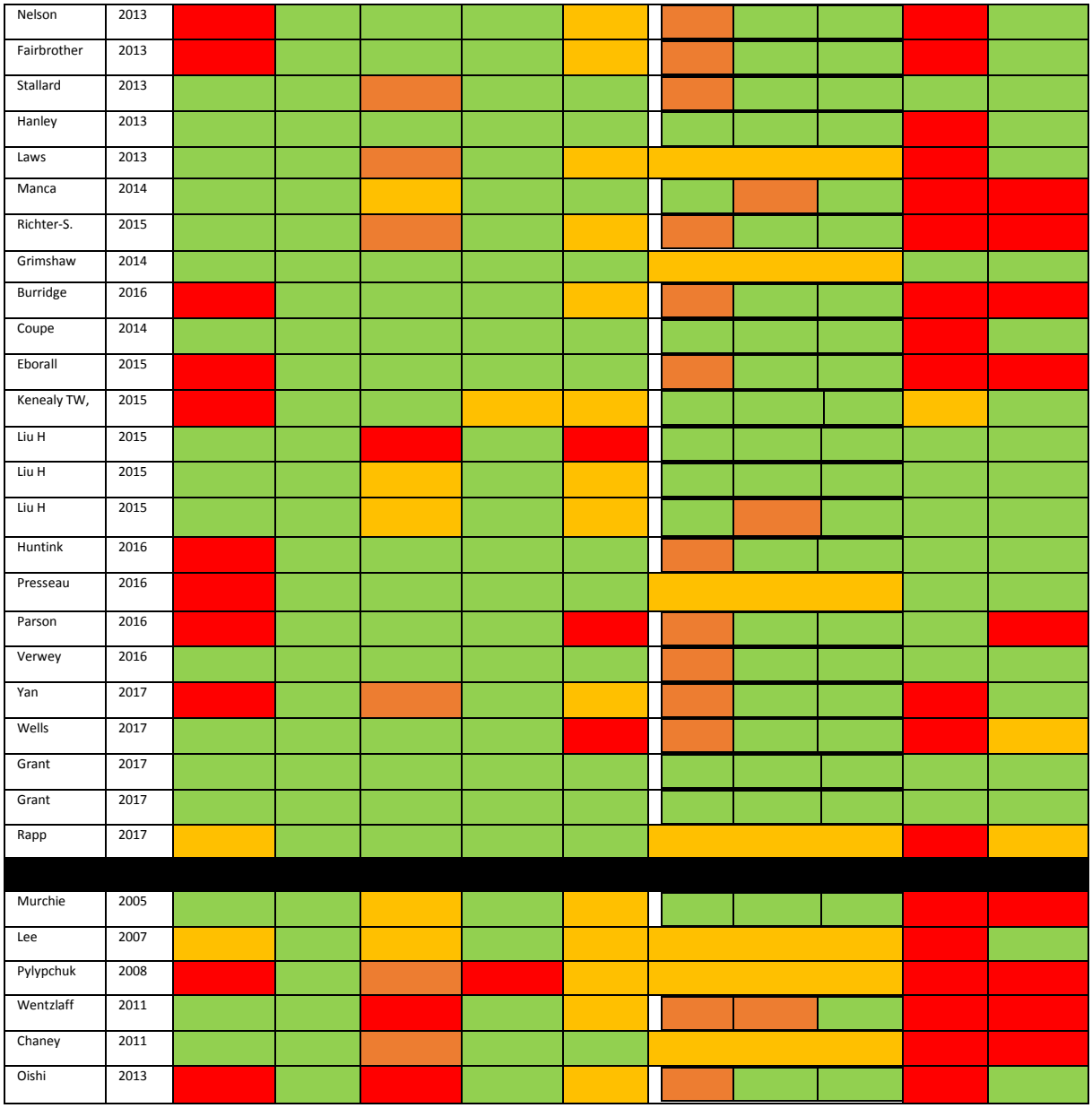
Verwey R, van der Weegen S, Spreeuwenberg M, Tange H, van der Weijden T, de Witte L	Process evaluation of physical activity counselling with and without the use of mobile technology: A mixed methods study	2016	Y	Y	Y	Evaluation of effectiveness	N	Mixed methods (using semi-structured interviews, questionnaires to patients and use of IT tool through system logging)	Descriptive analysis and triangulation of findings.
Parsons, J. A. Yu, C. H. Y. Baker, N. A. Mamdani, M. M. Bhattacharyya, O. Zwarenstein, M. Shah, B. R.	Practice doesn't always make perfect: A qualitative study explaining why a trial of an educational toolkit did not improve quality of care	2016	Y	Y	N	Effectiveness	N	In-depth semi-structured telephone interviews with physicians who received the tool kit. And written commentary from reflective feedback forms collected from 10% of practices randomised and approached) who participated in chart audit as part of the clinical data study.	Qualitative description which entails an inductively- derived thematic analysis, and triangulated with the written comments from the questionnaires
Yan LD, Chirwa C, Chi BH, Bosomprah S, Sindano N, Mwanza M, Musatwe D, Mulenga M, Chilengi R.	Hypertension management in rural primary care facilities in Zambia: a mixed methods study	2017	N	Y	Y	Evaluation of effectiveness	N	Data on novel retrospectively generated process and outcome indicators for hypertension management, informed by those from Western countries, but adapted to the Zambian primary care clinics. Extracted using EMR. Semi-structured in-depth interviews with health care providers and a representative from the central medication distribution agency .	We used an explanatory sequential design by conducting a quantitative analysis of outcome measures , which was then explained through a qualitative follow up component.
Wells S, Rafter N, Kenealy T, Herd, Geoff, Eggleton K, Lightfoot R, Arcus K, Wadham A, Jiang Y, Bullen C.	The impact of a point of care testing device on CVD risk assessment completion in New Zealand primary-care practice: A cluster randomised controlled trial and qualitative investigation	2017	N	Y	N	Evaluation of effectiveness	N	Qualitative data on practice processes for CVD risk assessment and feasibility of POC testing were collected at the end of the study by interviews and questionnaire.	Braun and Clarke's approach to thematic analysis was used to generate initial codes, collate codes into potential themes and refine the identified themes and categories into a coherent pattern.

Grant A, Dreischulte T, Guthrie B	Process evaluation of the data-driven quality improvement in primary care (DQIP) trial: active and less active ingredients of a multi-component complex intervention to reduce high-risk primary care prescribing	2017	Y	Y	Y	Evaluation of effectiveness	Y (NPT)	Data generation was by in-depth interview with key staff exploring participant's perceptions of the intervention components.	Analysis was iterative using the framework technique and drawing on normalisation process theory.
Grant A, Dreischulte T, Guthrie B	Process evaluation of the Data-driven Quality Improvement in Primary Care (DQIP) trial: case study evaluation of adoption and maintenance of a complex intervention to reduce high-risk primary care prescribing	2017	Y	Y	Y	Evaluation of effectiveness	Y (NPT)	Mixed-methods parallel process evaluation of a cluster trial, reporting the comparative case study of purposively selected practices.	Use of interviews at two time points and the use of quantitative data to explore whether the qualitative judgements made about implementation were consistent with observed data on reach, delivery, maintenance and effectiveness. Use of NPT alongside the cross and within-case comparisons.
Rapp AM, Chavira DA, Sugar CA, Asarnow JR	Integrated Primary Medical-Behavioral Health Care for Adolescent and Young Adult Depression: Predictors of Service Use in Youth Partners in Care Trial	2017	N	Y	Y	Evaluation of Effectiveness	Y (Behavioural Model of Health Service Use)	Secondary Analysis of data from the trial to investigator the predisposing factors (demographics), enabling factors (e.g. perceived stigma of depression) , need factors and outcomes (receipt of mental health services)	Statistical analyses, and plots of significant interactions. Investigating possible interactions between variables, and individual logistic regression for the possible independent variables, with mental health treatment as outcome. Algorithm to finally identify the subset of variables that best predicted mental health service use.

Synthesis		**2000 - 2017**	**16 labelled as process evaluations (13 after 2008, and 5 after 2015)**		**22 Y, and 16 N**	**44 studies**	**13 studies (7 Classic theories, 3 evaluation frameworks, 3 implementation theories)**	**2000-2004: 6 studies documented specific processes of care as part of the process evaluation, and were often reported as part of the main trial. The acceptability of an intervention was often investigated using surveys/questionnaires. 2005 onwards- 9 studies used only interviews to explore implementation and acceptability, 15 studies used interviews triangulated with other sources of data (e.g. chart audit). 5 studies used questionnaires or surveys. 1 study used secondary analysis of trial data.**	**Descriptive statistics were used for the quantitative data. Thematic, constant comparison and framework analysis for the qualitative data. The studies that used mixed methods, used the quantitative data to indicate level of implementation, reach and the dose. This was use to triangulate the qualitative findings on implementation and intervention acceptability.**
Oishi SM, Shoai R, Katon W, Callahan C, Unutzer J, Arean P, et al	Impacting late life depression: Integrating a depression intervention into primary care	2003	N	Y	Y	Post evaluation Implementation	N	Focus group discussions and semi structured interviews	Thematic analysis
Dietrich AJ, Oxman TE, Williams JW, Kroenke K, Schulberg HC, Bruce M, et al	Going to scale: Re-engineering systems for primary care treatment of depression	2004	N	Y	Y	Post-evaluation	Yes- Diffusion of Innovations theory	Documentary analysis of care manager logs, health care organisation's administrative data to access cooperation in implementation and changes in the processes of care in each practice. Clinical surveys	Descriptive
Lee PW, Dietrich AJ, Oxman TE, Williams Jr JW, Barry SL	Sustainable impact of a primary care depression intervention	2007	N	Y	Y	Post evaluation Implementation	N	Interviews	Descriptive evaluation
Pylypchuk G, Vincent L, Wentworth J, Kiss A, Perkins N, Hartman S, et al	Diabetes risk evaluation and microalbuminuria (DREAM) studies: Ten years of participatory research with a First Nation's home and community model for type 2 diabetes care in northern Saskatchewan	2008	N	N	N	Evaluation of effectiveness, and post intervention	N	documentary analysis, Population survey, pilot and randomised trial	documentary analysis

Wentzlaff DM, Carter BL, Ardery G, Franciscus CL, Doucette WR, Chrischilles EA, et al	Sustained Blood Pressure Control Following Discontinuation of a Pharmacist Intervention	2011	N	Y	Y	Post-evaluation implementation	N	routine monitoring data	Intention to treat analysis
Chaney EF, Rubenstein LV, Liu CF, Yano EM, Bolkan C, Lee M, et al	Implementing collaborative care for depression treatment in primary care: A cluster randomized evaluation of a quality improvement practice redesign	2011	N	Y	N	post evaluation Implementation	N	The study intervention is EBQI as applied to collaborative care implementation. The study uses a cluster randomized design as a formative evaluation tool to test and improve the effectiveness of the redesign process. Data sources include survey and administrative data sources, and the care manager registry-based measures (e.g. patients routinely referred outside of the trial).	The context evaluation is descriptive and uses subgroup analysis. (e.g. clinician adoption status)
Synthesis		**2003 - 2015**	**0 as process evaluations**	**5 Y, 1 N**	**4Y,**	**7 studies, (note the cross over with quality improvement studies)**	**NPT for 1**	**3 used interviews, 2 used documentary analysis, and 1 used the administrative data and registry data**	**Descriptive statistics, subgroup analysis and thematic analysis.**

Author	Year	Planning (Y/N/ NA)	Design and Conduct (Y/N/NA)							Reporting (Y/N/NA)	
		Team description	Purpose clearly stated	Interven-tion and causal assumptions	Justify choice of timing and methods.	Report if analysis was done blind to trial outcomes / or post hoc	COREQ for qual studies. (31 items under Domain 1: research team and reflexivity, Domain 2: study design, Domain 3: analysis and reporting)			Clearly labelled	Linked to a full report of evaluation components / protocol paper.
Tai SS et al.	1999										
Weiss	2004										
Jackie Sturt,	2006										
Byrne	2006										
Chew-Graham	2007										
Clark	2007										
Lovell	2008										
Chatterjee	2008										
Van Steenkiste	2008										
Chung	2010										
Gask L,	2010										
Casey	2011										
Chalder	2012										
Bennett	2013										
Carlise	2013										
Van der Weegen	2013										
Fairbrother	2013										
Ramadas A,	2015										
Naik	2015										
Vest	2015										
Hetlevik	2000										
Thornett	2002										
Ilag	2003										
Lobo	2003										
Oishi	2003										
Pearl	2003										
Smith S	2004										
Gask L,	2005										
Gask L	2006										
Heaven, B.	2006										
Fakiri	2008										
Slade	2008										
Van Den Bemt	2009										
Smith	2011										
Passey	2012										
Genichen	2012										
Walters JAE	2012										
Ratanawongsa	2012										
Lakerveld J	2012										
Paul	2013										



Notes on quality assessment: Quality was assessed using a pre-specified tool, based on the MRC PE guidance. 1) Planning: a) Degree of separation between outcome and process evaluation teams described. 2) Design and conduct: a) purpose clearly stated, b) Intervention clearly described, causal assumptions clarified. c) Justify choice of timing and methods. d) If applicable- Transparently whether the report of the process data are analysed blind to trial outcomes/ or post hoc. e) COREQ for qual studies. (31 items under Domain 1: research team and reflexivity, Domain 2: study design, Domain 3: analysis and reporting). 3) Reporting: a) Clearly labelled as PE. b) Published a full report of evaluation components or a protocol paper. These criteria were assessed by HL and MN and classified under yes (green), no (red), uncertain/unclear (orange), and not applicable (yellow). Additionally, studies with a qualitative study component was evaluated against the consolidated criteria for qualitative research checklist (COREQ) which has 31 individual items separated into 3 domains.(17) If more than one item was obviously or specifically mentioned for each of the three domains it was classified as yes (green), no (red) when it was obviously not present, and uncertain (orange).

Appendix 4- Illustrative examples for the synthesised findings

Implementation factors - illustrative examples
Mechanisms: Perceived Fit of the Intervention In a trial to increase the referral for diabetic retinopathy screening, physicians described that patient's lack of belief in screening, and access to specialists as key barriers to screening. Thus, the intervention of printed educational materials did not alter their referral behaviour. (Grimshaw)
Implementation: Roles and Responsibilities In study to integrate the role of a Depression Clinical Specialist with the primary care provider and the consulting psychiatrist- the process evaluation found "*DCSs spoke of the importance of a clear role within the health care team. The model envisions the DCS as a care manager who works in partnership with the patient and the PCP. DCSs pointed to the importance of not being perceived as taking over the patient's depression care. Instead, the DCS reports to the PCP whether a patient is experiencing side effects, for example, and discusses alternate treatment options, but it is the PCP who decides when to change dosage or medication type. DCSs noted the need to be flexible in working with different physician and system styles*." (Oishi)
Context: Health system structures From a process evaluation of the 'recruitment' of health care organisations in America to scale up an effective model of depression care- authors stated that: "*Additional momentum comes from the US Preventive Services Task Force (USPSTF) through its endorsement of depression screening in adults "in clinical practices that have systems in place to assure accurate diagnosis, effective treatment, and careful follow up." They state, "Benefits from screening are unlikely to be realized unless such systems are functioning well*." (Dietrich) The underlying capacity and knowledge of the implementers are described as conducive to their model of pro-active care for chronic depression using practice nurses: "*Practice nurses in the UK are employed by GPs to work in their practices as part of the primary healthcare team. They are at minimum Registered Nurses (RNs), usually with substantial nursing experience and some may have a specialist qualification in practice nursing, although it is not a formal requirement. A minority are also Registered Mental Health Nurses (RMHN), but most will have only received some theoretical background and short clinical placements in mental health settings during their RN course*." (Bennett)
Collaborative Approach "*The CBPR model guided development of a research/clinical partnership based on a facilitation team consisting of 'external facilitators' (research team), 'internal facilitators' (primary care leadership) and a 'clinical advisory committee' drawn from the primary care community. Qualitative themes focused on: how the intervention components ('evidence') aligned with local clinical cultures, barriers and facilitators to acceptance and adoption of the intervention processes within the context of clinical workflows and identified 'facilitators' of intervention uptake and sustainability*." (Naik) "*We found that using a Community-Partnered Participatory Research approach in the design phase (Vision) led to many changes in study design to improve the fit of the study with community priorities (e.g. Aligning community boundaries with existing county service planning areas), as well as enrich the study's potential scientific contributions (e.g., through expanded outcomes of community and policy relevance)*." (Chung)

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5,6 (published protocol
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6 (published protocol)
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5 (in protocol)
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6,25
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6,23-25
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1, and Appendix
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 2, and appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Table 1, Appendix
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	7-11
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	6,7 Table, Appendix
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	6, and table 1
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12-15
FUNDING			

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	16

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

APPENDIX 6

Appendix Overview

This appendix comprises of the supplementary files of the publications in Chapter 3.

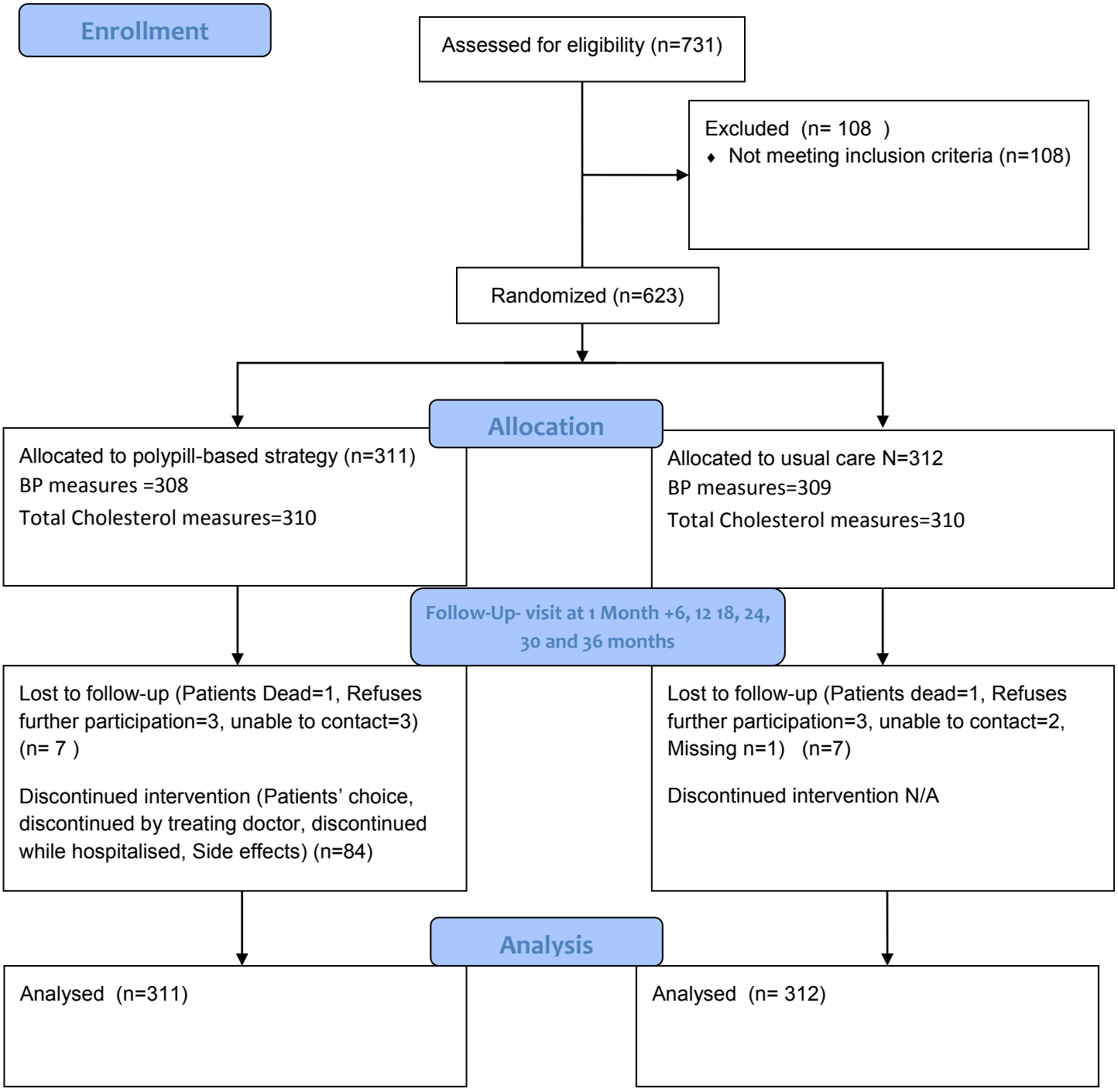
Supplementary files:

Relevant to the three publications include-

1) CONSORT Flow Diagram
2) CONSORT checklist of the completed RCT
3) Coding Framework
4) Interview Guides
5) Table of participant characteristics
6) Illustrative quotes

CONSORT
TRANSPARENT REPORTING of TRIALS

APPENDIX A: CONSORT 2010 Flow Diagram for Kanyini GAP



CONSORT 2010 checklist of information to include when reporting a randomised trial*

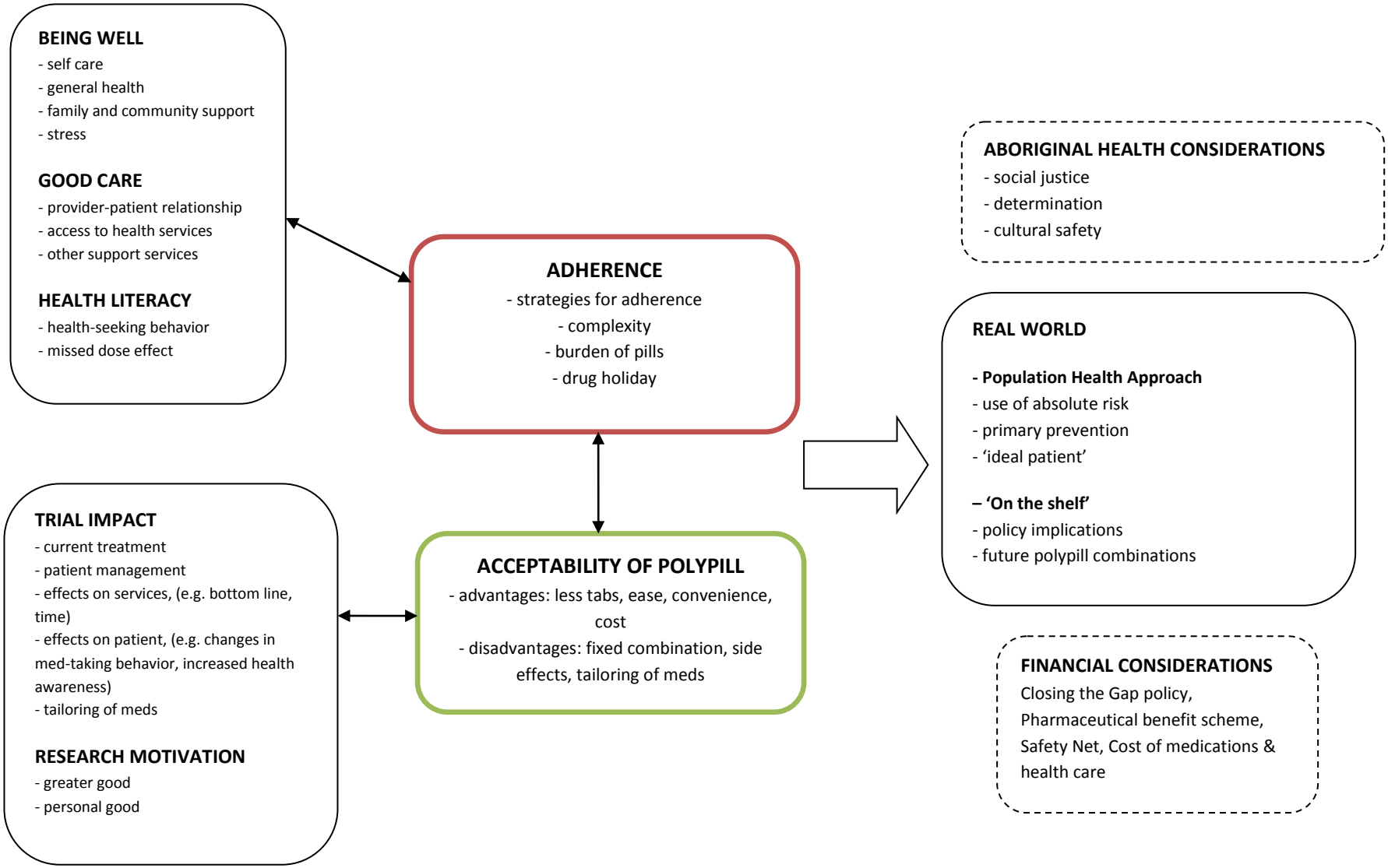
Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	2
	2b	Specific objectives or hypotheses	2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	2
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	No changes made
Participants	4a	Eligibility criteria for participants	2
	4b	Settings and locations where the data were collected	3
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	2-3
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	3
	6b	Any changes to trial outcomes after the trial commenced, with reasons	3
Sample size	7a	How sample size was determined	3
	7b	When applicable, explanation of any interim analyses and stopping guidelines	N/A
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	2
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	2
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	2
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	2

Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	N/A
	11b	If relevant, description of the similarity of interventions	2
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	3
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	3
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	4
	13b	For each group, losses and exclusions after randomisation, together with reasons	4
Recruitment	14a	Dates defining the periods of recruitment and follow-up	3-4
	14b	Why the trial ended or was stopped	4
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	5
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	4
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	4-5
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	N/A
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	5
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	5
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	6
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	9
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	7,9
Other information			
Registration	23	Registration number and name of trial registry	9
Protocol	24	Where the full trial protocol can be accessed, if available	In Ref: 18
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	9

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Additional File 3: Coding Framework

PEAK Coding Framework



SUPPLEMENTAL MATERIAL

Supplementary methods

The Kanyini GAP Study- health professionals interview guide (GP's)

Initial Broad Descriptive Questions	**Probing Questions (These are a guide only. It is not expected that you ask all these questions)**
OVERALL VIEWS ON POLYPILL IN CVD MANAGEMENT *To establish pre and post trial views of a general polypill strategy for CVD, as well as the specific KGAP polypill*	
What is your overall view of a polypill strategy in CVD management?	– Why did you become involved in this study? i.e. motivation for taking part o Experience in general being involved with the Kanyini GAP Polypill strategy/study? – What experience have you had with prescribing other fixed-dose combination or multidrug component medications in cardiovascular disease? What about other therapeutic areas? – Could you describe what you think are the negative/positive aspects of using a polypill strategy to manage CVD? o How does this compare to other therapeutic areas? o Have your views about prescribing a polypill changed since being involved in this study? Can you please describe? What did you think of the components that were in this polypill (Aspirin, BP lowering, statin)? – What would be your ideal combination pill?
OVERALL VIEWS ON PATIENT ADHERENCE TO CARDIOVASCULAR MEDICATIONS – *To understand conceptualisation and significance of medication adherence from prescriber perspective and what role they, other health care providers, the health system and policies play*	

What are your views on patient adherence with cardiovascular disease medications?	– How important do you think adherence to medications is with respect to cardiovascular disease outcomes?
	  o How does this compare to other therapeutic areas?
	– Thinking in terms of a few patients who you know best who are concomitantly prescribed anti-platelets, BP lowering and lipid lowering medications , either as fixed combination pills or not, how do you think these patients perceive the function of their cardiovascular medications?
	– Do you know if your patients take their medications?
	– In your experience, what do you think are the barriers/facilitators to patients adhering with cardiovascular medications? (e.g. medicine-, patient- health system/policy-, disease-related, cultural)
	  o What role does a patient's cultural background have?
	  o What role does current policy have?
	– What role do you think GP's play in supporting patients to take their medications?
	  o Is the polypill helpful in doing this?
	  o Does it help you be more effective in managing CV risk?
	  o What about other staff?

PROVIDER SATISFACTION/ PROBLEMS WITH THE POLYPILL STRATEGY USED IN KANYINI GAP

– *To illustrate the experience with prescribing the polypill, and to compare and contrast this with experience with other cardiovascular medications.* ***Note:*** *There is a particular interest in whether there is a difference in practice for polypill group at drug initiation.*
– *To understand if there was any difference in usual care management throughout the trial*

Could you describe what it has been like to look after your patients in the polypill group?	– What were the major advantages of prescribing the polypill used in Kanyini Gap? – What were the major disadvantages of prescribing the polypill used in Kanyini Gap? – What was your experience with commencing participants on the polypill? o Did you change/alter treatment prior to commencing on trial? – Did you change or alter treatment prior to commencing patients on trial? o How did this compare with your previous experience with starting cardiovascular medications? – How did you find tailoring your patients' medicines when they were on the polypill? – How do you decide if the ingredients in the polypill are or are not enough for your patients? – How do you know what needs to be increased, e.g. through targets, etc.? – Were there any times when you were not happy with the polypill and had to change to other medicines? If so, please describe. – Were there any problems prescribing additional treatments? – How did you find assessing response to treatment for patients on the polypill? – Were there any terminations of patients due to unawareness of trial or new treatment, etc.? – In your opinion, do you think being on the trial has influenced the behaviour of patients? (i.e. re RCTs – people may be more compliant, tend to follow protocols, etc.)
Could you describe what it has been like to look after your patients in the usual care group?	– What was your experience in providing usual care to the participants not taking the polypill throughout the trial? – Did you feel that you changed your management in any way for this group during the course of the study? If so, how?
PATIENT SATISFACTION/ PROBLEMS WITH THE POLYPILL STRATEGY *To illustrate feedback given to the prescribers from patients about the polypill* *To understand if the usual care patients reported any difference in management throughout the trial*	

What have been your patients' impressions/thoughts about being in the polypill group?	– Did you receive any feedback from your patients about their experience in the trial? If so, please describe. – Do you feel that your patients were satisfied with the care they received whilst in the polypill group? – What were the major advantages of taking the polypill from the patient perspective? – What were the major disadvantages of taking the polypill from the patient perspective? – How well tolerated was the polypill in general? o Did any of your patients experience any side-effect issues with the polypill? If so how did you manage these issues? – Did your patients report any problems accessing the medicines? o Any problems with filling the script from the pharmacy (cost, confusion etc)? o Any problems with the packaging or instructions? – Did your patients report any barriers to actually taking the medicines? If so, please describe – Is there anything else which could be done to make the treatment/polypill more effective?
– What have been your patients' impressions/thoughts about being in the usual care group?	– Do you feel that your patients were satisfied with the care they received whilst in the usual care group?

GENERAL IMPRESSIONS OF THE STUDY

To understand how the trial integrated into everyday practice

What has it been like for you to be involved in the GAP study?	– What was the impact on you and your health service in choosing to be a part of this trial?
	  ○ Did you experience any problems with the general administration of this trial? If so please explain.
	  ○ Were there any benefits to you or your practice as a result of participating in this trial? If so please explain.
	– Would you be interested in participating in future clinical trials as a result of your experience with this study? If no, why not?

SUITABILITY OF THE TRIAL DESIGN *To understand if other trial related variables may have impacted on outcomes*	

What are your thoughts about the design of the GAP polypill study?	– What was your experience with the screening process?
	  ○ Were you satisfied with the process of gathering baseline information about study participants?
	  ○ Were the eligibility criteria satisfactory?
	  ○ What did you think of using absolute risk based entry criteria?
	– Were there any difficulties experienced in communicating study information to participants?
	– How did you find the randomisation visit?
	– How did you find the follow-up and monitoring of your patients?
	– Did you experience any problems sharing/ coordinating care with providers who were not involved in the study?

TRANSLATION INTO CLINICAL PRACTICE AND POLICY *To understand how the trial results may or may not translate into practice.*	
If found to be beneficial, what would you see as the role of the polypill in everyday practice?	– What are your views on the use of the polypill in the study setting compared to in everyday practice? – How do you think a cardiovascular polypill will impact on your day-today professional practice? – If the polypill is found to be beneficial, what would be your advice to government on implementing its use in the general population?
CONCLUDING QUESTIONS	

– We will also be conducting some interviews with patients involved in the trial to understand their experiences. In your opinion, what areas to you think we should explore? – Are there any aspects about medication adherence that you would specifically like explored?
– Is there anything else you would like to say that we have not talked about in this interview? i.e. about the polypill or the study

The Kanyini GAP Study- health professionals interview guide (pharmacist)

Initial Broad Descriptive Questions	**Probing Questions (These are a guide only. It is not expected that you ask all these questions)** **Purpose of process evaluation is to establish overall views on a polypill based approach to CV risk management.**
OVERALL VIEWS ON POLYPILL IN CVD MANAGEMENT *To establish pre and post trial views of a general polypill strategy for CVD, as well as the specific KGAP polypill*	
What is your overall view of a polypill strategy in CVD management?	– Could you describe what you think are the negative/positive aspects of using a polypill strategy to manage CVD? o How does this compare to other therapeutic areas? o Have your views about prescribing a polypill changed since being involved in this study? Can you please describe? What did you think of the components that were in this polypill (Aspirin, BP lowering, statin)? – What would be your ideal combination pill?
OVERALL VIEWS ON PATIENT ADHERENCE TO CARDIOVASCULAR MEDICATIONS *To understand conceptualisation and significance of medication adherence from providers perspective and what role they, other health care providers, the health system and policies play*	

What are your views on patient adherence with cardiovascular disease medications?	– How important do you think adherence to medications is with respect to cardiovascular disease outcomes? ○ How does this compare to other therapeutic areas? – Thinking in terms of a few patients who you know best who are prescribed anti-platelets, BP lowering and lipid lowering medications in combination, how do you think these patients perceive the function of their cardiovascular medications? – In your experience, what do you think are the barriers/facilitators to patients adhering with cardiovascular medications? (eg medicine-, patient- health system/policy-, disease-related) – What role do you think you play in supporting patients to take their medications? – How do you think the polypill strategy compares to other patient adherence aids, i.e. Webster pack?

PROVIDER SATISFACTION/ PROBLEMS WITH THE POLYPILL STRATEGY USED IN KANYINI GAP – *To illustrate the experience with supplying the polypill, and to compare and contrast this with experience with other cardiovascular medications. Note: There is a particular interest in whether there is a difference in practice for polypill group at drug initiation.* – *To understand if there was any difference in usual care management throughout the trial*	
Could you describe what it has been like to look after your patients in the polypill group? **(drawing on your experiences)**	– What were the major advantages of supplying the polypill used in Kanyini Gap? – What were the major disadvantages of supplying the polypill used in Kanyini Gap? – What was your experience with participants commencing on the polypill? o Do you have any examples? o How did this compare with your previous experience with starting cardiovascular medications? o Where there any concerns by patients in starting the polypill, i.e. concern about efficacy, change of routine, etc? – How did you find counselling your patients about the polypill? – Did you think that you changed your management in any way for the participants who were taking the polypill? If so, how? – Were there any problems when additional treatments for cardiovascular disease were prescribed? i.e. need to tailor medications
PATIENT SATISFACTION/ PROBLEMS WITH THE POLYPILL STRATEGY *To illustrate feedback given to the providers from patients about the polypill* *To understand if the usual care patients reported any difference in management throughout the trial*	

What have been your patients' impressions/thoughts about being in the polypill group?	– Did you receive any feedback from your patients about their experience in the trial? If so, please describe.
	– Do you feel that your patients were satisfied with the care they received whilst in the polypill group?
	– What were the major advantages of taking the polypill from the patient perspective?
	– What were the major disadvantages of taking the polypill from the patient perspective?
	– How well tolerated was the polypill in general?
	  o Did any of your patients experience any side-effect issues with the polypill? If so how did you manage these issues?
	– Did your patients report any problems accessing the medicines?
	  o Any problems with filling the script from the pharmacy (**cost**, PBS safety net, confusion etc)?
	  o Any problems with the packaging or instructions?
	– Did your patients report any barriers to actually taking the medicines? If so, please describe

GENERAL IMPRESSIONS OF THE STUDY *To understand how the trial integrated into everyday practice*	
What has it been like for you to be involved in the GAP study?	– What was the impact on you and your health service in choosing to be a part of this trial? o Did you experience any problems with the general administration of this trial? If so please explain. o Were there any benefits to you or your pharmacy as a result of participating in this trial? If so please explain. – Would you be interested in participating in future clinical trials as a result of your experience with this study?
SUITABILITY OF THE TRIAL DESIGN *To understand if other trial related variables may have impacted on outcomes*	
What are your thoughts about the design of the GAP polypill study?	- Were there any difficulties experienced in communicating study information to participants? - Did you encounter any difficulties when the polypill patients were new to your pharmacy? - Did you experience any problems sharing/ coordinating care with providers who were not involved in the study?
TRANSLATION INTO CLINICAL PRACTICE AND POLICY *To understand how the trial results may or may not translate into practice.*	

If found to be beneficial, do you think the polypill could be used in everyday practice? (Last is the magic wand Q...)	– What are your views on the use of the polypill in the study setting compared to in everyday practice? – How do you think a cardiovascular polypill will impact on your day-today professional practice? – If the polypill is found to be beneficial, what would be your advice to government on implementing its use in the general population?
CONCLUDING QUESTIONS	
– We will also be conducting some interviews with patients involved in the trial to understand their experiences. In your opinion, what areas to you think we should explore? – Are there any aspects about medication adherence that you would specifically like explored?	
– Is there anything else you would like to say that we have not talked about in this interview?	

The Kanyini GAP Study- Patient interview guide

Purpose of the interview: ***Capture what it is like for people to manage CVD and how to manage their tablets, and how the burden of taking tablets in daily life could be made easier/better/worse. How a polypill might influence this (or not); or how the trial might influence this (or not).***

Area of Interest	Initial Broad Descriptive Questions	Possible Probing Questions **(These are a guide only. Depending on what the patient tells you, you do not have to ask all these questions or use the words exactly as written.)**

Health care experience	Can you tell me about your health care since you've been on the trial?	○ How is your health in general?
		○ What are some of the good/bad things about your health care?
		○ Are there differences or similarities with your health care since you've been part of this study compared to usual care?
		  ○ And compared to other illnesses?
		○ What type of support do you get from family, community or social groups with looking after your health?
		  ○ What kind of roles/responsibilities do you have in your family?

Satisfaction/ problems with the polypill strategy	What are your thoughts about your current treatment for your heart?	○ Do you know the 4 medications in the polypill and what they're for? (Aspirin, BP lowering x2, statin (lipid lowering/cholesterol, etc.) ○ How do you find the tablets you are taking? ○ What do you think are the major advantages of your current treatment (polypill or usual medications)? ○ What do you think are the major disadvantages of your current treatment (polypill or usual medications)? ▪ What things would worry you about changing your usual medications? ○ Would you be happy to continue taking your current treatment (polypill or usual medications)? ○ What might happen that would make you change from taking the polypill or your usual meds? ○ What problems have you experienced with your current treatment (polypill or usual medications)? (i.e. side effects, cost issues) ○ How can your doctor improve your current treatment? ○ What sort of support do you get in managing your blood pressure, cholesterol, etc?

Medication taking behaviour	Many people find it difficult to take their medications everyday. Has there been a time when you haven't been able to take your medications every day?
	OR
	What suggestions would you give to people, who do struggle with taking medications, i.e. what has worked for you?
		- How many pills do you take a day?
		- How easy do you find taking your medications?
		  o What are the things that help you to take your medications? (i.e. family, Webster pack, other memory aids, time of day, etc.)
		  o How would you know if you've not taken your medication?
		- When do you find it more difficult to take medications?
		  o What are the things that might make you stop taking a medication?
		- What other things might change the way you take your medications?
		- Can you describe any time or situation when you didn't want to take your medications?
		  o What things were influencing your decision?
		- Who would you speak to if you were having trouble with your medications?
		  o When have you had to do this?
		- Which of your medications do you think are the most important to you and why?
		- How do you usually get your supply of medications?
		- Have there been times when you share medications with family members?
		- Have there been times when you halve tablets, or just take them on alternate days for example?
		  o What has been the main reason/s for this?

	What has your experience been with taking medications throughout this study?	o How has your experience with taking your medication/s in this study been different / similar to the way you would usually take medications? o In what ways has this study changed the way you take your medications? o What things have made it easier or harder for you to take your medications while being involved in this study? o Has the cost of medications been an issue for you? o Have other costs, e.g. cost of attending GP, travel to the health service, other specialist services, etc. been an issue?

Translation to current practice	What has helped/prevented you from taking your medications throughout this study that might be different to everyday life? (*e.g. without being monitored as much as during the trial*)	• Now that the study is over, what things might change the way you take your medications (polypill or usual medications)?
		  ○ Do you think you would be able to take your current treatment in the same way that you have throughout the study?
		• What other things would help you take your medications?
		  ○ What type of support from nurses/health workers/AMS might assist you in taking your medications?
		  ○ What can the government/doctors/pharmacists do to help?

General views about the trial	What are your thoughts about the Kanyini Gap study in general?	• How have you found being involved in the study?
		  ○ What things did/didn't you like about being involved?
		• Tell me how you think the study worked, and what it was hoping to achieve?
		• What were the things that made you want to participate in the study initially?
		  ○ What were the benefits to you of participating?
		• What concerns did you have about participating in this study?
		  ○ Were there any things that may have stopped you from participating initially?
		  ○ What were the risks of participating in the study?
		• Once you were enrolled, what would have changed your mind about being in the study?
		  ○ Did you feel that you could withdraw at any time?
		• Did you know who to contact if you had any concerns about the trial?
		• What were your thoughts about your privacy throughout this study?

Concluding questions		• Are there things which we can do better to improve the study or the running of the trial? • Is there something else that you would like to say, that we have not talked about in this interview?

Supplementary Tables

Table 1: Patient characteristics

Characteristics	POLYPILL	USUAL CARE	TOTAL
Sample size	22	25	47
Age, years (SD)*	67.1 (8.4)	63.9 (10.3)	65.4 (9.5)
Gender (Female)	10 (46%)	12 (48%)	22 (47%)
Aboriginal/ Torres Strait Islander	6 (27%)	13 (52%)	19 (40%)
Primary prevention	12 (55%)	9 (36%)	21 (45%)
Secondary prevention	10 (46%)	16 (64%)	26 (55%)
Drug treatment (at baseline)			

High-risk primary prevention			
Yes to all 3 (BP* lowering, aspirin and statin)	7 (18%)	6 (24%)	13 (28%)
No to all 3	5 (23%)	3 (12%)	8 (17%)
Secondary prevention			
Yes to all 3 (BP* lowering, aspirin and statin)	7 (18%)	15 (60%)	22 (47%)
No to all 3	3 (14%)	1 (4%)	4 (9%)
Health service			
Indigenous health services (Aboriginal community controlled and government-run)	8 (36%)	13 (52%)	21 (45%)
General Practice	14 (64%)	12 (48%)	26 (55%)
Accessibility/Remoteness Index of Australia (ARIA) †			
ARIA 1	15 (68%)	15 (68%)	30 (64%)

ARIA 2-3	7 (32%)	10 (45%)	17 (36%)

* SD Standards deviation BP Blood pressure † ARIA 1- metropolitan and inner regional ARIA 2-3- outer regional and remote

Table 2: Provider characteristics

Characteristics	**GP**[*]	**Pharmacist**	**AHW/Nurse**[*]
Sample Size	25	13	9
Age groups [†2]			
20-39 (%providers)	5 (11%)	5 (11%)	6 (13%)
40-69	18 (38%)	7 (15%)	3 (6%)
Male Gender (%providers)	15 (32%)	10 (21%)	4 (9%)
Years practicing (median, range)	25 (2 to 35)	13 (2.5 to 32)	3 (0.5 to 17)
Years at site (median, range)	11.5 (0 to 30)	6 (0 to 12)	1 (1.2 to 17)
Formal cross-cultural training (%providers)	18 (38%)	3 (6%)	n/a
Adherence support services offered	n/a	10	n/a
Health Service			

Indigenous Health Service (%providers)	16 (34%)	n/a	9 (19%)
General Practice (%providers)	10 (21%)	n/a	n/a
Accessibility/Remoteness Index of Australia (ARIA)			
ARIA 1 (%providers)	16 (34%)	9 (19%)	6 (13%)
ARIA 2-3 (%providers)	10 (21%)	4 (9%)	3 (6%)

* GP General Practitioner AHW Aboriginal health Worker SD standard deviation † Missing data n=3

Table 3

Major Codes and their descriptions
<u>Adherence</u> This includes references to, comments from providers and patients on all aspects of patient adherence to medications such as strategies of using a routine, having the medications in a dose administration pack. This also includes observation of risks of non-adherence, (i.e. death, effects on family/community.) The burden of the number of medications and the complexity of medication regimes contributed to intentional non-adherence at times. **<u>Being well</u>** 'Being well' is described through comments, attitudes, perceptions of patients' own general health, i.e. physical and emotional well-being, self-care and lifestyle risk factors, other health issues, and protective/ supportive mechanisms in place such as family and community support. **<u>Good care</u>** This covers patient satisfaction with health care provision, such as accessibility to health care and other support services, and the provider-patient relationship. It also includes the collaboration between providers, pharmacists and IHSs. **<u>Health literacy</u>**

Health literacy includes patients' knowledge of the importance of adherence to medications, including how, when, why to take medications and their efficacy, etc. It also includes analysis of data around health seeking behaviour, i.e. patients' motivation to find out about their condition and to seek treatment, and also the 'missed dose effect'.

Acceptability of the Polypill

This code included descriptions of what were the advantages and disadvantages of the polypill strategy. Many of the patients liked the advantages of the ease and convenience because of the reduced number of tablets, single dosing, and cost savings was also listed as positive. Other advantages from the providers' point of view included being more aware of the participants' absolute risk and starting the patients on the three types of medications instead of taking the time to titrate to all medications. However, being unable to titrate and tailor the medications was listed as disadvantages. . Most of the providers suggested having other possible polypill combinations.

'Real World'

This code contained views from both patients and providers in regards to what they hoped to see after the trial. The responses varied from the polypill being just another 'combination' medication out there, to potentially being disappointed if it was not on the shelf, and that the polypill would be ideal only in certain circumstances, e.g. for primary prevention. Many of the providers and patients from the IHSs expressed the understanding and support for the polypill for the Aboriginal population given the higher incidence, possible limited literacy and difficulty in taking many medications.

Financial Considerations

The majority of patients reported knowing they have to spend the money on medications and health care, and would do so to improve their health. A number of policies are in place to reduce the cost of medications and health care for all Australians and these were mentioned often by the patients and pharmacists.

Aboriginal Health Considerations

This code contained views from patients and providers which specifically mentioned factors and issues concerning Aboriginal health such as burden of disease, access to culturally safe health services, role of the community and family in maintaining adherence.

Table 4: Further examples of quotes illustrating the results

Themes/ subthemes and further examples of the quotes

Acceptability of the polypill in improving adherence

Ease and convenience

*(My daughter) is very happy for me because I've never been used to taking tablets and I always find them a bit difficult to take. Because it's a capsule and because it's only one, she said "I'm very happy for you mum because it will be so much easier". (*Patient 17,urban GP clinic)

Cost savings

*I think (the trial) was trying to achieve (for) people possibly forgetting medication and it's all in the one pill so therefore they don't have to think I've got five pills to take, six pills to take, it's all going to be one. I thought that was the main thing and another thing was cost to people that, like myself that are aged pensioners, most people are struggling to live, we're not you know, because we own the house and things, we own everything, but I mean things could change. But I thought those were the two important things. (*Patient 41, urban GP clinic)

Adherence depends on other factors

Wanting to be well

As I said I just used to take my tablets all the time and it was just a routine. If you want better health you've got to take your medication and things like that. (Patient 23, regional GP clinic)

Importance of family

*(My grandson) comes and reminds me, he says "Nan, have you had your needle yet?" and that's good for me too because sometimes I don't remember, and my partner will say "have you taken your tablets today?(*Patient 1, urban IHS)

Good Care

I'd like to see in rural and remote areas more indigenous specific mental health issues and programs and that. More around narrative therapy than cognitive therapy. Because cognitive therapy don't work for our mob. Because we're story tellers. So we'd rather sit down and talk and tell our stories and get to the basis of the issues. Rather than say okay, you get depressed when this happens, let's teach you how to handle it. To me that's a bandaid treatment.
So because I know with, with the studies that I've done, mental health could also play a lot on the heart issues. And cholesterol and all that other type of stuff too.... A holistic approach to health. Not just saying okay, we've got mental health over here and general health over here. Get the two of them somehow working together (Patient 30, remote IHS)

You will know that I can guarantee that the majority of our people if we're getting signs of heart attack, shortness of breath, we'll ring GP, we'll ring an Aboriginal medical centre before we actually go, even call, think about even calling an ambulance because of the fact that how we're

going to be treated, how we're going to be spoken to over the phone. (AHW 26, urban IHS)

[I talk to my doctor about my medications because] I suppose I have certain ways of doing things. If I have a problem I like to be systematic and analyse why it went wrong and if I fix it, will it go wrong again. (Patient 16, urban GP clinic)

Importance of health literacy

When I question them and quiz them and say you know "how's your cholesterol going, is everything okay?" they just don't know. So at the end of the day again there's a lack of communication occurring somewhere along the line, so if they knew that they were taking a Polypill that was going to keep their blood pressure, cholesterol, thin their blood, do all that sort of stuff, then potentially they'd be more inquisitive to make sure that it was doing what it was supposed to be doing. (Pharmacist 13, pharmacy related to urban GP clinic)

Policies impacting healthcare costs

*Reduce the cost of them. Especially when you're on a lot like I am… a lot of people you know, pensioners are saying, it's just terrible that they do go without (their medications) sometimes because they just can't afford it. (*Patient 27, urban GP clinic*)*

Polypill in patient management

Limitations of a fixed dose combination

I think patients would need to be advised, or doctors would need to be advised to start the individual components of the polypill individually to start with to make sure there's not side effects, and then start the patient on it in the future because then you can be certain that there's no individual side effects to the different components. (GP 43, remote IHS)

Adequacy of the Polypill Components

*The fixed dose combination was fine, but then you're adding on extra medications as well, so, to get someone up to 80 of Simvastatin and so that sort of minimises some of the benefits of actually being on polypill because you're adding in extra medications anyway…There were often, the decisions around polypill were actually harder than I was expecting rather than just a great concept and you put them on polypill, there was often quite a lot of thought about how you're switching statins. I think one guy we even had strangely on a mixture of two statins because of what he was on before and what was in the polypill. (*GP 8, urban IHS)

Other combinations in the future

I think having a wider range of dosages. The concept's brilliant and the patients actually really enjoyed being on it. They really like having just one tablet. The feedback was consistently good from the patients, that they liked the concept of everything rolled into one. So having flexible dosages, a wider range of different choices would be a way round that. (GP 37, regional GP clinic)

Who could it be suitable for?

High-risk primary prevention patients

*I think the one difficulty when faced with a patient who really doesn't have much health literacy and much knowledge about their own cardiovascular risk one of the difficulties is convincing them that they need to be – will end up needing to be on four or five medications when they've been on none and I think a polypill is generally a very useful tool for doing that. (*GP 27, IHS)

A strategy to address CVD burden of disease in Indigenous patients

I mean when you see the people that are dying around you … the same age as you and even younger, it's all to do with health that they died not taking medication. Maybe if they were given the one pill instead of taking half a dozen they might be still here today. (Patient 4, urban IHS*)*

Well I think it could have significant impacts on Aboriginal health if it were to be introduced as a generally available medication. And I think we can't underestimate how much it may make some change because we do know that cardiac disease is the major cause of Aboriginal mortality. And I think if it's made easier to manage then you know, the impacts could be significant so and I think generally for the general population as well. But I think if there were a public policy imperative as to try to positively affect Aboriginal mortality then this is one approach that will aid that. (GP 23, urban IHS)

I still think it's not going to benefit the people that probably need the most benefit. So I think in some ways it's not necessarily addressing the equity gap because those that are most disadvantaged and most at risk are not going to be the ones that would benefit from this treatment, from this particular polypill. But from other polypills I don't know, maybe they would. (GP 40, remote IHS)

APPENDIX 7

Appendix Overview

This appendix comprises of the supplementary files of the publications Chapter 4.

Supplementary files:

"Protocol of a process evaluation of a family led rehabilitation post stroke in India"-

1) Template for the observations and documentary analysis
2) Interview Guides for the health provider
3) Interview guide for the carer
4) Interview guide for the patient
5) Consent form to participate in interviews

"Family- led rehabilitation post stroke in India- findings of a process evaluation alongside a randomised controlled trial"-

1) Participant characteristics and Illustrative quotes.
2) Coding Tree
3) CONSORT statement (main trial paper)
4) COREQ checklist

Additional File 1: Template for observations and documentary analysis

Name of researcher:

Date and length of time of observations:

Location/s at which the observations were carried out:

Hospital:	Description	Comments
Trial Set up (may be in site feasibility documentation and can be asked of the SC)		
Recruitment of the site		
Demographics, patient load that the hospital serves (may be in the site feasibility documentation)		
Average cost of inpatient care per day- funding, such as out of pocket etc., costs of a physiotherapists visit in usual care.		
Size of hospital		
Description of the stroke unit and organisation of care, work load		
Use of any policies, guidelines, tools (e.g. patient information sheets) for stroke management		
Usual routine activities e.g. frequency of MDT meetings, number of physiotherapists meetings with the patients and families, working environment		
Role of the SC in the unit, participation in the daily activities, role in recruitment of patients, informed consent process.		
Trial implementation		
* Observations of patients (usual care) stay in the unit -if patient is enrolled into trial, provide the ID. - number of ward rounds, presence of family, care provided by the stroke team e.g. education, or wound management etc., discharge		

planning, communication with carers/ family members		
* Observation of patients' (intervention)stay in the unit -if patient is enrolled into the trial, provide ID. -number of days in hospital, number of ward rounds, presence of family, care provided by the stroke team, communication with carers/ family members -Interactions with the SC. What is done? What components of the intervention are delivered and what do you observe are the reactions of the patients/carers?		
***Is there any chance of contamination?**		
Documentary analysis (by the monitors) For a sample of patients in usual care/ intervention arm: days admitted, PTs visits, communication with family, discharge plan: what it covers		
Trial Impact		
Effectiveness- analysis of the unblinding forms.		
Open field notes		
Memo *Researchers' overall reflections and impression of the site; and recommended plan of action if needed? E.g. if there is un-blinding, of if there is contamination.		.

Additional File 2: The ATTEND Study- health professionals (Stroke Unit) interview guide

Initial Broad Descriptive Questions	**Probing Questions (These are a guide only. It is not expected that you ask all these questions)**
OVERALL VIEWS ON BURDEN OF STROKE IN INDIA – *To understand conceptualisation and significance of burden of stroke from provider perspective and what role they, other health care providers, the health system and policies play*	
What are your views on the burden of stroke in India on an individual, community and systems level?	– Do you know what supports your patients have post stroke? What do you think are the barriers and facilitators in enabling their full recovery? o What role does a patient's cultural background have? o What role do the hospital and primary health care have in enabling patient recovery? o What role does current policy have? – What role do you think the stroke unit has in enabling a full recovery? o Is it more as an outpatient clinic? What resources are there?
Overall views on stroke rehabilitation management *To establish pre and post trial views of the usual stroke management and the intervention of a family led rehabilitation after stroke*	
What is your overall view of a family led rehabilitation after stroke?	o Why did you become involved in this study? i.e. motivation for taking part o Experience in general of being part of trial, What experience have you had RCTs? In what areas were they in eg drug trials? o Could you describe what you think are the negative/positive aspects of a family led rehabilitation, and early discharge? o How does this compare with the usual care provided? o Have your views about early discharge and training of family/caregiver at home changed since being in the trial? How so and why? o What are your thoughts about the 5 components of the intervention? 1. Information on stroke recovery trajectory, risk, identification and management of low mood, importance of repeated practice of specific activities 2. Joint goal setting with patient, nominated family caregiver and therapist (reviewed with coordinator as patient progresses and new goals set) 3. Positioning, transfers and mobility 4. Task orientated training (particularly walking, upper-limb and self-care tasks) with personalised copy of culturally appropriate manual 5. Discharge planning o What would be your ideal model of care for rehabilitation management post stroke? Is there anything more than what is being offered in the intervention that you would like to see?

PROVIDER SATISFACTION/ PROBLEMS WITH ATTEND

– *To illustrate the experience with ATTEND patients and contrast this with patients in usual care* ***Note:*** *There is a particular interest in whether there is a difference in practice for intervention group if randomised to SC visits.*

– *To understand if there was any difference in usual care management throughout the trial*

Could you describe what it has been like to look after your patients in the intervention group?	– Did you change or alter treatment prior to commencing patients on trial? – (for usual care PT) Were there any patients who did not need your care due to being involved in the trial? – In your opinion, do you think being on the trial has influenced the behaviour of patients? (i.e. re RCTs – people may be more compliant)
Could you describe what it has been like to look after your patients in the usual care group?	– What was your experience in providing usual care to the participants not being part of the intervention arm? – Did you feel that you changed your management in any way for this group during the course of the study? If so, how?
PATIENT SATISFACTION/ PROBLEMS WITH ATTEND *To illustrate feedback given to the providers from patients in ATTEND* *To understand if the usual care patients reported any difference in management throughout the trial*	
What have been your patients' impressions/thoughts about being in the intervention group?	– Did you receive any feedback from your patients about their experience in the trial? If so, please describe. – Do you feel that your patients were satisfied with the care they received from SC? – What were the major advantages and disadvantages of the family led rehabilitation from the patients' perspectives? Eg early discharge, costs?
What have been your patients' impressions/thoughts about being in the usual care group?	– Do you feel that your patients were satisfied with the care they received whilst in the usual care group?

GENERAL IMPRESSIONS OF THE STUDY *To understand how the trial integrated into everyday practice*	
What has it been like for you to be involved in the ATTEND study? (either as a PI, as part of the stroke team , as the SC)	– What was the impact on you the stroke unit in choosing to be a part of this trial? o Did you experience any problems with the general administration of this trial? If so please explain. o Were there any benefits to you or the stroke unit as a result of participating in this trial? If so please explain. – Would you be interested in participating in future trials as a result of your experience with this study? If no, why not?
SUITABILITY OF THE TRIAL DESIGN *To understand if other trial related variables may have impacted on outcomes*	
What are your thoughts about the design of ATTEND study? (mainly for the SC and PIs)	– (If PI- how was the recruitment process, what are your thoughts about the trial eligibility criteria?) – (If SC, or PI) Were there any difficulties experienced in communicating study information to participants? – How did you find the follow-up visits of your patients? – Did you experience any problems sharing/ coordinating care with providers who were not involved in the study? – Any thoughts about the primary outcomes

TRANSLATION INTO CLINICAL PRACTICE AND POLICY *To understand how the trial results may or may not translate into practice.*	
If found to be beneficial, what would you see as the role of ATTEND in everyday practice?	– What are your views on early supported discharge and family led rehabilitation if translated into into everyday practice? – How do you think incorporating ATTEND outside of the trial will impact on your day-today professional practice? Eg costs – If ATTEND is found to be beneficial, what would be your advice to government on implementing its use in the general population?
CONCLUDING QUESTIONS	
We will also be conducting some interviews with patients and carers involved in the trial to understand their experiences. In your opinion, what areas to you think we should explore? Are there any aspects about stroke management and rehabilitation post stoke that you would specifically like explored?	
Is there anything else you would like to say that we have not talked about in this interview?	

Additional File 3: The ATTEND Study- Carer interview guide

Purpose of the interview: ***Capture what it is like for carers to manage patients post stroke. How the burden could be made easier/better/worse. How the intervention package might influence this (or not); or how the trial might influence this (or not).***

Area of Interest	Initial Broad Descriptive Questions	Possible Probing Questions **(These are a guide only. Depending on what the carer tells you, you do not have to ask all these questions or use the words exactly as written.)**
Health care experience	Can you tell me about experience in caring for your family member? How did you find the care in the hospital?	- What type of support do you get from family, community or social groups with looking after your family member's health? - What other roles/responsibilities do you have in your family? How do you balance this with caring for your family member post stroke?
Satisfaction/ problems with the intervention package	What are your thoughts about the treatment for helping your family member post stroke? What has been the most helpful?	- What did you think of the hospital visit, the home visits? (if in the intervention arm) - What was helpful? (eg. stroke recovery trajectory, how to identify low mood, importance of specific activities) - What was not helpful? - Would you be happy to recommend this type of care to someone else, if applicable. - How can the doctor or the stroke unit improve their care? - What has been most important in helping your family member get better?

Asking about specific components if not already covered	Information about stroke trajectory, risk, identification of low mood Goal setting Positioning, transfers and mobility Task oriented training, the use of the cultural manual Discharge planning	- How do you know what you know about stroke? Is it from family, SC, doctor. - How was it trying to help your family member achieve goals that were set? o What are the things that helped? And what things didn't? - How was it to do the training and to maintain mobility etc? o What are the things that might make your stop helping your family member? (pain?, tiredness, low mood, others helping?) - Can you describe any time or situation when he or she didn't want to do your training exercises? o What were some reasons for stopping? - Who would you speak to if you were having trouble with following the rehab training and tasks for your family member? o When have you had to do this? - Did the discharge planning in the hospital help? In what way?
	Relationships	How would you describe your relationship with your health providers (stroke coordinators, doctors, nurses, physiotherapists? With your family member post stroke as compared to before the stroke? (could be sensitive)
Translation to current practice	Would you recommend this intervention to others?	- Has the cost of care been an issue for your family? If the intervention package required a fee, would you pay for it? Have other costs, e.g. cost of attending GP, travel to the health service, other specialist services, etc. been an issue? - Now that the study is over, would you think the intervention helped in your family members' recovery or would your family have managed anyway? (intervention arm) - What other things would have helped you in your recovery and what more supports would you like in an ideal situation?

General views about the trial	What are your thoughts about ATTEND trial in general?	• How have you found being involved in the study?
		  o What things did/didn't you like about being involved?
		• Tell me how you think the study worked, and what it was hoping to achieve?
		• What were the things that made you want to participate in the study initially?
		  o What were the benefits to you of participating?
		• What concerns did you have about participating in this study?
		  o Were there any things that may have stopped you from participating initially?
		  o What were the risks of participating in the study?
		• Once you and your family member were enrolled, what would have changed your mind about being in the study?
		  o Did you feel that you could withdraw at any time?
		• Did you know who to contact if you had any concerns about the trial?
		• What were your thoughts about your privacy throughout this study?

Concluding questions		• Are there things which we can do better to improve the study or the running of the trial? • Is there something else that you would like to say, that we have not talked about in this interview?

Additional File 4: The ATTEND Study- Patient interview guide

Purpose of the interview: ***Capture what it is like for people to manage post stroke. How to manage their disability, how the burden could be made easier/better/worse. How the intervention package might influence this (or not); or how the trial might influence this (or not).***

Area of Interest	**Initial Broad Descriptive Questions**	**Possible Probing Questions** **(These are a guide only. Depending on what the patient tells you, you do not have to ask all these questions or use the words exactly as written.)**
Health care experience	Can you tell me about your stroke? How was the care in the hospital?	- What are some of the good/bad things about your health care? - What type of support do you get from family, community or social groups with looking after your health? o What kind of roles/responsibilities do you have in your family?
Satisfaction/ problems with the intervention package	What are your thoughts about your current treatment for your stroke?	- What did you think of the in hospital visit, the home visits? - What was helpful? (eg. stroke recovery trajectory, how to identify low mood, importance of specific activities) - What was not helpful? - Would you be happy to recommend this type of care to someone else, if applicable. - How can your doctor or the stroke unit improve your current treatment? - What has been most important in helping you get better?

Asking about specific components if not already covered	Information about stroke trajectory, risk, identification of low mood Goal setting Positioning, transfers and mobility Task oriented training, the use of the cultural manual Discharge planning	- How do you know what you know about stroke? Is it from family, SC, doctor. - How was it trying to achieve goals that were set? o What are the things that helped? And what things didn't? - When do you find it more difficult to do training and to maintain mobility etc? o What are the things that might make you stop? (pain?, tiredness, low mood, others helping?) - Can you describe any time or situation when you didn't want to do your training exercises? o What things were influencing your decision? - Who would you speak to if you were having trouble with following the rehab training and tasks? o When have you had to do this? - Did the discharge planning in the hospital help? In what way?
	Relationships	How would you describe your relationship with the SC? With your nominated carer? (could be sensitive)
Translation to current practice	Would you recommend this intervention to others?	- Has the cost of care been an issue for you? If the intervention package required a fee, would you pay for it? Have other costs, e.g. cost of attending GP, travel to the health service, other specialist services, etc. been an issue? - Now that the study is over, would you think the intervention helped in your recovery or would you have managed anyway? - What other things would have helped you in your recovery and what more supports would you like in an ideal situation?

General views about the trial	What are your thoughts about ATTEND trial in general?	• How have you found being involved in the study?
		  o What things did/didn't you like about being involved?
		• Tell me how you think the study worked, and what it was hoping to achieve?
		• What were the things that made you want to participate in the study initially?
		  o What were the benefits to you of participating?
		• What concerns did you have about participating in this study?
		  o Were there any things that may have stopped you from participating initially?
		  o What were the risks of participating in the study?
		• Once you were enrolled, what would have changed your mind about being in the study?
		  o Did you feel that you could withdraw at any time?
		• Did you know who to contact if you had any concerns about the trial?
		• What were your thoughts about your privacy throughout this study?

Concluding questions		• Are there things which we can do better to improve the study or the running of the trial? • Is there something else that you would like to say, that we have not talked about in this interview?

ATTEND Study Interview evaluation

INFORMATION FOR PARTICIPANTS

Introduction

You are invited to take part in the interview evaluation of the ATTEND study, which is part of the process evaluation of the study. As a patient or carer involved in this study you would be aware that this is a research study which looks to compare an Early Supported Discharge with a trained family-led caregiver-delivered, home-based rehabilitation program with usual care. You are invited to take part in the study to share your views about your health care experience and also about the study.

We know that patients' rehabilitation is likely to be affected by things such as cultural issues, costs of medications and additional support, relationships with your health providers. This might be very important in whether family led rehabilitation is effective. We are therefore seeking to explore your views on the advantages and disadvantages of family led rehabilitation post stroke in India.

Your views on these issues will help us understand what role family led rehabilitation has in providing best practice care for post stroke patients. The findings will help us understand the research and how it could work in India.

Who can participate in the interview?

Participants and their carers from both usual care and intervention arm in the ATTEND trial will be invited to participate in this interview evaluation from a sample of participating sites.

What is required in the interview?

If you participate in this study you will be interviewed by a study team member. We would like to talk to you for around 30-60 minutes. The interview process is informal and flexible as our main aim is to hear your experiences and views. We will fit within your schedule and if necessary speak with you over more than one visit if that is more convenient. Please let us know what works well for you.

What will happen once we have collected your information?

We would like to record your interview(s).

All information will remain confidential. Study information will be stored in a securely locked file and password assessed electronic folder at the George Institute for Global Health and will be accessed only by study team members. Nothing written in reports will link you personally to the study.

Ethics Approval

This study has been approved by the Human Research Ethics Committee (University of Sydney, Australia) and your local Ethics Committee.

Contact Details

If you have any problems, concerns, questions or complaints about this study, you should preferably contact

<Investigator Name>
<Designation>
<Site Name>
<Site Address>
<Contact Number>

OR

Name of the ethics committee member : _____
Designation : _____
Contact No : _____

OR
The Manager
Human Ethics Administration
University of Sydney
NSW 2006, Australia
Telephone +61 2 8627 8176; Facsimile +61 2 8627 8177
Email: ro.humanethics@sydney.edu.au

This information sheet is for you to keep.

ATTEND Study Interview evaluation
PARTICIPANT CONSENT FORM

Participant:

Name: …….

Address: ……..

- ☐ I have read the participant information sheet
- ☐ I feel free to accept or refuse to participate in the interview
- ☐ I have had a chance to ask questions and all of my questions have been answered to my satisfaction
- ☐ I have been given and I understand the information on the interview concerning its nature, purpose, and duration, including any known or expected inconvenience.
- ☐ I agree that some of my words (not my name) will be used in the study reports
- ☐ I agree that the interview will be taped
- ☐ I do not have any objections to the interview record being kept at the end of the study
- ☐ By signing this form, I give my free and informed consent to take part in this study as outlined in the information sheet and this consent form. I understand that I am free to withdraw from the study at any given time. I have been given a copy of this consent form. By signing this form I have not given up my legal rights.

Name of participant:……

Signature of participant: ……..**Date:**……

Name of interviewer: ……

Signature of interviewer: ……...**Date:** ……

Supplementary file 1

Table 1: Characteristics of the patients and site characteristics of the health providers interviewed

Characteristics of patients interviewed	Intervention patients (N=11)	Usual care patients (N=11)
Age ranges		
25-39	3	2
40-55	4	6
55-75	4	3
Gender		
Male	8	6
Female	3	5
Education		
No schooling	2	1
Primary school completed	2	3
High school completed	2	2
College/ University completed	5	5
Carer Type		
Spouse	3	5
Daughter/daughter in law	2	4
Son/Son-in law	4	1
Mother/ Father	1	1
Brother/ Sister	1	0
Site		
Government Academic hospital	3	5
Christian Missionary hospital	7	4
Private Corporate hospital	1	2

Sampled Hospital characteristics	Site 1	Site 2	Site 3	Site 4	Site 5	Site 6
Geographical Location	Central, urban	North, urban	South, urban	North, rural	South, urban	South, urban
Type of hospital	Government Academic hospital	Government Academic hospital	Christian Missionary hospital	Christian Missionary hospital	Private Corporate hospital	Private Corporate hospital
Size of hospital	1766 beds	1500 beds	1750 beds	120 beds	270 beds	250 beds

Use of stroke management guidelines	Present	Present	Present	Not specifically, general assessment and management	Present	Present
Presence of allied health team for outpatient follow up	Occupational, Speech and physiotherapists	Occupational, Speech and physiotherapists, Specialised stroke unit nurses	Physiotherapists	Physiotherapists	Occupational, Speech and physiotherapists	Physiotherapists
Health providers interviewed (N=28) 7 Doctors 4 Hospital Physiotherapists 1 Clinical Nurse 8 *Stroke Coordinators 8 * Blinded Assessors *(additional 2 stroke coordinators and blinded assessors from a Christian hospital and corporate hospital)	1 Doctor 1 Hospital Physiotherapist 1 Clinical Nurse 1 Stroke Coordinator 1 Blinded Assessor	1 Doctor 1 Hospital Physiotherapist 0 Clinical Nurse 1 Stroke Coordinator 1 Blinded Assessor	2 Doctors 1 Hospital Physiotherapist 0 Clinical Nurse 1 Stroke Coordinator 1 Blinded Assessor	1 Doctor 1 Hospital Physiotherapist 0 Clinical Nurse 1 Stroke Coordinator 1 Blinded Assessor	1 Doctor 0 Hospital Physiotherapist 0 Clinical Nurse 1 Stroke Coordinator 1 Blinded Assessor	1 Doctor 0 Hospital Physiotherapist 0 Clinical Nurse 1 Stroke Coordinator 1 Blinded Assessor

Box 1: Illustrative quotes across the themes

Early supported discharge welcomed in concept

"Discharging them early is helping them to reduce the burden of cost of hospital. The core hospital cost was cut down for them because most of the patients who are in and around our place are very much low socioeconomic rate. Early discharge helped them to get back to home quickly, and also the cost was reduced so that really helped them." (Stroke coordinator)

"*Every day we are turning back at least three, on an average three patients with stroke who needs admission, we are turning back for lack of beds. So, if this trial can prove that early assisted discharge is fruitful, then the bed turnover time can be faster."* (Neurologist)

Stroke Education is needed

"*I studied B.Com in College. Now I am sitting like this, not useful to anyone and worrying about giving trouble to others around me…Just conduct a meeting and say avoid eating oil, alcohol. Now a days even kids are getting this disease*." (Intervention Patient)

"*A patient came to me with a stroke. It was a five-day old stroke. The patient has complete hemiplegia. When I told the patient you have come after five days. If you could have come within six hours or four and a half hours, there was a drug which could have been given to you which could have made him better. Then the patient relative asked, "I never knew we should come within three hours. You never told me. You are a doctor, we are laymen. We don't know that we should come within that hour…"* (Neurologist)

ATTEND is an acceptable model of care

"*She says when (the stroke coordinator) went to their house and gave the treatment they could make out the mood of her father and it was always like he was very excited and happy when (the stroke coordinator) came…they have told us to continue with the exercises. And my father keeps on doing those all the time. Now he does not require much support from us. So he does it every morning and evening...We were told that within six months improvement will be there. Now that has happened even before six months. After that also we are continuing...I could not have done so much with my limited knowledge***."** (Intervention Carer)

"I see from the patient's perspective. That their goal is ultimately being independent. They want to return to (their) profession. So for that case ATTEND has covered everything about being functional. That's all, from the therapists view we have to make that person quite functional rather than teaching him only one exercise to the caregiver." (Stroke Coordinator)

Sustaining patient and carer motivation was a key challenge

"We used to give the caregiver a goal setting scale and a training pattern in mobility training. These three are more important. Sometimes the patient is not very much cooperative like the patient is really depressed, then we have to counsel the caregiver and the patient. You have to do it, otherwise the complications will be more aggressive or exaggerate." (Stroke Coordinator)

"It's very difficult. He has got stroke and because of taking care of him I was not able to take care of kids. Whatever I am earning is spending on him. No improvement at all…His parents are old and with their earnings only I was able to manage and take care. My two kids are very small. He said he has completed MBA. Now he is not able to speak...We couldn't buy clothes. We couldn't eat properly…" (Intervention carer)

ATTEND is a sustainable model of care especially for those with limited access to rehabilitation

"*There is one who stays ahead of our lane. But she was aged, around sixty-five, she was an old woman. She was a victim of stroke. Her whole body had become numb. So I was the one who had gone to her house and helped her perform exercises. I had told her family members about what to do. I am doing this because the same thing has happened to my father."* (Intervention carer)

"*To be honest, I didn't think there was any other way that a person with stroke could actually manage, because most of our patients are from the villages…there are no physiotherapists out there who will go to the homes or whom patients can go to and get help. Even before this study started out, we were giving the relatives itself the education that they needed and trying to teach them to help their patients…Most patients cannot afford for to go to a physiotherapist.* " (Neurologist)

Nodes
Nodes\\Context
Nodes\\Context\cultural issues
Nodes\\Context\Health system
Nodes\\Context\Health system\guidelines
Nodes\\Context\Health system\stroke registry
Nodes\\Context\Impact of stroke on the patient
Nodes\\Context\Impact of stroke on the patient\Bowel problems
Nodes\\Context\Impact of stroke on the patient\other health considerations
Nodes\\Context\Impact of stroke upon the family
Nodes\\Context\Impact of stroke upon the family\Family relationships
Nodes\\Context\Impact of stroke upon the family\Financial implications
Nodes\\Context\Socio-economic and policy issues
Nodes\\Context\Stroke awareness
Nodes\\Context\Stroke Burden
Nodes\\Context\usual stroke care
Nodes\\Context\usual stroke care\learning from community member
Nodes\\Context\usual stroke care\navigation of the system
Nodes\\Context\usual stroke care\outpatient rehabiliation
Nodes\\Context\usual stroke care\recommendations
Nodes\\Context\usual stroke care\recovery
Nodes\\Context\usual stroke care\stroke unit
Nodes\\Context\usual stroke care\treatment options
Nodes\\Implementation
Nodes\\Implementation\Adoption
Nodes\\Implementation\Cost Considerations
Nodes\\Implementation\Fidelity and Dose
Nodes\\Implementation\Fidelity and Dose\blinding or unblinding
Nodes\\Implementation\Fidelity and Dose\data collection
Nodes\\Implementation\Fidelity and Dose\Extent of any contamination
Nodes\\Implementation\Implementation barriers and facilitators
Nodes\\Implementation\Implementation barriers and facilitators\Building of capacity
Nodes\\Implementation\Implementation barriers and facilitators\development of ATTEND
Nodes\\Implementation\Implementation barriers and facilitators\Ethical dilemma of RCT in resource poor setting
Nodes\\Implementation\Implementation barriers and facilitators\staff recruitment
Nodes\\Implementation\Implementation barriers and facilitators\staff training
Nodes\\Implementation\Implementation barriers and facilitators\support from clinical coordinating team
Nodes\\Implementation\Implementation barriers and facilitators\work load on trial staff
Nodes\\Implementation\Recruitment and Reach
Nodes\\Implementation\Recruitment and Reach\demographic description
Nodes\\Implementation\Recruitment and Reach\Research motivation
Nodes\\Interview conduct
Nodes\\Mechanisms of Impact
Nodes\\Mechanisms of Impact\ATTEND intervention
Nodes\\Mechanisms of Impact\ATTEND intervention\early mobilisation
Nodes\\Mechanisms of Impact\ATTEND intervention\Early supported discharge
Nodes\\Mechanisms of Impact\ATTEND intervention\Education component
Nodes\\Mechanisms of Impact\ATTEND intervention\Focus on functional recovery

Nodes
Nodes\\Mechanisms of Impact\ATTEND intervention\For whom
Nodes\\Mechanisms of Impact\ATTEND intervention\home visits
Nodes\\Mechanisms of Impact\ATTEND intervention\Intervention manual
Nodes\\Mechanisms of Impact\ATTEND intervention\Joint goal setting
Nodes\\Mechanisms of Impact\ATTEND intervention\pain during rehabilitation
Nodes\\Mechanisms of Impact\ATTEND intervention\patient motivation and mental health
Nodes\\Mechanisms of Impact\ATTEND intervention\Percieved effectiveness of ATTEND
Nodes\\Mechanisms of Impact\ATTEND intervention\phone calls
Nodes\\Mechanisms of Impact\ATTEND intervention\polypill of stroke rehabilitation
Nodes\\Mechanisms of Impact\ATTEND intervention\recommendations for ATTEND
Nodes\\Mechanisms of Impact\ATTEND intervention\SC and family relationship
Nodes\\Mechanisms of Impact\ATTEND intervention\training of family member
Nodes\\Mechanisms of Impact\ATTEND intervention\use of audiovisual aids
Nodes\\Mechanisms of Impact\ATTEND intervention\usual care vs intervention
Nodes\\Mechanisms of Impact\Maintanence
Nodes\\Mechanisms of Impact\Maintanence\changing expectation
Nodes\\Mechanisms of Impact\Maintanence\community requirements
Nodes\\Mechanisms of Impact\Maintanence\Health system requirements
Nodes\\Mechanisms of Impact\Maintanence\Policy requirements
Nodes\\Mechanisms of Impact\Trial Impact
Nodes\\Mechanisms of Impact\Trial Impact\advocacy
Nodes\\Mechanisms of Impact\Trial Impact\BA's involvement
Nodes\\Mechanisms of Impact\Trial Impact\changes for service delivery
Nodes\\Mechanisms of Impact\Trial Impact\increase research capacity
Nodes\\Mechanisms of Impact\Trial Impact\Stroke collaboration

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Please note this checklist is based on the published trial outcomes paper which is referred to in our manuscript (ref 11): The ATTEND Collaborative Group, Family-led rehabilitation after stroke in India (ATTEND): a randomized controlled trial. Lancet. 2017. http://dx.doi.org/10.1016/S0140-6736(17)31447-2

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	1
	2b	Specific objectives or hypotheses	1
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	1
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	Not applicable
Participants	4a	Eligibility criteria for participants	1-2
	4b	Settings and locations where the data were collected	2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	3
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	3-4
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Not applicable
Sample size	7a	How sample size was determined	4
	7b	When applicable, explanation of any interim analyses and stopping guidelines	Not applicable
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	2
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	2
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	2 2
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to	

		interventions	2
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	2
	11b	If relevant, description of the similarity of interventions	Not applicable
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	4-5
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	4-5
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	3
	13b	For each group, losses and exclusions after randomisation, together with reasons	3
Recruitment	14a	Dates defining the periods of recruitment and follow-up	5
	14b	Why the trial ended or was stopped	5
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	3-4
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	3-4
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	5
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Not applicable
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	5-6, 10
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	6
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	11
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	11
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	10-11
Other information			
Registration	23	Registration number and name of trial registry	1
Protocol	24	Where the full trial protocol can be accessed, if available	1
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	5

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Consolidated criteria for reporting qualitative studies (COREQ): 32-item checklist

Developed from:
Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. International Journal for Quality in Health Care. 2007. Volume 19, Number 6: pp. 349 – 357. (as recommended by the EQUATOR network)

No. Item	Questions/description	Reported on Page
Domain 1: Research team and reflexivity		
Personal Characteristics		
1. Interviewer/facilitator	Which author/s conducted the inter view or focus group?	7
2. Credentials	What were the researcher's credentials? E.g. PhD, MD	7
3. Occupation	What was their occupation at the time of the study?	N/A
4. Gender	Was the researcher male or female?	7
5. Experience and training	What experience or training did the researcher have?	In pre-specified protocol (11)
Relationship with participants		
6. Relationship established	Was a relationship established prior to study commencement?	7
7. Participant knowledge of the interviewer	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	7
8. Interviewer characteristics	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	7, 17
Domain 2: study design		
Theoretical framework		
9. Methodological orientation and Theory	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	6, 7
Participant selection		
10. Sampling	How were participants selected? e.g. purposive, convenience, consecutive, snowball	7
11. Method of approach	How were participants approached? e.g. face-to-face, telephone, mail, email	7 (and elaborated in published protocol) (11)
12. Sample size	How many participants were in the study?	10
13. Non-participation	How many people refused to participate or dropped out? Reasons?	N/A
Setting		
14. Setting of data collection	Where was the data collected? e.g. home, clinic, workplace	7
15. Presence of non-participants	Was anyone else present besides the participants and researchers?	N/A
16. Description of sample	What are the important characteristics of the sample? e.g. demographic data, date	7 & Supplementary file 1

Data collection		
17. Interview guide	Were questions, prompts, guides provided by the authors? Was it pilot tested?	7 (and elaborated in the published protocol) (11)
18. Repeat interviews	Were repeat interviews carried out? If yes, how many?	N/A
19. Audio/visual recording	Did the research use audio or visual recording to collect the data?	7
20. Field notes	Were field notes made during and/or after the interview or focus group?	7
21. Duration	What was the duration of the interviews or focus group?	7
22. Data saturation	Was data saturation discussed?	N/A
23. Transcripts returned	Were transcripts returned to participants for comment and/or correction?	N/A
Domain 3: analysis and findings		
Data analysis		
24. Number of data coders	How many data coders coded the data?	7
25. Description of the coding tree	Did authors provide a description of the coding tree?	7 and supplementary file 2
26. Derivation of themes	Were themes identified in advance or derived from the data?	7
27. Software	What software, if applicable, was used to manage the data?	7
28. Participant checking	Did participants provide feedback on the findings?	N/A
Reporting		
29. Quotations presented	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	10-13, and additional illustrative quotes in the supplementary file
30. Data and findings consistent	Was there consistency between the data presented and the findings?	10-13, Figure 2 and supplementary file 1
31. Clarity of major themes	Were major themes clearly presented in the findings?	10-13
32. Clarity of minor themes	Is there a description of diverse cases or discussion of minor themes?	10-13 (incorporated into major headings)

APPENDIX 8

Appendix Overview

This appendix comprises of the supplementary files of the publication in Chapter 5.

Supplementary files:

"Exploring use of economic evidence for investment in prevention" -

1) Interview guide
2) Coding Tree
3) Documentary Analysis

THE GEORGE INSTITUTE
for Global Health

General Framework for Economic Evaluation of Prevention

Overview of consultation themes

Context (role of evidence (in general) in decisions around investment in disease prevention programs)

- Could you tell me a bit about your role and the role of your organisation/ department in making investment decisions in disease prevention programs?
- In your experience, what role does evidence (generally) play in these decisions to initially invest/not invest in disease prevention programs?
    - ***If some role***: What evidence is relevant? How is it gathered?
    - ***If no or minimal role:*** What factors would influence a decision? Do you think that decision making could be improved with a more evidence-based approach? If so, what sort of evidence do you have in mind? What can be done to promote greater use of evidence?

Role of economic evidence

- What do you see specifically as the role of ***economic*** evidence in your organisation/department?
- In your mind, what sort of evidence does this constitute? In other words, what sort of data are we looking at here? How does that data then inform your decision making?

Design and implementation

- How do you (or your organisation) come up with ideas for new programs in the area of disease prevention?
- What type of evidence do you use? Where do you get it?
- What role does economic evidence have in this phase of design and development of new programs?

Economic evaluation

- Once you've decided on program to fund, is there a process in your organisation for building in evaluation? Is it routinely followed? What sort of evaluation does this involve? What are you looking for in these evaluations? What sort of data are you looking to collect?
- What role, if any, is there for economic evaluation?
    - **If no role or minimal:** should there be a greater role? Is this something you are working towards? How?
    - **If there is a role:** How has this role developed in your organisation? What capacity do you have for carrying out these evaluations? Are they commissioned to external organisations?
- Do you use specific guidelines in either conducting or commissioning economic evaluations**?**
    - **If so**, how would you rate the usefulness of such guidelines?
    - **If not,** is this something that would be of use? Have you had any previous experience with such guides?
- What sort of support would be of use to you and your organisation/department?

The content of economic evaluation

The central idea of this study is that there is a perception amongst many practitioners that economic evaluation evidence – as it is conventionally presented - is not well suited to the evaluation of prevention programs. In particular, the conventional focus on individual level health outcomes (such as life years gained, cases of illness prevented) doesn't fully capture what it is that many disease prevention programs try to achieve (many of which are outside health) and are based on too short a timeframe. As such, it is argued that they unfairly penalise disease prevention vis-a vis other type of health sector programs when decisions are made over the allocation of funding.

- How would you respond to such a point? Do you agree with this criticism?
- What sort of evidence would be important to you in making decisions regarding investment? For instance if we did an evaluation on a health promotion program and were unable to detect changes in 'hard' health outcomes, but saw changes in process and behavioural indicators, how would such evidence figure in your decision to fund such a program?
- What role is there for outcomes in other sectors (e.g. education and employment)?
- What role is there for outcomes that occur decades into the future?

- What other type of outcomes/indicators might be important?
- Do you have any suggestions about making such evidence available to decision makers?

Use of economic evaluation

- What do you see as advantages associated with greater use of economic evaluation evidence in investment in disease prevention programs?
- What do you see as possible downsides?
- What are the factors that might hinder the use of current economic evidence in decision making? Have you experienced a situation where economic evidence was not available but could have been useful? Is there anything that can be done to better promote its use?
- What are some current gaps in the economic evidence base in prevention?
- What have you observed about how colleagues in other departments and agencies (within and outside health) have used economic evidence? What are your thoughts about the positives and negatives about their approach?
- Are there any other issues around the use of economic evidence in your organisation/department that we haven't covered?

Supplementary file 2: Coding Tree

Hierarchical Name
Nodes\\Build research capability
Nodes\\Content of economic evaluation
Nodes\\Content of economic evaluation\Participant definition or approach to evaluation
Nodes\\Content of economic evaluation\Participant definition or approach to evaluation\Conflicting stakeholder views
Nodes\\Content of economic evaluation\Participant definition or approach to evaluation\Definition or approach to evaluation
Nodes\\Content of economic evaluation\Participant definition or approach to evaluation\Financial drivers
Nodes\\Content of economic evaluation\Recommendations
Nodes\\Context
Nodes\\Context\Academic
Nodes\\Context\Health
Nodes\\Context\organisation purpose
Nodes\\Context\Treasury
Nodes\\Decision making
Nodes\\Decision making\Applicability of evidence to policy makers
Nodes\\Decision making\Available resources (people, $)
Nodes\\Decision making\Available time frame (ROI)
Nodes\\Decision making\Business case
Nodes\\Decision making\Capacity to be implemented
Nodes\\Decision making\Champions
Nodes\\Decision making\Collaboration
Nodes\\Decision making\Duty of care
Nodes\\Decision making\Financial implications of investment
Nodes\\Decision making\Financial implications of investment\Direct cost to government
Nodes\\Decision making\Financial implications of investment\Savings to budget or avoided costs
Nodes\\Decision making\Flexibility and autonomy
Nodes\\Decision making\Health equity
Nodes\\Decision making\Holistic or intersectoral
Nodes\\Decision making\Institutional considerations
Nodes\\Decision making\Organisational structure
Nodes\\Decision making\Politics
Nodes\\Decision making\Risk and balancing interests
Nodes\\Definition of evidence
Nodes\\Definition of evidence\Activity Based Funding
Nodes\\Definition of evidence\Anecdotal
Nodes\\Definition of evidence\Economic evidence
Nodes\\Definition of evidence\Performance metrics
Nodes\\Definition of evidence\Process data
Nodes\\Definition of evidence\Research

Nodes\\Design and implementation of program
Nodes\\Design and implementation of program\Baseline
Nodes\\Design and implementation of program\Funding needs
Nodes\\Design and implementation of program\Infrastructure
Nodes\\Design and implementation of program\Leverage
Nodes\\Design and implementation of program\Long term investment
Nodes\\Design and implementation of program\Measurability of project
Nodes\\Design and implementation of program\Mismatched evidence
Nodes\\Design and implementation of program\Responsibility
Nodes\\Design and implementation of program\Scalability
Nodes\\Design and implementation of program\Workforce
Nodes\\Evaluation
Nodes\\Examples of programs
Nodes\\Focus on prevention
Nodes\\Focus on prevention\Cost-sharing
Nodes\\Focus on prevention\Cultural shift
Nodes\\Focus on prevention\Difficult to evaluate
Nodes\\Focus on prevention\Duty of care and accountability
Nodes\\Focus on prevention\Marketability of product
Nodes\\Focus on prevention\Measurability
Nodes\\Focus on prevention\Need economic evidence for funding
Nodes\\Focus on prevention\Political climate
Nodes\\Focus on prevention\Popularity
Nodes\\Focus on prevention\Types of intervention
Nodes\\Role of economic evaluation
Nodes\\Role of economic evaluation\Cost benefit analysis
Nodes\\Role of economic evaluation\Costing
Nodes\\Role of economic evaluation\Extent
Nodes\\Role of economic evaluation\In house versus external
Nodes\\Role of economic evaluation\Return of investment
Nodes\\Strategies

Supplementary Table: Documentary analysis

In their guidelines or evaluation frameworks for economic analysis, what types of analysis do they suggest?

NSW Population Health research strategy	NSW Health will undertake, support and commission research that: • where appropriate, focuses on: ○ economic evaluations (p7)
NSW Government Evaluation Framework August 2013	Evaluation is a key tool to support evidence based policy and decision making in government (p.2) Evaluation can provide the necessary evidence to improve services and guide better resource allocation decisions (p.2) Evaluation is about asking questions of our programs such as (p.5): • Do they provide value for money • Is there a better way to achieve the same result? Can resources be allocated more efficiently Table 1 p. 3 Types of evaluation: Summative – CE and CBA – answers the questions of efficiency by standardising outcomes in terms of their dollar value to answer questions of value for money. These analyses can also be used in formative stages to compare different options. Questions it answers: What are the net effects; is the program the best use of the resources it costs? The following should be considered when choosing programs for evaluation p.8: • Size of investment – resource intensive programs should be evaluated to ensure they deliver intended outcomes and provide the best value for money Appendix A: Glossary of terms p.19: • CBA/Cost efficiency analysis: Evaluation of the relationship between program costs and outcomes. Can be used to compare different programs with the same outcomes to determine the most efficient intervention.
NSW Government Advertising Handbook	Section 7 (1) of the Act sets out the requirements for cost benefit analysis and peer review of government advertising campaigns (p.6) • Requires CBA if the cost of that campaign I likely to exceed $1M • Peer review if cost of the campaign is likely to exceed $50K The Cabinet Standing Committee on Communications and Government advertising needs to approve all advertising programs likely to exceed $1M Agencies proposing advertising campaign should prepare the CBA – and should contact NSW Treasury for advice and guidance (refers to document: NSW Treasury Circular 10/11 Economic Appraisal Guidelines -

	Economic appraisal guidance for government advertising) The purpose of the peer review is to provide informed and objective feedback on the need and cost effectiveness of the proposed advertising, as well as to monitor compliance of all campaigns with the relevant legislation and policies (p.10). As part of developing an advertising strategy, agencies should determine and document how they intend to measure the effectiveness of their advertising activities (p.11).
NSW Government Guidelines for Economic Appraisal 2007	Cost-benefit analysis and Cost-effectiveness analysis. • Both techniques require as many of the benefits and costs as is possible to be quantified in monetary terms • CEA is used when major benefits can't be valued in dollar terms (or when it will be unduly expensive to undertake the valuation) • CEA is most often used in areas such as education, health, law and order and the environment – where CBA can prove more difficult • Unquantified benefits and costs should be taken into account
Principles and Guidelines for Economic Appraisal of Transport Investment and Initiatives. Transport Economic Appraisal Guidelines 2013	CBA is the preferred approach. Economic impact analysis is used to measure quantified but non monetised effects. However when the benefits are similar or a particular objective is required, CEA may be applicable to transport projects.
Sydney's Walking Future 2013	One of the priorities in this strategy is to deliver cost effective solutions (p.9), however the criteria used is not reported.

In the reports of prevention strategies, if done, how are the economic outcomes described?

NSW Get Healthy Information and Coaching Service: The first five years 2009-13.	Outcomes reported: • Uptake and usage (p.6,7) • Relationship between promotional efforts and uptake • Starting risk factor profile • Change in behaviour and health outcomes(weight, waist circumference, BMI, physical activity, healthy eating behaviours • Maintenance of behaviour and health outcomes at 12 months Costing study was undertaken (ref 26) • Marginal cost of 26 week program smaller than the increase in achievements • Mean coaching costs ranged from $640 to $1030 • Marketing costs were $350 per person • Reports plans for further economic evaluation and cost-benefit analysis
NSW Government Guidelines for Economic Appraisal 2007	NA
Healthy Spaces and Places 2009	NA
Walking Strategy and Action Plan 2015-2030	No economic outcomes described
Sydney's Walking Future 2013	NA
Closing the gap: 10 years of Housing for Health in NSW. An evaluation of a healthy housing intervention	Costs per house of different maintenance activities were reported (p. 35)

Cross sectoral work- in what ways are the economic analysis done and how are health outcomes incorporated? (eg transport)

NSW Population Health research strategy	NSW Health will undertake, support and commission research that (p7) • include large scale, collaborative, cross-area or state-wide research projects. • uses cross-jurisdictional or whole of government collaborations where appropriate
NSW Government Evaluation Framework August 2013	The following should be considered when choosing programs for evaluation p.8: • Cross-sectoral involvement – programs which are partly or wholly funded by other jurisdictions
NSW Government Guidelines for Economic Appraisal 2007	Example p. 51: Department of Community Services has developed a database of material on certain social welfare costs and benefits, including aspects of health, education, child care and so on to assist analysis in such areas.
Principles and Guidelines for Economic Appraisal of Transport Investment and Initiatives. Transport Economic Appraisal Guidelines 2013	• The cost of a crash to society is the value of the trauma and property damage caused by the crash. The estimated cost of crashes (crash cost values) can be found in Appendix 4. The costs are expressed using human capital or willingness to pay values. NSW Treasury recommends that analysis be undertaken using both methods for a period to gauge the degree of significance of the change in appraisal results due to two approaches. The value of statistical life (VSL) is the parameter used in evaluation of safety benefits in economic appraisals of infrastructure or related projects. A literature review (Appendix 4 Table 46) indicates that VSL ranges from $1.9m to $9.8m covering various countries. A study conducted for the then Roads and Traffic Authority (now Roads and Maritime Services) estimated the value that the NSW community is willing to pay or forego in exchange for a reduction in the probability of crash related injuries and death using a stated choice (SC) methodology. This value was estimated to be $6.41million in Dec 11 prices, which had been officially endorsed by the then Roads and Traffic Authority and acknowledged by TfNSW and NSW Treasury. • There are several tools and approaches suggested for use when there are wider socio-economic and environmental impacts of transport interventions ○ Multi-criteria assessment - main strength of MCA is that benefits which are unable to be readily quantified in monetary terms and are of major importance are included in the evaluation. Also, MCA has increased transparency as the criteria and objectives are stated and considered explicitly. On the other hand, the limitations of MCA are that there is a lack of theoretical framework, the weighting framework maybe subjective and it is harder to take into account impacts occurring at different times. ○ Goal Achievement Matrix - can be used in the analysis of impacts that are not readily able to be quantified in monetary terms (such as social objectives), which are prevalent in transport and land planning projects. The advantages of GAM are that it explicitly considers a wide range of goals, allowing social, environmental and economic outcomes to appropriately influence decision making. It is a simple tool that can be used by stakeholders as a means to promote community wide consultation, allowing

	differing impacts to be considered. It is also able to include equity effects and impacts that are not easily monetised in traditional cost benefit analysis. disadvantage of the tool is that there is no common framework or system of measurement that can be applied to estimate the level of achievement of all goals. The success of the tool is determined by the weights applied to the goals, which tend to be more subjective rather than objectively determined. Furthermore, any interaction and interdependence of objectives are not taken into account. ○ Strategic merit testing - a technique used to check if the proposed project aligns with the economic, environmental and social objectives, policies and strategies of the government. ○ Appraisal Summary Technique has been broadly used in the assessment of the economic, environmental and social impacts of a project • Accident costs can be estimated based on two main approaches: Willingness to Pay (WTP) and Human Capital Cost ○ Human capital cost has several limitations and therefore WTP methods are being used more widely. As the accident costs derived from the WTP approach are usually higher than those from the Human Capital Approach, a higher priority to safety is given if the WTP accident cost values are used in the economic appraisals. ○ Cost per person based on severity of injury and cost per crash is estimated and recommended for use in NSW transport economic appraisals (Table 47, p. 269) ○ Value of a statistical life - $6,698,897 ○ Value of a statistical life year - $325,434
Healthy Urban Development Checklist 2009	• The purpose of the checklist is to assist health professionals to provide advice on urban development policies, plans and proposals. • No economic analysis
Healthy Spaces and Places 2009	Provides a guide for planning, designing and creating sustainable communities that encourage healthy living No economic analysis
Walking Strategy and Action Plan 2015-2030	No economic analysis undertaken • Walking strategy reports on the health benefits of walking. Also reports the productivity benefits of walking • Reports (from a previous government study) that walking infrastructure has been shown to deliver a net health benefit of 144 cents for each Km walked.
Sydney's Walking Future 2013	Reports the inter-sectoral benefits of walking – health, wellbeing, the environment and communities
Closing the gap: 10 years of Housing for Health in NSW. An evaluation of a healthy	Program is designed to improve health outcomes (infectious diseases and chronic disease), however it also reports additional program benefits such as education and community capacity building.

housing intervention	
NSW Healthy Eating and Active Living Strategy: Preventing overweight and obesity in New South Wales 2013-2018	Working in partnership is a guiding principle of the strategy – it recognises that many factors influence overweight and obesity which requires a multi-sectoral approach and the development of strategic partnerships across government, industry, business, the non-government sector and research groups

A few of the participants have mentioned 'reducing health inequalities' as an objective – how is this detailed in these documents and how is this measured?

NSW Population Health research strategy	NSW is committed to the use of research evidence in informing decisions to improve population health and reduce health inequalities (p2)
	NSW Health will undertake, support and commission research that (p7):
	• where appropriate, focuses on:
	  ○ disadvantaged communities and population groups (to reduce health inequities)
	  ○ The broad determinants of health
	Aim of the framework: High quality, relevant research is generated and used to improve policy and program effectiveness which will lead to better population health and reduced health inequities in NSW (p8)
	Key strategy (S2) (p8). Maximise the use of research to improve population health and reduce health inequities
	S2.1: Facilitate synthesis of and access to research evidence
	• 2.1.3 Ensure that the use of existing NSW Health population health datasets promotes equity
	  ○ exploring gaps in data collection systems with the aim of providing enhanced demographic information for the purpose of measuring equity (p19)
	  ○ exploring other methods of monitoring health of marginalised groups through health data linkage, and using data from social welfare agencies
	S2.2: Develop policy and practice environments that value and use research evidence
	S2.3: Foster research environments that promote the use of research evidence in policy and practice
	Research priorities (p12):
	• Relevance to addressing health inequities within the NSW population

NSW Get Healthy Information and Coaching Service: The first five years 2009-13.	Priority groups for the GHS: • Aboriginal people • Culturally and linguistically diverse communities • People from low socio-economic areas • Those living in remote, rural and regional areas if NSW • People at risk of diabetes GHS Aboriginal program: aboriginal specific resources and three extra coaching calls Pro-active marketing to target adults from lower socioeconomic areas Demographics of participants reported includes education, Aboriginal status, SEIFA and remoteness (ARIA index). GHS is attracting participants in the lowest quintiles of advantage with a higher proportion of participants from the 3rd, 4th and 5th quintiles (most disadvantaged) than would be expected from the proportion of NSW adults in those quintiles.

	Greater proportion of participants from regional locations compared to major cities (p.14)
NSW Government Advertising Handbook	7.5% of advertising campaign press expenditure should be placed in ethnic newspapers (p.9) 3% of total government advertising campaign electronic media expenditure is to be placed in ethnic electronic media 10% of press expenditure to be placed in community language (ethnic and indigenous) newspapers 5% of total electronic media expenditure in community language (ethnic and indigenous) electronic media All advertising and public information videos are required to have captioning (for hearing impaired community)
NSW Government Guidelines for Economic Appraisal 2007	Types of benefit (p. 22) • Benefits to consumers not reflected in revenue flows: ○ Equity considerations of pricing policies may result in the service not being charged, however these benefits should be quantified as much as possible or described in detail if quantification is not possible Economic Assessment Of Environmental Impacts • Inter-generational equity principle - the present generation should ensure that the health, diversity and productivity of the environment is maintained or enhanced for the benefit of future generations
Principles and Guidelines for Economic Appraisal of Transport Investment and Initiatives. Transport Economic Appraisal Guidelines 2013	• Not related to health inequalities – however in terms of equity, low-income mobility benefits are incorporated into the analysis. • Infrastructure Australia – a strategic priority is 'Improving social equity and quality of life in our cities and regions'. • Greater equity of access is reported as an unquantifiable benefit of transport interventions (Table 2.1 p. 50) • Social inclusion is a consideration in transport evaluation and
Healthy Urban Development Checklist 2009	• Recognises that population growth, if not carefully planned for and managed may not contribute positively to the health of the community and may perpetuate the health inequalities that currently exist in NSW • Equity is a guiding principle in the development of the checklist. Equity is understood here to mean that access to all aspects of a community (including health, safety, open space, transport and economic development) is fair to all residents regardless of socioeconomic status, cultural background, gender, age or ability
Walking Strategy and Action Plan 2015-2030	Reports walking is the most equitable form of transport for short trips available to people of all ages, incomes and locations.
NSW Healthy Eating and Active Living Strategy: Preventing overweight and obesity in New South Wales 2013-2018	Reducing inequity is one of the guiding principles of the strategy.