Investigating Clinical Pathway Effects in Hospitals: Current Evidence and Proposal for a Realist Approach

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By

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ABSTRACT

Clinical pathways (CPWs) are tools used by healthcare professionals to guide evidence-based practice by improving multidisciplinary communication, teamwork, and care planning to optimize patient outcomes. CPWs are continually developed and implemented in several healthcare settings; however, the evidence of their effectiveness in hospitals is debatable to date. There is no coherent theory that explains how CPWs work in different healthcare settings.

The overall objective of this thesis is to investigate the effects of CPWs implemented in hospitals. The first part (study 1) of this thesis described a statistical method to refine an operational definition for CPWs that is useful for conducting CPWs research in healthcare. The refined operational definition was used to synthesize evidence from CPW literature. The second part (study 2) of the thesis investigated the effects of CPWs in hospitals following the Cochrane systematic review methodology. The key finding in this review was that stand-alone CPWs may reduce in-hospital complications and hospital costs compared to usual care (low-certainty evidence) and it is uncertain whether stand-alone CPWs reduces the length of hospital stay or improve adherence to recommended practice by healthcare providers (very low-certainty evidence). The final section of the thesis (study 3) is a realist review protocol following the realist methodology to describe an evidence-based approach for developing a realist program theory with the aim of filling the theoretical void on how clinical pathways work in hospitals to generate intended outcomes.

Taken together, these studies make a valuable addition to the growing body of research on clinical pathways implemented in hospitals. There is an urgent need to develop an internationally agreed definition for clinical pathways that can inform the development of plausible theories on how they work in hospital environments.

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LIST OF ABBREVIATIONS

CBA:	Controlled before-after study
CCEMG-EPPI:	The Campbell and Cochrane Economics Methods Group (CCEMG) and the Evidence for Policy and Practice Information and Coordinating Centre (EPPI-Centre)
CPW:	Clinical pathway
EPOC:	Cochrane Effective Practice and Organisation of Care Group
GDPD:	Gross Domestic Product Deflators
GRADE:	The Grading of Recommendations Assessment, Development and Evaluation
HC:	Hospital care
IOM:	Institute of medicine
ITS:	Interrupted time-series study
ICC:	Intracluster correlation coefficient
MD:	Mean difference
NRCT:	Non-randomised controlled trials
PDSA	Plan-Do-Study-Act
PC:	Primary care
PHC:	Primary health care
PRISMA:	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO:	International prospective register of systematic reviews
RCT:	Randomised controlled trials
SPSS:	Statistical Package for the Social Sciences
SMD:	Standardized mean difference
WMD:	Weighted mean difference
CMO:	Context-mechanism-outcome
EAP:	Explanatory account propositions

CHAPTER 1: GENERAL INTRODUCTION

1.1 Problem Statement

Due to the global call for improvement in the quality of healthcare services delivered in hospitals, clinical pathways have emerged as an intervention to help address quality gaps during the delivery of patient-centered care [1, 2]. However, there is conflicting evidence and an ongoing international debate on the effects of clinical pathways in hospitals [3]. While some studies evaluating clinical pathways effects in hospitals reported beneficial outcomes, others found no effect or unwanted outcomes [3]. Scarce healthcare resources are continually expended for the development, implementation and evaluation of clinical pathways in hospitals. To date, there is weak evidence to support the impact of clinical pathways on patient and health system outcomes. It is therefore timely to investigate the true effects of clinical pathways in hospitals and further strengthen the evidence base for health planning and decision making purposes.

1.2 Clinical pathways and their potential to improve quality of healthcare

Globally, health systems are continuously searching for effective and efficient ways to provide patient care without comprising quality [4]. The Institute of Medicine (IOM) defines quality as "the degree to which health services for individuals and populations, increase the likelihood of desired health outcomes and are consistent with current professional knowledge" [5]. About two decades ago, the IOM released two landmark reports on safety and quality in healthcare; *To Err is Human and Crossing the Quality Chasm* [1, 6]. Both reports from the IOM aimed at sensitizing healthcare stakeholders to prioritize the reduction of adverse events and preventable medical errors associated with patient care. Ever since, health systems, healthcare professions and healthcare institutions have focused on the need to improve the quality of health care delivery to deliver optimum value.

The incorporation of new evidence into clinical setting or practice is a daunting task for many healthcare managers and care providers. The enormity associated with sorting and prioritizing clinical evidence to improve patient care presents challenges to many healthcare systems to date [7, 8]. The slow uptake of updated clinical evidence into practice predisposes patients to harm, poor outcomes and increased healthcare costs [8]. This problem is referred to as the "evidence-practice gap" which contributes to undesired variation in patient

outcomes, e.g. morbidity and mortality rates. James Brent, a renowned physician in clinical quality improvement and patient safety referred to the three most common causes of undesired variation in healthcare as "the complexity of clinical practice, a lack of valid information identifying best care across a range of choices, and physicians' continued reliance upon subjective recall in making clinical judgments" [9]. Collectively, these factors contribute to errors and unintended patient outcomes in healthcare settings.

Over the years, quality improvement initiatives such as Lean, Six-sigma, Continuous Quality Improvement, etc., and tools such as surgical checklists, clinical pathways, etc., have been implemented in different healthcare contexts to reduce variation and achieve health system goals [10-13]. Clinical pathways (CPWs) are developed in healthcare as a strategy for improving care processes by translating guideline recommendations into a local context to provide state-of-the-art care [14]. Also, CPWs are often implemented as knowledge translation tools that recommend the best available evidence for a clinical condition or practice area during an episode of care [14-16]. Since their evolution in the 1980s, CPWs have been widely implemented in hospital care and gradually implemented in primary care settings [15].

With the continuous rise in the global burden of chronic diseases, variation in clinical practices and increased costs associated with poor quality patient care, [17] CPWs have emerged as an improvement tool in many health systems to help address these issues [18]. When implemented appropriately, CPWs have the potential to support clinical decision-making processes to improve the quality of patient care. Several studies have demonstrated the potential of CPWs to streamline care processes, contain cost, foster patient-centered care and promote teamwork in hospital environments [19-21]. While some studies found improvement in patient outcomes [22], reduced length of hospital stay [23] and hospital costs [24], others reported no difference or worsened outcomes [25, 26] after using a clinical pathway for patient management. Despite the number of resources and time dedicated to the development and implementation of CPWs in hospitals, their effects are debatable to date. Therefore, it is timely to investigate how CPWs work and to further assess their effectiveness in hospital environments. The literature synthesis on effects of CPWs in hospitals will inform future governmental and organizational effort to bridge quality gaps in patient care provided in hospitals.

1.3 Evidence base for clinical pathways in healthcare

To date, useful evidence of complex healthcare interventions is limited and varied [27]. CPWs are complex interventions with different interacting components that are developed as paper or electronic-based documents [14]. The widespread use of CPWs in hospitals has been reported in the USA, Australia, Canada, Europe, and Asia [14]. With the enormous resources committed to the development and implementation of CPWs in healthcare to reduce practice gaps across health systems and improve care coordination, the evidence on their effectiveness in healthcare settings is inconclusive to date [14, 28].

Different types of evaluation designs, specifically observational methods are frequently used to assess the effects of complex interventions in healthcare including CPWs [29]. This notion may be due to the cost-effectiveness associated with implementing observational designs compared to experimental trials that may be impractical to carry out in real-world settings. However, variation in the evaluation approaches also contributes to the differences in the outcomes observed when examining effects from similar contexts [30]. Observational study designs have been purported to have the propensity for bias that distorts effect estimates and are often excluded in quantitative evidence synthesis, e.g. Cochrane systematic reviews of complex health interventions [31].

Randomized trials are traditionally referred to as the gold standard for conducting quantitative-systematic reviews [32]. A Cochrane systematic review on effects of CPWs in hospitals care by Rotter et al. (2010) identified studies that reported positive effects on patient outcomes such as reduced in-hospital complications, after the implementation of CPWs in hospital settings [14]. However, the review also found undesired results such as increased mortality, increased re-hospitalization rates, reduced provider satisfaction among others, in similar hospital settings [14].

Building on the systematic review by Rotter et al. (2010) and to align with the Methodological Expectations for Cochrane Intervention Reviews (MECIR) standards for conducting systematic reviews [33], this thesis similarly followed the Cochrane Effective Practice of Care (EPOC) care group [34] approach to update the evidence base on the effects of CPWs in hospitals.

1.4 Clinical pathways for hospital care

CPWs have been implemented in hospitals since the 1980s and their use is continually on the rise in many health systems [35]. In 2006, Vanhaect and colleagues reported on the prevalence of CPWs in 23 countries via an international survey [36]. The total number of individual patients on a pathway was used to estimate the overall prevalence reported in the study. The study showed that there was substantial variation in the use of CPWs across the countries surveyed [36]. Although modest increases in the utilization and uptake of CPWs were reported in Wales, Scotland and the United Kingdom, the overall usage was rated as "low" [36]. The survey did not provide information on the type of clinical conditions assessed.

The updated version of the survey published in 2014 included data from 163 countries with a 25% response rate [37]. In line with the previous study, the survey found significant differences in the use of pathways and suboptimal involvement of patients in pathway development [37]. Both studies called for the creation of an evidence base for CPWs and a call for better understanding of CPWs to support clinicians, patients and health policymakers during decision-making processes.

As noted in the previous section, hospitals are complex healthcare environment with several interacting components complimenting each other to deliver quality patient care [38]. Contextual factors such as collaboration, team relationships, organizational priorities, patient and staff engagement among others are important factors that can influence the successful implementation, uptake and sustainability of CPWs in healthcare settings [39]. Due to the quality of reporting of the included studies in the Cochrane review by Rotter et al. in 2010, it was challenging to identify contextual elements associated with successful CPW implementation. While statistical pooling as done by Rotter et al. (2010) showed limited evidence that CPWs have the potential to decrease the number of in-hospital complications and improve professional documentation among healthcare professionals, a realist approach may better suited to address these complex contextual factors [14].

1.5 Issues with clinical pathways research

Like other complex interventions, integration of CPWs in healthcare environments is faced with issues regarding conceptualization, implementation, evaluation and sustainability in

healthcare environments. A literature review on definitions for CPWs by De Blesser et al. (2006) identified 37 concepts used to describe CPWs [40]. Examples of the CPW definitions identified include critical pathway, care maps, algorithm, protocol, etc. [40]. This variation in the definition of a CPW implies that there is no internationally agreed-on definition or a commonly used language for CPWs. The difference in definition of CPWs makes it difficult to synthesize, appraise and collate evidence to assess their effects in different healthcare settings.

Owing to the variation in the number of resources committed to the development and implementation of CPWs, their effectiveness in practice settings varies [14]. When pathways are implemented top-down in a healthcare setting, they may be viewed as "cookbook medicine," and their uptake may be suboptimal with little or no effect. However, in environments where there is a shared vision with organizational support, they are more likely to be embedded with little chaos [41]. It is probable that the ongoing confusion regarding CPWs effects in healthcare is related to challenges in the conceptualization of this quality improvement tool. This confusion makes the identification, cataloging, synthesizing and development of an evidence base for CPWs effectiveness difficult.

Kinsman et al. (2010) developed a four-criteria checklist to assist researchers in the objective identification of CPWs studies from the literature and advanced the methodological direction towards the development of an evidence base for CPWs [16]. The research undertook a four-stage process to create the first operational definition for conducting the first Cochrane systematic review on the effects of CPWs in healthcare published in 2010. This thesis aims to update the evidence base for the effects of using CPWs in healthcare with a focus on hospitals.

1.6 Systematic Reviews and Clinical pathways

Over the years, researchers have called for the judicious use of evidence-based medicine in healthcare settings [42]. They argued that the use of weak or outdated evidence during patient care increases the risk of significant harm to patients and increased costs to the health system. With the enormous volume of literature published daily about new knowledge, diagnostic tests or medical procedures, it is challenging for clinicians to be up to date with current evidence in their practice area [43]. It is frequently stated that an average of 17 years is

required for research evidence to reach clinical practice [43]. This time lag is unacceptable due to the potential for a significant level of harm for patients, especially those who are critically ill. The gap in translating research knowledge into practice settings is the focus of many organizations such as the Cochrane Collaboration and the Joanna Briggs Institute which develop, disseminate and support efficient ways to present evidence in a rigorous, reliable, portable and useful format [44, 45].

A systematic review was initially used to answer the questions asked by this thesis because it was purported to be an unbiased and cost-effective option to rigorously and broadly appraise the international literature on the true effects of clinical pathways in hospitals. A systematic review (SR) is defined as a methodical approach to identify, assess and synthesize published primary studies to investigate a specific research question [46]. "It attempts to gather all empirical evidence that fits pre-specified eligibility criteria into answering a specific research question" [47]. When conducted appropriately, SRs may provide reliable findings from which valuable conclusions can be drawn and policy decision made. In contrast to a traditional narrative review (NR) that aim to provide an overview of a research topic, a SR applies rigorous strategies to systematically gather evidence around a focused research question [48].

A systematic review protocol is usually written to describe the systematic process and guidelines to be followed in answering the research questions. The protocols are typically registered in a database, e.g. PROSPERO [49] and the aim is to permit objective reporting and increase the replicability of the review. Where applicable, meta-analysis is an add-on to systematic reviews. It is a statistical pooling of similar underpowered studies to examine intervention effects. The five necessary steps of conducting of a systematic review include (1) identifying the research question; (2) literature search (3) study quality assessment; (4) synthesizing and summarizing the evidence and (5) interpret findings [50]. With a positivist lens to quantify the effects of clinical pathways in hospitals, this thesis follows the systematic review methodology.

1.7 The Cochrane Effective Practice and Organisation of Care Group (EPOC)

For 20 years, Cochrane has produced systematic reviews of primary research on human health and health policy, and these have been internationally recognized as the highest

standards in evidence-based recommendations [51]. A sub-group of Cochrane, EPOC, focuses on reviews of interventions that are designed to influence or improve professional practice and the delivery of effective health services in healthcare organizations [34]. This thesis follows the evidence synthesis approach recommended by the Cochrane EPOC group for conducting systematic reviews of complex interventions. Table 1-1 lists the types of study designs included in Cochrane EPOC reviews to evaluate complex interventions such as clinical pathways [52].

Table 1–1. **Cochrane EPOC study designs**

Type of study	**Study characteristics**
Randomised controlled trial (RCT) OR randomised trial	An experimental study in which people are allocated to a control and an experimental group using random assignment to prevent bias. Cluster randomised studies are experimental studies where a group of subjects (as opposed to individuals) are randomised. Cluster randomised studies reduce or eliminate the contamination of care providers during clinical trials.
Non-randomised controlled trial (NRCT) OR non-randomised trial	An experimental study in which people are allocated to different interventions using methods that are not random.
Controlled before-after study (CBA)	A study in which observations are made before and after the implementation of an intervention, both in a group that receives the intervention and in a control group that does not.
Interrupted-time-series study (ITS)	A study that uses observations at multiple time points before and after an intervention ('the interruption'). The design attempts to detect whether the intervention has had an effect significantly greater than any underlying trend over time.

Source: Cochrane website: https://epoc.cochrane.org/sites/epoc.cochrane.org/files/public/uploads/EPOC Study Designs About.pdf

The preliminary results of the systematic review update conducted by this thesis likewise showed inconclusive evidence on the effects of clinical pathways in hospitals. During the review of the meta-analytic summaries for all the multiple comparisons assessed by the systematic review, it became apparent that the systematic review methodology was not

ideally suited for evaluating complex health interventions such as CPWs and might be a key reason for the dearth of quality evidence generated on this topic so far.

With the aim of informing future researchers, this thesis described another methodological approach (realist synthesis) developed by Ray Pawson to evaluate complex health interventions including CPWs [53]. In contrast to systematic reviews, realist methods utilize multiple sources of data including qualitative studies to elicit theoretical accounts of how an intervention works or not. Also, the realist analytical framework ensures the incorporation of contextual factors that contribute to the successful implementation of CPWs in different hospital environments. This approach is in stark contrast to systematic reviews where contextual factors are disentangled from the other intervention components resulting in difficulty in identifying recipe for intervention success, equivocal results, and limited use for policy [54].

1.8 Realist Reviews

The use of theory is vital to the field of implementation science because they help us to understand how interventions work and achieve their intended outcomes [55]. Apart from the use of systematic reviews for evaluating complex interventions, realist synthesis is another viable approach to generate evidence on complex interventions for policy and decision making in healthcare [56]. “Realist synthesis focuses more explaining “why,” “how,” “for whom” and “to what extent” interventions work” [56]. The goal of a realist synthesis is to develop a program theory that explains how interventions or programs work. In contrast to systematic reviews, the purpose of a realist review is to develop a program theory that describes how interventions or programs work [57]. Realist reviews are theory building exercises that attempt to understand multiple layers of causality and the associated mechanisms that generate multiple impacts in different contexts. Since healthcare interventions are theory incarnate [58], realist approaches are more suited in answering key policy questions that involve social interactions between multiple actors in different health contexts such as CPWs.

Initially developed by Ray Pawson, realist reviews follow realist philosophy which is grounded in social science and assumes that the world is real and humans interact with reality which limits or constructs our interpretation [57]. Realist approaches acknowledge the role of

contextual factors in modulating mechanisms that account for multiple outcomes observed at the micro, meso and macro level [57]. In contrast to traditional systematic reviews, realist reviews utilize numerus sources of information (published and grey) and study designs (qualitative and quantitative) related to the program theory to answer its research questions [59]. The analysis in a realist review focuses on eliciting the contexts-mechanisms-outcome (CMO) configurations that are used to develop, refute or refine the intervention program theory [60]. Because realist review identifies critical elements and mechanisms that can explain causality patterns in different contexts, they are crucial for implementation science [61]. Following a realist approach, this thesis also attempts to describe in depth the steps required to create a program theory for CPWs in hospitals.

1.9 Thesis objectives

The objectives of this thesis are to:

1. Develop a working definition for clinical pathway research
2. Assess the effects of clinical pathways in hospitals
3. Propose a method for developing a realist program theory for clinical pathways in hospitals.

1.10 Ethics approval

This research was deemed ethics exempt by the University of Saskatchewan Behavioural Research Ethics Board (BEH 13-255).

1.11 Thesis structure

The research is presented in a manuscript-style thesis format, which consists of three parts, each prepared as a stand-alone manuscript. Collectively, the papers contribute to the overarching research purpose to investigate the effects of CPWs in hospital care and to propose an alternative research method for developing a theory for CPWs in hospitals. Manuscripts are presented as single thesis chapters with their corresponding methods following this general introduction section (Chapter 1).

Based on the lack of agreement for the definition of a clinical pathway and following the Cochrane systematic review approach to investigate CPW effects, this thesis began by refining an exisiting operational definition for a clinical pathway that is sensitive enough to capture relevant studies in broader healthcare contexts. This methodological approach is

necessary to easily permit the objective identification of relevant CPW studies for conducting the systematic review. This process will ensure only studies considered as CPWs studies were considered for analysis attempt to reduce confounfing bias that can impact the findings of the systematic review.

The first manuscript (Chapter 2), "What is a clinical pathway? Refinement of an operational definition to identify clinical pathway studies for a Cochrane systematic review" contributes to the evidence base for methods and describes the process of identifying relevant literature for CPWs research. The manuscript focuses on the process of refining an operational definition for CPW research and proposes the use of the refined definition for the future synthesis of CPWs literature. The refined definition for a CPW was used to conduct the systematic review update to assess the effects of clinical pathways in hospitals in this thesis.

The second manuscript (Chapter 3), "Clinical pathways for secondary care and the effects on professional practice, patient outcomes, length of hospital stay and costs" contributes to the evidence base on the effects of clinical pathways in hospital settings. Following the EPOC methods for conducting systematic reviews, the manuscript updates and adds to the body of evidence on the effects of clinical pathways implemented in hospitals on patient outcomes, professional practice, length of stay and costs.

Upon completion of the systematic review update on the effects of CPWs in hospitals following the Cochrane EPOC methodology, it was apparent that a different approach was needed to answer the research questions asked by this thesis. This was because majority of the qualitative studies that could have better inform the evidence generated by the systematic review have been excluded and it was difficult to attribute clinical pathway success or failure to intervention effects alone. This prompted an alternative way to investigate the effects of clinical pathways in hospitals and a realist approach was proposed by this thesis.

The third manuscript (Chapter 4), "Development of a program theory for clinical pathways in hospitals: protocol for a realist review" contributes to the evidence base on theoretical methods for implementing clinical pathways in hospitals. The manuscript describes a process for developing a program theory for implementing clinical pathways in hospitals.

The final thesis section is the “Discussion and Conclusion” (Chapter 5), which summarizes the research results from all the independent research and provide general conclusions and recommendations based on the findings from the entire thesis.

CHAPTER 2: WHAT IS A CLINICAL PATHWAY? REFINEMENT OF AN OPERATIONAL DEFINITION TO IDENTIFY CLINICAL PATHWAY STUDIES FOR A COCHRANE SYSTEMATIC REVIEW (MANUSCRIPT 1)

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2.1 Abstract

Clinical pathways (CPWs) are a common component in the quest to improve the quality of health. CPWs are used to reduce variation, improve quality of care, and maximize the outcomes for specific groups of patients. An ongoing challenge is the operationalization of a definition of CPW in healthcare. This may be attributable to both the differences in definition and a lack of conceptualization in the field of clinical pathways. This correspondence article describes a process of refinement of an operational definition for CPW research and proposes an operational definition for the future syntheses of CPWs literature. Following the approach proposed by Kinsman et al. (BMC Medicine 8(1):31, 2010) and Wieland et al. (Alternative Therapies in Health and Medicine 17(2):50, 2011), we used a four-stage process to generate a five criteria checklist for the definition of CPWs. We refined the operational definition, through consensus, merging two of the checklist's criteria, leading to a more inclusive criterion for accommodating CPW studies conducted in various healthcare settings. The following four criteria for CPW operational definition, derived from the refinement process described above, are (1) the intervention was a structured multidisciplinary plan of care; (2) the intervention was used to translate guidelines or evidence into local structures; (3) the intervention detailed the steps in a course of treatment or care in a plan, pathway, algorithm, guideline, protocol or other 'inventory of actions' (i.e. the intervention had time-frames or criteria-based progression); and (4) the intervention aimed to standardize care for a specific population. An intervention meeting all four criteria was considered a CPW. The development of operational definitions for complex interventions is a useful approach to appraise and synthesize evidence for policy development and quality improvement. This step was pivotal to permit the objective identification of CPW studies required to conduct the Cochrane systematic review on effects of CPWs in hospitals.

Keywords

Clinical pathways Quality health improvement Systematic reviews

2.2 Background

The optimization of patient safety and quality in healthcare remains the primary focus of quality improvement initiatives [1]. The health quality improvement movement has stimulated researchers and managers in healthcare to be innovative in developing new ideas to address issues relating to patient safety and sub-standard care [2, 3]. Several quality improvement concepts, such as Lean, Plan-Do-Study-Act cycles, Continuous quality improvement, etc., and tools such as clinical pathways (CPWs), surgical checklists, etc., have been implemented in a variety of healthcare settings to sustain and support these continuous quality improvement concepts.

CPWs are a common component of these improvement initiatives. They aim to organize and standardize care processes, thus maximizing patient outcomes and improving organization efficiency [4, 5]. Originating in the USA, CPWs have been used in healthcare since the 1980's. Their goal is to improve patient outcomes, such as mortality rate and others, while containing costs and without compromising quality [6, 7]. Different terms, including care maps, critical pathways, local protocols or algorithms are used to describe the construct of CPWs and may be developed as paper-based or electronic documents [8]. The widespread use and prevalence of CPWs in hospitals is reported in the USA, Australia, Canada, Europe, and Asia [5, 9]. In Canada, CPWs are viewed as a patient-informed knowledge translation tool to ensure clients receive the best available care [10, 11]. The myriad of terms used to describe a CPW has led to conceptual confusion in the field of pathway research.

2.3 Aim and purpose of this paper

The present paper aims to (1) describe the process of refinement and rigorous testing used to obtain an 'operational definition' for CPW research, and to (2) propose an operational definition for future syntheses of CPWs literature.

This paper builds on the initial evidence, appraised by Kinsman et al. (2010) [7], where a team of Cochrane review authors developed a set of criteria for the practical operational definition of a CPW.

2.4 Purpose and conceptualization of CPWs

CPWs are mainly implemented for specific groups of patients meeting a pre-specified criterion. The implementation of CPWs may be driven by a variation in the quality of care and outcomes for patients with similar health conditions: cardiovascular, respiratory, surgical, cancer, etc. Usually, the aim of the implementation is to reduce a pre-identified variation in patient outcomes and costs and, more recently, to keep patients and families informed about their course of treatment or care.

There are several challenges to CPW research, similar to other complex health service implementation efforts such as conceptualization, implementation, evaluation, and sustainability [8, 12]. De Blesser et al. (2006) [13] identified 37 primary definitions for CPWs used in the literature and various terms have been used to describe CPWs in different health settings. There is not a standard definition to identify CPW studies. This paper aims to fill that gap, by proposing a method for the development and refinement of an operational definition for CPW research in healthcare. Clarity of the CPW concept, especially for research, is pivotal to the development of an evidence base; a base that policymakers, healthcare professionals, patients, and other front-line users can refer to for rational decision-making.

2.5 Working definition on CPWs

In 2010, a team of Cochrane authors developed an operational definition for CPWs. The definition can be used to appraise and synthesize international literature on CPWs in hospitals [7]. From three seminal articles [13, 14, 15] on CPWs, five operational criteria for CPW definition were rigorously developed [5, 7]. The criteria were subsequently tested on 10 CPWs articles among the review team in a two-stage process. After achieving 100 % agreement, they were applied in the identification of relevant articles for a Cochrane systematic review on CPWs in hospitals published in 2010 [5].

Recent attempts to apply the criteria to CPWs studies conducted in primary care was problematic due to poor reporting of the CPW intervention in the literature. A modification of the original five operational criteria was proposed and agreed by all review authors. This change increased the sensitivity of the operational definition to accommodate relevant

literature on CPWs, spanning across a broader context of healthcare settings, including primary care.

2.6 Methods

Developmental process and refinement of an operational definition for CPWs

In 2010, a team of Cochrane review authors undertook a four-stage process to develop a list of criteria to generate an operational definition for CPWs in hospitals. This followed a methodology proposed by Kinsman et al. (2010) [7] and Wieland et al. (2011) [16]. The process required (1) identification of articles exploring the scope and definition of CPWs (or similar terms); (2) synthesis of previously suggested components and generation of draft criteria for testing; (3) pilot testing the level of agreement between review authors when applying criteria to identified studies; and (4) modification of the criteria to maximize agreement between review authors [7].

The rigorous testing of the criteria with 10 CPW articles, and with 100 % agreement among review authors, led to the development of a practical operational definition for CPWs: (1) the intervention was a structured multidisciplinary plan of care; (2) the intervention was used to channel the translation of guidelines or evidence into local structures; (3) the intervention detailed the steps in a course of treatment or care in a plan, pathway, algorithm, guideline, protocol or other 'inventory of actions'; (4) the intervention had timeframes or criteria-based progression (that is, steps were taken if designated criteria were met); and (5) the intervention aimed to standardize care for a specific clinical problem, procedure or episode of healthcare in a specific population [7].

An intervention was a CPW if it met the first criterion together with three of the other four criteria. The operational definition further supported the identification of relevant full text studies that were eventually used in finalizing the first systematic review on CPWs in hospital care in 2010 [7].

2.7 Rationale for refinement of the operational definition for CPWs

A recent attempt by the review team to conduct a systematic review on CPWs in primary care was hampered by the challenge of applying the above operational definition in a primary care setting, with the major problem during the protocol development for the systematic review [17] being the identification of relevant CPW studies in a primary care context.

This is due to the requirements of criteria numbers 3 and 4. The application of these two criteria is problematic, because several articles explicitly met criterion 3 but not criterion 4, or vice versa, and thus had to be excluded.

TR and LK pilot tested the new criteria on five CPWs studies [18, 19, 20, 21, 22] in primary care identified during the protocol development for a systematic review on CPWs in primary care [17]. Consensus was reached among review authors that, by merging the two criteria, the definition would be more inclusive. Thus, the new operational definition for CPWs was narrowed to a four criteria checklist.

2.8 Results

Pilot test of the new operational definition for consistency

Two review authors (CP and AB) independently pilot-tested the refined operational definition containing the four criteria-checklist, with LA serving as an arbitrator to resolve any disagreement during the process. The two review authors had no contact during the pilot test. The pilot test was conducted on 20 articles selected randomly from the 27 included articles from the 2010 Cochrane systematic review on CPWs in hospitals. The aim of the pilot-test was to ensure that the number of articles retrieved for the full text extraction phase in 2010 remained unchanged when using the modified criteria. The results of the pilot-test were collated and a reliability analysis for qualitative variables was estimated using the kappa statistic [23]. Statistical analysis was conducted using SPSS V. 22 (SPSS, Chicago, IL). See table 2-1 for data layout.

Table 2–1. **Observed and expected percentage agreement; data layout**

	CP		
AB	Include	Pending	Totals
Include	17^{a}	0^{b}	17^{m1}
Exclude	0^{c}	3^{d}	3^{m0}
Totals	17^{n1}	3^{n0}	20^{n}

Legend: (a) and (d) represent the number of times the two observers agree while (b) and (c) represent the number of times the two observers disagree, m_1 = row total number for inclusions, m_0 = row total number of exclusions, n_1 = column total for inclusions, n_0 = column total for exclusions

Observed agreement =17/20 = 85%

Expected agreement (pe) = [(n1 /n) ∗ (m1 /n)] + [(no /n) ∗ (mo /n)]

Pe = [(17/20) ∗ (17/20)] + [(3/20) ∗ (3/20)] = 0.722 + 0.023 = 0.75

The first independent pilot testing, applying the new criteria to the previously published CPW articles described above, generated 85 % observed and 75 % expected agreement, respectively (Table 2-2). For the reliability analysis, the kappa test statistic was 0.99 with a *P* value <0.001, implying perfect agreement between the two reviewers (Table 2-3).

Table 2–2. Inter-rater reliability analysis of 20 articles on clinical pathways in hospital care; data layout

AB * CP		Cross-tabulation		
Count				
		CP		Total
		1.00	0.00	
AB	1.00	17	0	17
	0.00	0	3	3
Total		17	3	20

AB, reviewer 1; CP, reviewer 2; 1.00, Included; 0.00, Pending

Table 2–3. **SPSS output for Kappa statistic**

Symmetric measures					
		Value	Asymp. Std. Error[a]	Approx. T[b]	Approx. Sig.
Measure of Agreement	Kappa	1.000	0.000	4.472	0.000
N of Valid Cases		20			

Approx. Sig. = *P* value

Refined criteria for CPW operational definition

The four criteria derived from the refinement process described above are (1) Is it a structured multidisciplinary care plan? (2) Is it used to channel the translation of guidelines or evidence into local structures? (3) Does it detail the steps in a course of treatment or care in a plan, pathway, algorithm, guideline, protocol or other 'inventory of actions' (i.e. the intervention had time frames or criteria based progression)? (4) Does it aim to standardize care for a specific clinical problem, procedure or episode of care in a specific population?

Henceforth, an intervention was considered a CPW if it contained all the four criteria in the new operational definition. Subsequently, the new definition will be applied to identify (1) relevant titles and abstracts for an on-going update of a Cochrane systematic review on CPWs in hospitals, and (2) a new Cochrane systematic review on CPWs in primary care.

Prospectively, the systematic review will follow the validated Cochrane Effective Practice and Organization of Care (EPOC) methodology for complex interventions, and will consider randomized controlled trials, non-randomized controlled trials, controlled before and after, and interrupted time series study designs [18].

2.10 Discussion

This article describes the process of development, refinement, and testing of a practical working definition for CPWs. It also supports the inclusion of relevant primary research articles only in our Cochrane systematic review update on CPW effectiveness in hospital and primary care. The initial criteria, rigorously developed in 2010 using the Kinsman et al. (2010) [7] and Wieland et al. (2011) [16] approach for a Cochrane systematic review, is a milestone in the field of CPW research. The first proposed operational definition of a CPW ultimately led to the successful completion of the first Cochrane EPOC review on CPWs in hospitals.

It is imperative to understand that we created an operational definition for CPWs in hospital and primary care settings, rather than undergoing a scientific concept analysis [24]. We propose the development of minimum inclusion criteria and an operational definition for systematic reviews of complex interventions such as CPWs. This is due to the high level of resources required of Walker and Avant's gold standard concept analysis process and the likelihood that the required expertise and time required may not be feasible for healthcare

decision makers or implementers. Our belief is that this approach serves as a preliminary step to ensure all-important studies are catalogued while simultaneously including only the relevant evidence. Future work will be conducted to ascertain the sensitivity of the refined criteria in identifying pathway studies in primary care.

Although it has been established in previous literature that CPWs are complex interventions, this information is not sufficient and useful for the development of an evidence base for CPWs in the international literature. There is variation in the terms used to depict a CPW, therefore referring to a CPW as a complex intervention without standardizing its elements only adds to complexity and confusion towards the attainment of a standard definition. The pilot test for the operational criteria and reliability analysis shows a significant high level of agreement among reviewers. This demonstrates that the resulting criteria have the potential to be clear and objective enough to permit further research relevant to the field of CPWs. This methodology may be refined and applied to similar fields also challenged with the issue of cataloguing and reviewing the evidence for complex health service interventions.

Refining the working definition for a clinical pathway to encompass broader healthcare contexts can help generate and advance a positive discourse towards an internationally agreed definition for CPWs in healthcare. An internationally agreed definition for CPWs in healthcare can benefit researchers by ensuring the identification and inclusion of relevant literature for future CPWs syntheses. This step will also strengthen the internal and external validity of findings from future research and make appropriate policy recommendations that benefit patients and the health system. From a healthcare providers' perspective, an internationally agreed definition for CPWs will alleviate the confusion among care providers on the components of a CPW. Also, this move will improve the shared understanding and goals of CPWs which is vital for care decision making processes to maximize clinical outcomes for patients.

2.11 Conclusion

Worldwide CPW implementation and usage in healthcare is on the rise. The lack of an agreed-upon definition of a CPW and what is not a CPW remains a significant challenge for many CPW researchers and clinicians. This paper describes the process of developing, refining, and pilot testing a set of criteria to be used for a practical operational definition for

CPWs in healthcare, following the Kinsman et al. (2010) [7] and Wieland et al. (2011) [16] approach.

Future researchers considering the development, implementation, and evaluation of CPWs should adopt the developed definition or modify them to fit into their future research. This step will advance the discourse towards an internationally agreed-upon definition of what constitutes a CPW in healthcare and create a practical impact from a research, healthcare provider and patient standpoint.

TRANSITION FROM CHAPTER 2 TO CHAPTER 3

The refined operational definition for a clinical pathway provides a working definition to identify, catalog and appraise the clinical pathway literature. The following four criteria for an operational definition for a CPW includes:

1. the intervention was a structured multidisciplinary plan of care;
2. the intervention was used to translate guidelines or evidence into local structures;
3. the intervention detailed the steps in the course of treatment or care in a plan, pathway, algorithm, guideline, protocol or other 'inventory of actions' (i.e., the intervention had time-frames or criteria-based progression);
4. the intervention aimed to standardize care for a specific population. An intervention meeting all four-criteria was considered a CPW

The next manuscript will use the refined operational definition to update a Cochrane systematic review and examine the effects of CPWs in hospitals.

CHAPTER 3: CLINICAL PATHWAYS FOR SECONDARY CARE AND THEIR EFFECTS ON PROFESSIONAL PRACTICE, PATIENT OUTCOMES, LENGTH OF STAY AND HOSPITAL COSTS - A COCHRANE SYSTEMATIC REVIEW UPDATE (MANUSCRIPT 2)

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3.1 Abstract

Background

Clinical pathways are structured, multidisciplinary care plans used by health services to detail essential steps in the care of patients with a specific clinical problem. They aim to translate evidence into practice and optimize clinical outcomes, whilst maximizing clinical efficiency. This is the first update of the original Cochrane review by Rotter et al. (2010) guided by the study protocol from Rotter et al. (2007).

Objectives

To investigate the effect of clinical pathways (CPWs) on professional practice, patient outcomes, length of hospital stay, and costs in hospital settings, as compared to usual care.

Search methods

For this update, we searched the following databases from 7 August 2014 to 1 March 2017: Cochrane Central Register of Controlled Trials (CENTRAL) and bibliographic databases including MEDLINE, Embase, CINAHL, Amed, PsycINFO, HMIC, Cochrane-HTA, ClinicalTrials.gov, WHO ICTRP, Cochrane-NHS EED and Global Health. We also searched the reference lists of relevant articles.

Selection criteria

We included randomised trials, non-randomised trials, interrupted time series studies and controlled before-after studies.

Data collection and analysis

Two review authors independently screened all titles, abstracts and full text manuscripts to assess eligibility and methodological quality. We grouped and assessed studies according to those comparing clinical pathways with usual care and those comparing clinical pathways as part of a multifaceted intervention with usual care.

Main results

We identified 12 additional studies from the updated searches. Overall, 39 studies involving 15,911 participants met the study inclusion criteria for final analysis. Thirty-two studies compared stand-alone clinical pathway intervention with usual care, and seven studies compared clinical pathways (as part of a multifaceted intervention) with usual care. Twenty-eight studies focused on non-invasive clinical conditions.

Stand-alone clinical pathway interventions

Stand-alone CPWs interventions may reduce 90-day mortality in hospitals (odds ratio (OR) 0.83, 95% confidence interval (CI) 0.62 to 1.12; 6 studies, 3828 participants; low-certainty evidence). Stand-alone CPWs interventions may reduce hospital readmissions up to six months (OR 0.74, 95% CI 0.48 to 1.15; 7 studies, 1391 participants; low-certainty evidence). Stand-alone CPWs may reduce in-hospital complications (OR 0.46, 95% CI 0.33 to 0.64; 7 studies, 2012 participants; low-certainty evidence). Overall, it is uncertain if stand-alone CPW interventions reduce length of hospital stay (Mean difference (MD) -0.83 days 95% CI -1.21 to -0.45, 20 studies, 5782 participants; very-low certainty evidence). Stand-alone CPWs interventions may reduce hospital cost (MD USD -1171.52, 95% CI -1835.86 to -507.18; 7 studies, 1264 participants; low-certainty evidence). Overall, it is uncertain if stand-alone CPW interventions improves adherence to recommended practice in hospitals (studies were not combined; very-low certainty evidence).

Multifaceted clinical pathway interventions

Statistical meta-analysis was not feasible for all the outcomes examined under this comparison group due to insufficient number of primary studies. Overall, it is uncertain if multifaceted CPW interventions reduce 90-day mortality (studies were not combined; very-low certainty evidence). It is uncertain if multifaceted CPW interventions reduce hospital readmissions (studies were not combined; very-low certainty evidence). Multifaceted CPW interventions may reduce length of hospital stay (studies were not combined; low-certainty evidence). Finally, it is uncertain if multifaceted CPW interventions reduce hospital costs (studies were not combined; very-low certainty evidence)

Authors' conclusions

The findings suggest that stand-alone clinical pathways may reduce in-hospital complications and hospital costs compared to usual care (low-certainty evidence). It is uncertain whether stand-alone clinical pathways reduce length of hospital stay because the certainty of evidence is very-low. Multifaceted clinical pathway interventions implemented in hospitals compared to usual care make little or no difference on hospital readmissions and length of stay (low-certainty evidence). It is uncertain if multifaceted clinical pathway interventions reduce 90-day mortality and hospital costs because the certainty of evidence is very-low. Future research should ensure the use of rigorous evaluation designs and report on implementation factors used during the pathway development. Also, economic evaluations of clinical pathways are needed to help healthcare mangers and policy makers make important decisions on the timing and level of implementation of clinical pathways.

How up-to-date is this review?

The review authors searched for studies that had been published up to 1 March 2017.

3.2 Background

3.2.1 Description of the condition

With continuous advocacy for patient-centered care by the public, health systems are continually faced with the task of delivering safe and high quality services to patients [62]. The adoption of clinical pathways worldwide is gradually on the increase and substantial resources have been expended on pathway development, implementation, and sustenance in hospitals [63]. However, individual studies investigating the impact of clinical pathways (CPWs) have reported conflicting outcomes [14]. Some studies found that the introduction of CPWs for different types of clinical conditions such as deep vein thrombosis [64], community acquired pneumonia [65] and septic shock [66] can reduce the length of hospital stay, while others such as Trombetti et al. (2013) [67] and Bernard et al. (2011) [68] found increased or no benefit regarding length of hospital stay for malnourished and diabetic patients respectively.

Rigorous evaluation of the effectiveness of CPWs in hospitals and improved understanding of the reasons behind their success or failure, are necessary before additional resources are expended on developing and implementing more CPWs. There is limited research on theories underpinning how CPWs work in different healthcare contexts. Furthermore, there is paucity of information reported on successful implementation strategies for CPWs in different hospital settings. This information is needed to attribute the success or failure of a CPW to the implementation process used in the study [41].

3.2.2 Description of the intervention

CPWs aim to link evidence to practice for specific health conditions and, therefore, optimize patient outcomes and maximize clinical efficiency [69]. For this review, CPWs are defined as structured multidisciplinary care plans which detail essential steps in the care of patients with a specific clinical problem [14]. They support the translation of clinical guidelines into local protocols and clinical practice [70]. Whilst clinical guidelines provide generic recommendations, CPWs detail the local structures, systems and time-frames to address these recommendations. With the myriad of terms used to describe a CPW, they are also referred to as 'integrated care pathways', 'critical pathways', 'care plans', 'care paths', 'algorithms' and 'care maps' [15]. In addition to the support of evidence-based practice, CPWs have been

proposed as a strategy to optimize resource allocation in a climate of rising healthcare costs [71] as they may improve organizational efficiency [15].

3.2.3 Clinical pathway definition

A three-stage process was undertaken to develop an operational (working) definition for a CPW. This process was described in the previous version of this review Rotter et al. (2010) [14]. Recently, the operational definition was refined following the rigorous approach suggested by Kinsman et al. (2010) [16] and Wieland et al. (2011) [72] to accommodate relevant literature on CPWs, spanning across a broader context of healthcare settings, including primary care [15]. Two review team members independently pilot-tested the new definition on 20 studies, randomly selected from the 26 included studies from the first version of this review [14]. LA served as an arbitrator to resolve any disagreement during this process.

The pilot test generated 85% observed and 75% expected agreement, respectively, with a kappa statistic of 0.99 ($P < 0.001$), implying perfect agreement between the two review authors. The following four criteria for a CPW operational definition, derived from the refinement process described above, are (1) the intervention was a structured multidisciplinary plan of care; (2) the intervention was used to translate guidelines or evidence into local structures; (3) the intervention detailed the steps in a course of treatment or care in a plan, pathway, algorithm, guideline, protocol or other 'inventory of actions' (i.e. the intervention had time-frames or criteria-based progression); and (4) the intervention aimed to standardize care for a specific population. We considered an intervention meeting all four criteria to be a CPW [15].

3.2.4 How the intervention might work

CPWs may serve as strategies to reduce variation in hospital practice by providing evidence-based care recommendations. CPWs have the potential to reduce in-hospital complications, improve patient outcomes and enhance efficiency in the health system [14]. They are most commonly developed locally via consensus or adapting clinical practice guidelines and they interact with other contextual and behavioural factors to achieve desirable outcomes [73].

Even though CPWs are used as knowledge translation tools to provide best available evidence during an episode of care, there seems to be no coherent theory that adequately

explain how they work in practice settings [74, 75]. To date, there has been limited research focused on understanding the mechanisms through which CPWs work [76]. Because CPWs are multidisciplinary and have multifaceted components, contextual factors must be considered during their implementation [77]. Several theories to explain the normalization of new knowledge into practice have been identified in the literature [75, 78]. These theories are broadly classified into (1) individual related theories: cognitive theories [79], educational theories [79], and motivational theories [79]; and (2) social interaction and context theories: theories of communication [79], social learning theory [79], team work theories [79], leadership theories [79], theory of organizational learning and culture [79], complexity theory [79], and economic theories [79].

Behavioural change theories emphasizes the incorporation of patient and healthcare professionals' perspectives about existing care standards to facilitate optimum adherence of the pathways [79]. The outcomes of CPW implementation may be most easily detected when prior compliance to clinical standards has been poor, as this leaves potential for substantial improvements. In contrast, CPW implementation in settings demonstrating already highly compliance have detected little or no improvement [39]. CPWs may help to overcome the barrier of updating clinical standards in a practice area that is not feasible for individual healthcare professionals. Organizational theories may provide insights into critical elements from a macro health systems perspective that are required for change and sustainability processes (e.g. barriers to change, organizational culture, vision, and focus).

3.2.5 Why it is important to do this review

This review is part of a series of Cochrane systematic reviews of CPWs, to investigate their effects on professional practice, patient outcomes, length of hospital stay, and hospital costs. This review focuses on the effects of CPWs in hospitals and updates a previous Cochrane Review [14]. The conduct of this update was supported by the Saskatchewan Health Research Foundation. The previous version of this Cochrane Review included 26 studies that met the inclusion criteria at that time from eight countries (Australia, Canada, Japan, Norway, Taiwan, Thailand, UK, and USA). Despite the limitations, the systematic review by Rotter et al. (2010) concluded that clinical pathways are associated with reduced in-hospital complications and improved adherence to recommended practice without negatively impacting on length of hospital stay and hospital costs.

In recent years, there has been a gradual rise in the uptake of CPWs in healthcare contexts, but the evidence regarding their effects are remains inconclusive [37]. In addition to the absence of a standardized definition, heterogeneity in CPW implementation strategies, evaluation approaches, selected outcomes and study design contribute to equivocal findings on effectiveness [15]. A thorough understanding of the implementation process is critical to the success or failure of CPWs in the healthcare environment. This updated Cochrane systematic review aims to rigorously investigate the effects of clinical pathways in hospital settings, especially on professional practice, patient outcomes, length of hospital stay, and hospital costs. It also aims to improve our understanding of implementation strategies that may contribute to the effectiveness of CPWs in various practice settings.

3.3 Objectives

To investigate the effect of clinical pathways on professional practice, patient outcomes, length of hospital stay, and costs in hospital settings compared to usual care.

3.4 Methods

Criteria for considering studies for this review

3.4.1 Types of studies

Following the Effective Practice and Organisation of Care (EPOC) methodological design criteria, we included randomised trials, cluster-randomised trials, non-randomised trials, controlled before-after studies, and interrupted time series studies [52].

Controlled before-after studies are experimental studies with at least two intervention sites and two control sites without randomization during the allocation process [52]. Data are collected from the control and intervention groups before the intervention is introduced and then further data are collected after the intervention has been introduced. We reassessed all controlled before-after studies from the 2010 review to ensure they met the current EPOC standards for controlled before-after studies for this updated review.

For non-randomised trials, participants are allocated to different groups by investigators in a non-random fashion. They may pose a greater risk of bias compared to the randomised trials [52]. We reassessed the non-randomised trials from the 2010 review to ensure they included at least two intervention sites and two control sites in this updated version.

Interrupted time series studies represent a robust method of measuring the effect of an intervention as a trend over time; it is a useful design when recruitment of a control cohort is impractical, for example, change in hospital policy. Three or more data points are collected before and after the intervention as a minimum standard and the intervention effect is measured against the pre-intervention trend [52].

3.4.2 Types of participants

We considered two groups of participants relevant for this review.

- Health professionals, including doctors, nurses, physiotherapists, pharmacists, occupational therapists, social workers, dietitians, psychologists, psychiatrists, speech pathologists, and dentists involved in CPW utilization in the hospital setting.
- Hospitalized patients (inpatient and outpatient settings) with clinical conditions managed using a CPW, irrespective of diagnosis.

3.4.3 Setting

We included studies conducted in hospitals evaluating the impact of CPWs.

3.4.4 Types of interventions

The interventions included in this review are clinical pathway interventions that met the working definition described earlier under the section “clinical pathway definition”. We included clinical practice guidelines that were tailored to a local context. For analysis, we included two comparisons:

- Stand-alone clinical pathway versus usual care.
- Multifaceted interventions including a clinical pathway versus usual care.

We expected that most studies would compare a clinical pathway intervention with usual care in the same setting. We included studies of multifaceted interventions if the clinical pathway aspect could be separately assessed from other elements of the intervention. For example, a multifaceted intervention that included the introduction of a case management model, professional education, introduction of a clinical pathway and structural change, such as the introduction of information technology support with the aim being to enhance evidence-based practice. In such an instance, we included studies in which a multifaceted intervention

incorporating a clinical pathway was compared to the same intervention without a clinical pathway element.

3.4.5 Types of outcome measures

Based on our experience with the previous review by Rotter et al. (2010) [14], we expect to find variation in the range of follow-up and criteria used for assessing outcomes in the included studies. Thus, we included all objectively measured outcomes.

Primary outcomes:

- 90-day mortality
- Hospital readmission (up to 6 months)
- In-hospital complications

Secondary outcomes:

Patient outcomes

- Length of hospital stay
- Hospital costs and charges
- Adherence to recommended practice

For this review, we define invasive procedures as medical procedure that penetrates the body, usually by puncturing the skin or inserting instruments into the body [80].

3.5 Search methods for identification of studies

Electronic searches

We searched the following databases with no language restrictions from August 2008 to March 2017:

1. The Cochrane Central Register of Controlled Trials (CENTRAL).
2. Bibliographic databases, including MEDLINE, Embase, CINAHL, HMIC, Amed, Cochrane-NHS EED, and Cochrane-HTA.
3. Cochrane Database of Abstracts of Reviews of Effectiveness (DARE) was searched for related reviews.

We searched electronic sources using a strategy developed incorporating the methodological component of the EPOC search strategy combined with selected MeSH terms and free text terms relating to clinical or critical pathways. This search strategy was translated into the

other databases using the appropriate controlled vocabulary as applicable. The MEDLINE search strategy is provided in Appendix 1.

Searching other resources

Grey literature

- Web of Science (www.webofknowledge.com).
- OpenGrey (www.opengrey.eu).

Trial registries

- The Word Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) search portal (apps.who.int/trialsearch).
- ClinicalTrials.gov (clinicaltrials.gov)

In addition to databases, we searched other resources for published and unpublished studies.

1. We hand searched high-yield journals and conference proceedings which had not already been hand searched on behalf of the Cochrane Collaboration.
2. We reviewed reference lists of all papers and relevant reviews identified.
3. We contacted authors of relevant articles regarding any further published or unpublished work.
4. We contacted researchers with expertise relevant to the review topic for other studies.

3.6 Data collection and analysis

Selection of studies

We imported the search results into our reference management software and removed duplicate records. Three pairs of review authors (SS and CP), (LK and PW), and (AM and UR) independently screened all titles and abstracts for manuscripts eligible for full-text assessment. We resolved any disagreement by discussion or with a third author who served as an arbitrator (TR). Two review authors (AL and CP) independently assessed all full text studies with the review inclusion criteria and resolved disagreements by discussion or with the use of an arbitrator (TR).

Data extraction and management

We extracted data using a modified standardized data extraction form based on the Cochrane EPOC Group's data collection checklist [81], created with Microsoft Access and extracted directly from trial reports. We retrieved the full text copies of all potentially relevant papers

identified during the titles and abstract phase. We sent non-English studies for translation through the EPOC editorial base to examine eligibility for inclusion in the final review. Two review authors (AL and CP) independently extracted information. When necessary, we sought additional information on study characteristics, study design, intervention types and outcomes reported from the authors of primary studies. We recorded details on the number of retrieved references, the number of obtained full text papers and the number of included and excluded studies (Figure 3-1). We managed this data in Clarivate Analytics Endnote [82]. We imported all extracted data into Review Manager 5 for further analysis [83].

Assessment of risk of bias in included studies

Two review authors (AL and CP) independently assessed the risk of bias of included studies, any disagreements were referred to a third review author (TR). We used the nine-point criteria from the Cochrane EPOC group for assessing risk of bias in randomised trials, non-randomised trials, and controlled before-after studies: allocation sequence generation; allocation concealment; baseline outcome measurements; baseline characteristics; incomplete outcome data; knowledge of allocated interventions; protection against contamination, selective outcome reporting; other risks of bias [84]. For interrupted time series studies, there are seven criteria: intervention independent of other changes; pre-specified effect shape; intervention unlikely to affect data collection; blinding; incomplete outcome data; selective outcome reporting; other bias [84]. We rated each component and categorized it in a 'Risk of bias' table as 'low risk', 'unclear risk', or 'high risk', as described in the *Cochrane Handbook for Systematic Reviews of Interventions* [85]. We did not exclude any study based on risk of bias. We earmarked studies given an overall rating of "high risk" and "unclear risk" for sensitivity analysis order to examine their influence on the pooled effect estimates.

Measures of treatment effect

We reported all data in natural units. In the case of missing standard deviations, we undertook the appropriate transformation. For continuous outcome measures, we reported a summary effect size and the weighted mean difference (WMD) with corresponding 95% confidence intervals (CIs). Additionally, we estimated a standardized mean difference (SMD) and summary effect size for outcomes with different scales. For dichotomous data, we calculated an absolute crude event rate (risk difference, RD) or odds ratio (OR). Where applicable, we calculated the crude event rate (risk ratio, RR) for all outcomes and included the P-values as

reported by the study authors. We performed all analyses using Review Manager 5 [83]. To assess the effects of CPWs based on the type of hospital intervention provided to the patient, we defined and categorized invasive procedures as hospital interventions that require an opening of the skin tissue, for example surgery and vice versa for non-invasive procedures.

Unit of analysis issues

To avoid unit of analysis error in cluster-randomised trials, we applied an intracluster correlation coefficient (ICC) to calculate the effective sample size and account for the impact of clustering on the statistical power of the study [86]. We re-calculated cluster-randomised trials that did not account for clustering with respect to the number of participants per group also called "computing an effective sample size" with an estimate of an ICC taken from a ICC database of the University of Aberdeen [87]. Where possible, we selected a similar intervention with comparable study characteristics reporting an ICC.

Dealing with missing data

If a primary study did not provide information about standard deviation and P values, we used the approximate or direct algebraic connection between the stated confidence intervals, or P values, and the standard deviation and calculated the inverse transformation to the individual or pooled standard deviation [85]. In other instances, we attempted to contact the primary author for additional information.

Assessment of heterogeneity

Owing to the variation in practice settings, clinical conditions examined, and the focus of the CPW intervention, we envisaged clinical, statistical and methodological heterogeneity. We assessed statistical heterogeneity using the Chi^2 test using $P < 0.10$ and quantified statistical heterogeneity using the I^2 statistic. The review team decided that pooled estimates with an I^2 statistic value greater than 60% would be considered to have substantial statistical heterogeneity [85]. We also assessed statistical heterogeneity in the results of each meta-analysis by visual inspection of the forest plots [85].

Assessment of reporting biases

We assessed potential publication bias in the results of each meta-analysis by visual inspection of funnel plots and for individual studies [85].

Data synthesis

Previous studies (including EPOC reviews) have demonstrated that implementation of interventions to improve professional practice benefit from being multifaceted and including the following features: 1) evidence-based content; 2) adaption for local use; 3) clinician involvement in CPW development; 4) use of an implementation team; 5) evidence-practice gap identification prior to implementation; 6) identification of potential barriers to change; 7) incorporation of reminder systems; 8) incorporation of audit and feedback into implementation; 9) use of education sessions, and 10) use of local opinions leaders as part of the process [88-92].

For this update review, we applied this 10-criteria checklist for implementation strategies of complex interventions to all included studies. We extracted relevant information on the implementation strategies for implementing CPWs, as reported in the primary studies. Further, we ranked each study based on an overall implementation score with an equal weight applied to each criterion on the checklist. A study ranked 'high' if seven or more implementation strategies were used, 'medium' if four to six implementation strategies were used and 'low' for up to three implementation strategies reported in the primary study.

We followed the EPOC recommendation regarding re-analysis of individual studies and data synthesis. We presented the description of included studies and the certainty of evidence in a tabular format for each type of outcome using **Summary of findings table 1**, **Summary of findings table 2** and assessed the effects of the included studies, based on the quality, size and direction of effect observed. We used a random-effects model meta-analysis to statistically combine similar studies. Where meta-analysis was not applicable due to dissimilar measures reported by individual studies, we reported the average effect size using plain language summaries as appropriate.

We considered reported hospital cost data as indirect costs, as full costing approaches and hospital charges. There was insufficient reported data to synthesize full economic evaluations. We updated the cost/charges effects of CPWs (cost/charges analysis), but not the cost-effectiveness, for all studies that report on cost measures. Cost/charges data is presented in USD for the common price year 2016 by using the "CCEMG-EPPI-Centre Cost Converter" (Version 1.5), a web-based tool that can be used to adjust an estimate of cost

expressed in one currency and price year to a target currency and, or price year, or both [93]. We adjusted costs/charges for inflation by applying Gross Domestic Product deflators ('GDPD values') or using government recommended rates [94]. Additionally, we have provided the costing method and the undiscounted cost data to allow readers to recalculate the results using any discount rate (Appendix 2**)**.

Three studies utilized interrupted time series design [95-97]. All three met minimum criteria including number of points pre- and post-intervention, and the utilization of appropriate models. Owing to the disparate nature of outcomes reported by the interrupted time series studies, we presented the results from individual studies in a narrative format. For interrupted time series data presented in a graphical format, we extracted data using the plotdigitizer software recommended by EPOC [98]. We saved each graph as a JPEG file and opened via the plotdigitizer software and the raw data was extracted by dragging the cursor over each data point.

Summary of findings

Two review authors (AL and CP) independently assessed the certainty of the evidence (high, moderate, low and very-low) using the five GRADE considerations (risk of bias, consistency of effect, imprecision, indirectness, and publication bias) as described in Guyatt et al. (2008) [99]. We created two 'Summary of findings' tables for the two main comparisons examined in this review (Summary of findings table 1 and Summary of findings table 2) and, included the primary outcomes and all patient important outcomes: 90-day mortality, hospital readmission up to six months, in-hospital complications, length of hospital stay, hospital costs, adherence to recommended practice.

Subgroup analysis and investigation of heterogeneity

To explore trends that may explain the observed variation in the pooled estimates of the included studies, we conducted subgroup analysis and reinvestigated heterogeneity based on the country where the studies were conducted, the conditions for which the pathway was designed, study year and settings where the CPWs were implemented.

Sensitivity analysis

We conducted sensitivity analysis, where feasible, based on the risk of bias inherent in the included studies. To examine the robustness of the pooled estimates, we compared the

computed effect estimates of the pooled outcomes when we retained studies rated at high and unclear risk of bias in the meta-analysis plots, with pooled estimates generated by only including studies rated at low risk of bias alone.

3.7 Results

Description of studies

See: table 3-1 for Characteristics of included studies.

3.7.1 *Results of the search*

The search from 2008 up to March 1, 2017 yielded 14,888 records. We excluded 14,764 records upon review of the titles and abstracts. We screened the remaining records by reviewing 100 full text papers and included 12 studies. Two articles [25, 100] from the published 2010 review were reported in duplicate and have been combined into one [25] for a total of 26 studies. Overall 39 studies are included in this review update. See Figure 3-1 for PRISMA flow chart.

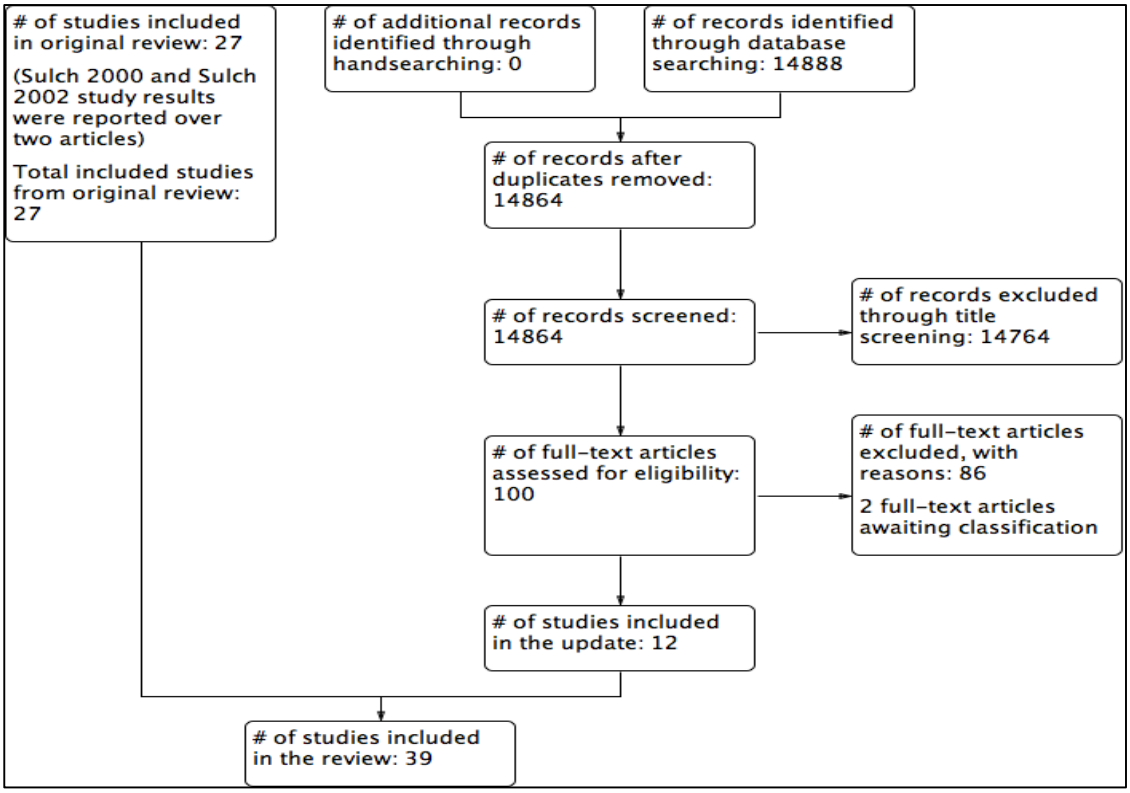

Figure 3-1: PRISMA study flow chart

3.7.2 *Included studies*

In total, thirty-nine studies met the inclusion criteria for the definition of a CPW and methodological quality for this update. Twenty-seven studies had been included in the previous version of the review [14]. See table 3-1 below for characteristics of included studies.

Table 3–1. **Characteristics of included studies**

Study ID	CPW condition/Procedure	Type of ward	Type of hospital	Sample size	Study type	Country	Overall risk of bias
Comparison 1: **single CPW intervention versus usual care**							
Aizawa 2002	TURP	Surgical / Urology unit	Acute	69	P-RCT	Japan	Unclear risk
Brook 1999	Mechanical ventilation	Medical ICU	ICU	321	P-RCT	USA	Low risk
Bernard 2011	Type 2 Diabetes Mellitus	Emergency Department	ED	176	P-RCT	USA	Unclear risk
Bittinger 1995	Heart Failure	ICCU and Medical unit	Acute	30	P-CRT	USA	High risk
Carratala 2012	Community Acquired Pneumonia	Emergency Department	ED	401	P-RCT	Spain	High risk
Chadha 2000	Menorrhagia and urinary incontinence	Gynaecological unit	Acute	946	CBA	UK	High risk
Choong 2000	Femural neck fracture	Orthopaedic unit	Acute	111	NRCT	AUS	Unclear risk
Costantini 2014	End of life care	End of life ward	Extended care	308	C-RCT	Italy	High risk
Cunningham 2008	Asthma	Emergency Department	ED	251	C-RCT	UK	High risk
Delaney 2003	Laparotomy and Intestinal Resection	Rehabilitation	Extended care	64	P-RCT	USA	High risk
Doherty 2006a	Asthma care	Medical units of the hospitals	Acute	187	CBA	AUS	High risk
Dowsey 1999	Hip and knee arthroplasty	Orthopaedic unit	Acute	163	P-RCT	AUS	Unclear risk
Doig 2008	Malnutrition	ICU	ICU	1118	C-RCT	AUS/NZ	Low risk
Falconer 1993	Stroke Rehabilitation	Stroke Rehabilitation	Extended care	121	P-RCT	USA	Unclear risk
Gomez 1996	Suspected MI	Coronary Care unit/ Chest pain evaluation unit	Acute	100	P-RCT	USA	High risk
Johnson 2000	Asthmatic children	Emergency and Paediatric wards	Acute	110	P-RCT	USA	High
Kim 2002	Atrial fibrillation	Emergency Department	ED	18	P-RCT	USA	Unclear risk
Kinsman 2012	MI	Emergency Department	ED	115	C-RCT	AUS	Low risk
Kiyama 2003a	Gastrectomy	Surgical ward	Acute	85	P-RCT	Japan	Unclear risk
Kollef 1997	Mechanical ventilation	Medical & Surgical ICU	ICU	357	P-RCT	USA	Low risk
Marelich 2000	Mechanical ventilation	Medical ICU	ICU	253	P-RCT	USA	Low risk
Marrie 2000	Pneumonia	Emergency Department	Acute	1743	C-RCT	Canada	Unclear risk
Panella 2009	Heart Failure	Medical Unit	Acute	429	C-RCT	Italy	Unclear risk

ProCess 2014	Septic shock	Emergency Department	ED	895	P-RCT	USA	Low risk
Roberts 1997	CPW Chest Pain/ possible MI	Emergency/ telemetry observational units	ED	165	P-RCT	USA	Unclear risk
Rotter 2014	Radical laparoscopy prostatectomy	Surgical ward	Acute	254	ITS	Germany	Low risk
Smith 2004	CPW COPD	Medical Units	Acute	1230	CBA	AUS	High risk
Sulch 2002	Stroke Rehabilitation	Stroke Rehabilitation	Extended care	152	P-RCT	UK	Unclear risk
Tilden 1987	Identification of battered woman	Emergency Department	ED	892	ITS	USA	High risk
Trombetti 2013	Malnutrition	Medical Unit	Acute	694	P-RCT	Switzerland	Unclear risk
Usui 2004	Pneumonia	Medical Units/ respiratory medicine	Acute	61	NRCT	Japan	High risk
Verdu 2009	DVT	Medical Unit	Acute	88	NRCT	Spain	High risk
Comparison 2: **Multifaceted intervention including a CPW versus usual care**							
Bauer 2006	Bipolar disorder	Mental health outpatient clinic VAMC	Other	306	P-RCT	USA	Low risk
Bookbinder 2005	Palliative care	Palliative Care	Extended care	267	CBA	USA	High risk
Brattebø 2002	Mechanical ventilation	Surgical ICU	ICU	285	ITS	Norway	Low risk
Chen 2004	Asthmatic children	Pediatric unit	Acute	42	P-RCT	Taiwan	Unclear risk
Cole 2002	Care of delirium in older medical patients	Medical units	Acute	227	P-RCT	Canada	Low risk
Kampan 2006	Diabetic patients admitted with hypoglycaemia	Medical unit	Acute	65	P-RCT	Thailand	Unclear risk
Philbin 2000	Patients with heart failure	Medical Units	Acute	2906	C-RCT	USA	Unclear risk

P-RCT = patient randomised clinical trial; C-RCT = cluster randomised clinical trial; NRCT = non-randomized controlled trial; CBA = controlled before-after study; ITS = interrupted time series; USA = United States of America; UK = United Kingdom; AUS = Australia; NZ =New Zealand; DVT= deep vein thrombosis; TURP = transurethral resection of the prostate; MI = myocardial infarction; COPD = chronic obstructive pulmonary disease; Acute = General acute hospital; ICU = Intensive care unit; ED = Emergency department; Extended care = Rehabilitation or palliative facilities; Other = Psychiatric or mental health clinic/ hospital; ICCU = intensive coronary care unit

3.7.3 Study designs

From the 2010 review, nineteen of the included studies were randomised trials [23, 25, 26, 101-115] four were controlled before-after [116-119], two were non-randomised trials [120, 121] and two were interrupted time series studies [95, 96]. Out of the nineteen randomised trials, two were cluster-randomised trials [113, 114]. The review update resulted in the inclusion of twelve additional studies with ten randomised trials [65-68, 122-127] in which five were C-RCT [122-126], one non-randomised trial [64] and interrupted time series study [97] each.

3.7.4 *Clinical conditions*

Included studies targeted a wide range of conditions. Across the 39 studies, there were 25 (64%) different conditions targeted. Chest pain [23], mechanical ventilation [102, 111, 112], stroke rehabilitation [25, 26], asthma [107, 118, 123]), congestive heart failure [125, 127] and pneumonia [65, 113, 121] was examined in more than one study. See Appendix 2 for information on all included pathway conditions or clinical indications.

3.7.5 *Country*

Sixteen studies (41%) were conducted in the United States [23, 26, 66, 68, 96, 102, 104, 106, 107, 109, 112, 114-116, 127], five (13%) in Australia [105, 118, 120, 126, 128], three (8%) in Japan [101, 110, 121], three (8%) in the United Kingdom [25, 117, 123]), two (5%) in each of: Canada [113, 129], Italy [125, 130] and Spain [64, 65]. One (3%) study each in Germany [97], Thailand [108], Taiwan [103], Norway [95] and Switzerland [67]. One (3%) study [124] was conducted in two countries (New Zealand and Australia).

3.7.6 *Setting*

The settings of the studies were extracted and recorded into one of five categories representing various areas of the hospital. Nineteen studies (49%) were conducted in a general acute ward (for example medical, surgical, pediatrics, gynecology) [23, 64, 97, 101, 103, 105, 107, 108, 110, 113, 114, 117-121, 125, 129], five (13%) in an extended stay facility (for example rehabilitation or palliative care, end of life) [25, 26, 104, 116, 122], Six (15%) in an ICU [95, 102, 111, 112, 124, 127], eight (21%) studies were conducted in the emergency department (ED) [65, 66, 68, 96, 109, 115, 123, 126], and one (3%) [106] in another area (mental health outpatient clinic).

In ten (26%) studies, the CPW was designed for an invasive procedure [95, 97, 101, 102, 104, 105, 110-112, 120]. Twenty seven (69%) studies [24-26, 64-68, 96, 103, 106-109, 113-116, 118, 121-124, 126-129] described CPWs for a non-invasive diagnosis (for example diabetes, stroke, asthma, deep vein thrombosis, sepsis) and two (5%) studies [23, 117] described CPWs for combined invasive / non-invasive procedures (for example, suspected myocardial infarction with or without percutaneous transluminal coronary angioplasty).

To improve comparability, we categorized the studies into two groups:

(1) Those describing patients managed with a CPW compared to usual care.
(2) Those describing patients managed within a multifaceted intervention including a CPW compared to usual care.

For this review update, all twelve additional studies identified compared stand-alone CPW to usual care. Overall, thirty two (82%) studies compared a stand-alone CPW to usual care [23, 25, 26, 64-68, 96, 97, 101, 102, 104, 105, 107, 109-113, 115, 117, 118, 120-126, 128] and seven (18%) studies [95, 103, 106, 108, 114, 116, 129] compared a multifaceted intervention (including a CPW) to usual care. We did not identify further studies which combined the CPW with other interventions (multifaceted interventions). Multifaceted pathway interventions were combined with case management elements [103, 106, 108, 116, 129] or with complex quality improvement programs [114, 116]. Other investigators used single pathway interventions together with counselling methods [106, 108, 114, 116] or in conjunction with external providers such as primary care or extended care agencies [106, 114]. Further multifaceted strategies include posters [95], physician order sheets [116] and reminders by the study nurse [129].

3.8 Outcomes

3.8.1 Patient outcomes

Objectively measured patient outcomes reported by included studies comprised of 90-day mortality [25, 65-67, 102, 111, 124, 128], hospital readmissions up to six months [23, 65, 101, 115, 120, 125], and in-hospital complications [65, 66, 101, 104, 105, 110, 112, 120].

3.8.2 *Utilization, coverage and access: Length of stay (LOS)*

LOS was calculated and reported as total length of hospital stay in hours or in days from admission until discharge. However, one study calculated LOS from the day of surgery to the day of discharge [110]. Most of the included studies predefined LOS as an outcome indicator and a surrogate for hospital costs. We present the length of hospital stay data in days.

3.8.3 *Resources use: Hospital costs*

Hospital costs data were reported as direct or indirect hospital costs in USD, Japanese JEN, EUROS, and Thailand's BAHT. Hospital charges were reported in USD or country specific insurance points (See 'types of outcome measures' section for a brief description of the differences between costs, charges, and insurance data). Within this highly variable set of

cost measures reported, a direct costing approach (e.g., treatment costs as direct costs were included in the cost estimates; time cost or lost wages and other indirect costs were not) was used by two studies [106, 109], excluding professional fees in both USA settings. One study [110] included direct costs and professional fees. For this update, hospital cost was reported by two studies [131, 132]. Panella et. al (2009) reported on direct hospital costs and Verdu et. al (2009) used cost estimates (cost-efficiency indicators) to assess the effects of CPWs on hospital cost. Direct and indirect cost were included in the cost estimates reported in two studies [115, 133] although it was unclear which costing method was used and which costs were included (i.e. professional costs) in the Kampan et al (2006) study. Hospital charges in USD was reported as median hospital charges by Falconer et al. (1993) [26] and as mean hospital charges by three studies [23, 107, 114]. A surrogate for hospital charges in the form of insurance points was reported in two Japanese investigations [101, 121]. Because of the different methods used for generating hospital costs and the highly differing cost outcomes included in this review update (hospital costs, charges and insurance data), we presented an overview of the costing method used and which costs/charges were in- and excluded from the calculations in tabular form (Appendix 2).

3.8.4 Quality of care**:** Adherence to recommended practice

The only quality of care measure is adherence to recommended practice by healthcare professionals using a clinical pathway for the management of patient's clinical condition. For this review, we measured adherence to recommended practice by the proportion of documentation performed by healthcare professionals while using CPWs for patient management in hospital settings.

3.8.5 Other outcomes

We did not find any study reporting on other planned outcomes such as ICU admissions, discharge destination, staff satisfaction and time to mobilization post-surgery.

See Appendix 2 for tabular description of all outcomes reported by the primary studies.

3.9 Implementation Process

The process for developing and implementing the CPW was extracted and recorded according to whether evidence-informed strategies had been utilized. Overall six (15%) studies [95, 103, 106, 116, 124, 126] were scored as having a "high" implementation score,

20 (51%) studies [24-26, 64, 68, 96, 97, 101, 104, 105, 107, 111, 112, 114, 117, 118, 122, 123, 128, 129] were scored as having a "medium" implementation score and 12 (31%) studies [23, 65-67, 102, 108-110, 113, 115, 120, 121] were scored as having a "low" implementation score. The most frequent implementation strategy utilized was clinician involvement during the CPW development (31 studies). The use of an implementation team, identification of evidence-practice gaps prior to implementation and the use of educational sessions were each reported in 23 (59%) studies. Audit and feedback was reported in 15 (38%) studies, use of local opinion leaders was reported in 14 (36%) studies, incorporation of reminder systems was reported in 12 (31%) studies and the identification of potential barriers to change was reported in eight studies. Full details of all Implementation strategies reported in all included studies are presented in Table 3-2.

Table 3–2. Implementation strategies reported in included studies

Study ID	Clinician involvement in CPW development	Implementation team	Evidence-practice gap identification prior to implementation	Identification of potential barriers to change	Reminder systems	Audit and feedback	Education sessions	Local opinions leaders	Overall rating
Aizawa 2002	Y	Y	-	-	-	Y	-	N	Low
Bauer 2006	Y	Y	Y	Y	Y	Y	Y	Y	High
Bernard 2011	Y	Y	Y	N	N	N	Y	N	Moderate
Bittinger 1995	Y	Y	-	N	N	N	Y	Y	Moderate
Bookbinder 2005	Y	Y	Y	Y	Y	Y	Y	-	High
Brattebø 2002	Y	Y	Y	Y	Y	Y	Y	-	High
Brook 1999	Y	-	Y	-	-	-	-	-	Low
Carratala 2012	-	N	N	N	N	N	Y	N	Low
Chadha 2000	Y	Y	-	-	Y	N	Y	Y	Moderate
Chen 2004	Y	Y	Y	Y	-	Y	Y	Y	High
Choong 2000	Y	-	-	-	-	-	-	-	Low
Cole 2002	Y	Y	Y	-	-	Y	Y	-	Moderate
Costantini 2014	Y	Y	Y	N	N	N	Y	Y	Moderate
Cunningham 2008	Y	-	Y	N	-	Y	Y	Y	Moderate
Delaney 2003	Y	Y	-	Y	-	Y	-	-	Low
Doherty 2006a	Y	Y	Y	Y	Y	N	-	-	Moderate

Doig 2008	Y	Y	Y	N	Y	Y	Y	Y	High
Dowsey 1999	Y	-	-	-	Y	Y	-	Y	Moderate
Falconer 1993	Y	Y	N	-	-	Y	Y	-	Moderate
Gomez 1996	Y	-	Y	-	-	-	-	-	Low
Johnson 2000	Y	Y	-	-	N	N	Y	Y	Moderate
Kampan 2006	-	Y	-	-	-	Y	-	-	Low
Kim 2002	-	-	Y	-	-	-	-	-	Low
Kinsman 2012	Y	Y	Y	N	Y	Y	Y	Y	High
Kiyama 2003a	-	-	Y	-	-	-	-	-	Low
Kollef 1997	N	-	-	-	Y	N	Y	Y	Low
Marelich 2000	Y	Y	-	-	Y	-	-	-	Low
Marrie 2000	-	-	-	-	Y	-	-	-	Low
Panella 2009	Y	Y	Y	N	N	N	Y	Y	Moderate
Philbin 2000	Y	Y	-	-	-	Y	Y	-	Moderate
ProCess 2014	Y	Y	-	N	N	N	N	N	Low
Roberts 1997	Y	-	Y	-	-	-	-	-	Low
Rotter 2014	Y	N	Y	N	N	N	Y	Y	Moderate
Smith 2004	Y	Y	Y	-	-	Y	Y	-	Moderate
Sulch 2002	Y	-	Y	Y	-	-	Y	Y	Moderate
Tilden 1987	-	Y	Y	-	Y	-	Y	-	Moderate
Trombetti 2013	-	-	-	N	N	N	N	N	Low
Usui 2004	Y	-	-	-	-	-	-	-	Low
Verdu 2009	Y	Y	Y	N	N	N	Y	N	Moderate

3.10 **Excluded studies**

57 excluded studies did not meet the Cochrane EPOC minimal inclusion criteria for study designs; the controlled before-after study and non-randomised trials lacked two control and two intervention groups respectively. 19 excluded studies did not meet the CPW content criteria used in this review (see types of interventions for additional information) and 10 studies were not conducted in hospital settings.

3.11 **Risk of bias in included studies**

3.11.1 Allocation (selection bias)

17 of the 39 studies (44%) adequately described the random sequence generation during intervention allocation and were at low risk of bias. Random sequence generation was not

used in seven studies [64, 110, 116, 117, 120, 121, 128] and was considered unclear in 15 studies (39%).

Allocation concealment was undertaken in 14 studies (36%), unclear in 20 studies (49%) and was not present in six studies [64, 116, 117, 121, 123, 128].

3.11.2 *Baseline outcome measurements*

Baseline outcomes were similar between the CPW group and usual care in 14 studies [65, 67, 68, 107, 111, 113, 114, 117, 123, 125, 127, 128], it was unclear whether measurements were similar in 27 studies (64%).

3.11.3 *Baseline characteristics*

Baseline characteristics for the CPW and usual care groups were similar in 31 studies (80%) and unclear in four studies (13%). There were differences in the baseline characteristics between the CPW group and usual care group in three studies [104, 117, 121].

3.11.4 *Intervention independent of other changes*

The implementation of a CPW in the hospital was independent of other changes in one study [97] and unclear in one study [95]. Due to the presence of other factors (media regarding topic, hospital push for improved charting), the intervention was not independent of other changes in one study [96].

3.11.5 *Shape of intervention effect prespecified*

Prespecification of the intervention effect was provided in one study [97] and unclear in the remaining two studies [95, 96].

3.11.6 *Intervention unlikely to affect data collection*

Sources and methods of data collection were the same before and after the intervention in all the three interrupted time series studies [95-97].

3.11.7 *Incomplete outcome data (attrition bias)*

Outcome data was complete in 27 studies (69%), and unclear in nine studies (26%). Loss to follow up of more than 20% occurred in two studies [64, 127].

3.11.8 *Knowledge of the allocated intervention prevention*

The use of objective outcomes or blinding of the assessment of the primary outcome variables was achieved in 23 studies of the 39 studies. Blinding of the primary outcome variables was not present in nine studies [24, 25, 104, 114, 116, 117, 122, 123, 126] and unclear in six studies (18%).

3.11.9 *Protection against contamination*

There was a low risk of contamination of the intervention between the CPW and usual care group in 17 studies (45%). Eight studies [23, 66, 68, 101, 102, 106, 116, 123] were judged as having a high risk from contamination of health professionals and contamination was unclear in 13 studies (36%).

3.11.10 *Selective reporting*

The risk of selective reporting was low in most studies (add number of studies and references). In eight studies [96, 103, 110, 113, 115, 116, 118, 121] some outcomes listed in the methods section were missing in the results or incompletely reported in the study.

3.7.11 *Other potential sources of bias*

Six studies [23, 96, 107, 113, 116, 127] reported the influence of extraneous variables such as cultural and leadership styles, exposure to other educational offerings, healthy worker effect and data entry errors. Other potential source of bias was unclear in 11 studies (31%). Figure 3-2 depicts the risk of bias across included studies.

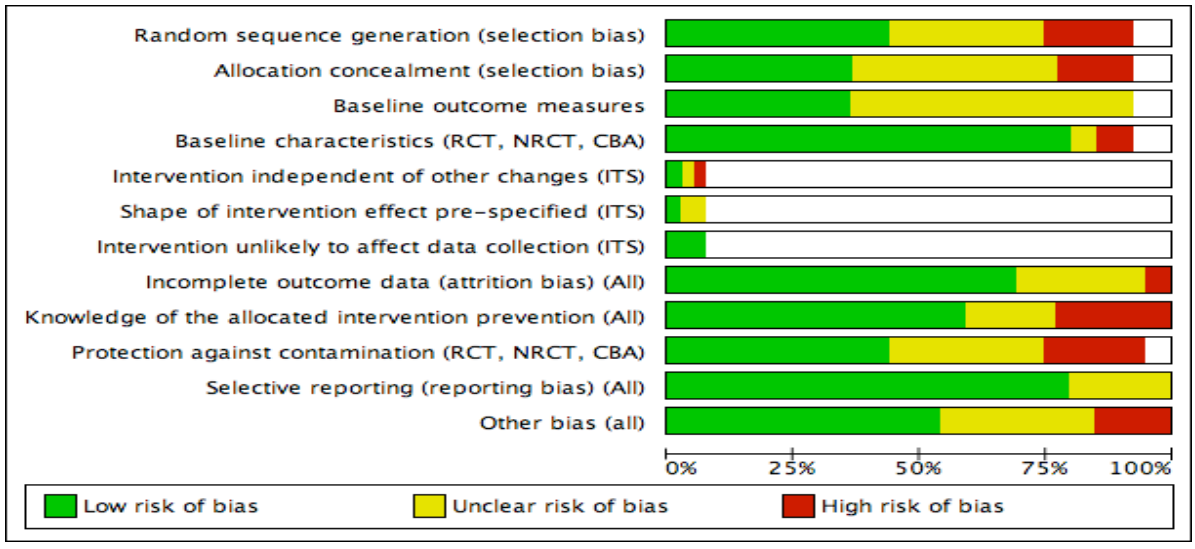

Figure 3-2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

3.12 **Effects of interventions**

See below for **Summary of findings table 1** and **Summary of findings table 2** for the main comparisons; patient outcomes (90-day mortality, hospital readmissions up to six months, in-hospital complications), LOS, hospital costs and adherence to recommended practice. See Appendix 3 for all data analysis and meta-analyses on comparable studies reporting on the primary and secondary outcomes. We also provided the data collection form used for this review update in Appendix 4.

Table 3–3. **Summary of findings table 1**

Stand-alone clinical pathways compared to usual care						
Patient or population: hospitalised patients **Setting:** hospitals **Intervention:** stand-alone clinical pathway **Comparison:** usual care						
Outcomes	**Anticipated absolute effects*** **(95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with usual care	**Risk with stand-alone clinical pathway**				
90-day mortality	Study population		OR 0.83 (0.62 to 1.12)	3828 (6 RCTs)	⊕⊕⊖⊖ Low[1, 2]	Random-effects analysis: OR 0.83 (95% CI 0.62 to 1.12)
	217 per 1000	187 per 1000 (146 to 237)				
Hospital readmission (up to 6 months)	Study population		OR 0.74 (0.48 to 1.15)	1391 (7 RCTs)	⊕⊕⊖⊖ Low[1, 3]	Random-effects analysis: OR 0.74 (95% CI 0.48 to 1.15)
	97 per 1000	7464 per 1000 (49 to 110)				
In-hospital complications	Study population		OR 0.46 (0.33 to 0.64)	2012 (7 RCTs)	⊕⊕⊖⊖ Low[3, 4]	Random-effects analysis: OR 0.46 (95% CI 0.33 to 0.64)
	125 per 1000	62 per 1000 (51 to 90)				
Length of hospital stay	The mean length of hospital stay was 12.5 days	MD 0.83 days lower (1.32 lower to 0.45 lower)	-	5782 (22 RCTs)	⊕⊖⊖⊖ Very low[2, 3, 5]	Random-effects analysis: MD -0.83 (-1.21 to -0.45)
Hospital costs and charges	The mean cost was USD 11,163	MD 1171.52 USD lower (1835.86 lower to 507.18 lower)	-	1264 (7 RCTs)	⊕⊕⊖⊖ Low[3, 5]	Random-effects analysis: MD -1171.52 (95% CI -1835.86 to -507.1)
***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **MD**: mean difference; **OR:** odds ratio; **RT**: randomised trial; **USD**: US dollar						

GRADE Working Group grades of evidence
High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect **Moderate-certainty:** we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low-certainty:** our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low-certainty:** we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded one level due to imprecision (confidence interval contains harm and benefit).
[2]Downgraded one level due to publication bias (funnel plot strongly implies publication bias).
[3]Downgraded one level due to serious risk of bias (high risk of concealment, randomisation, performance bias).
[4]Downgraded one level due to indirectness (variation in type of complications assessed).
[5]Downgraded one level due to inconsistent results (substantial heterogeneity was found).

3.12.1 *90-day mortality*

Within the category of stand-alone pathway interventions, six studies [65, 66, 102, 111, 124, 128] with 3828 patients were combined because they were comparable and reported on in-hospital mortality up to 90 days after the use of a CPW. Two studies [66, 124] found increased mortality within a 90-day period after the use of a CPW. The result showed an odds ratio (OR) favouring the CPW group compared to usual care with OR 0.83 (95% CI 0.62 to 1.12; P = 0.22; Analysis 1.1.1). There was low-certainty of evidence (Summary of findings table 1). We explored further by conducting sensitivity analysis by excluding studies with high and unclear risk of bias from the analysis, the resulting effect estimate was OR 1.04 (95% CI 0.87 to 1.24; P = 0.66; Analysis 1.1.2).

3.12.2 *Hospital readmissions (up to 6 months)*

Seven studies (1391 participants) reported on hospital readmissions for all causes, and characterized with follow up periods up to six months. Aizawa et al. (2002) reported one readmission event from 32 patients on the CPW versus no readmissions from 37 patients in the usual care group within six months [101]. Choong et al (2000) reported a follow up period of 28 days and two events for 55 patients in the CPW group versus six events from 56 usual care patients [120]. Carratala et. al (2012) reported 18 events from 200 patients in the CPW group versus 15 events from 201 usual care patients [65]. Panella et al (2009) found 17 rehospitalization events from 214 patients following a CPW compared to 30 events for 215 patients managed with usual care (P = 0.053).

In the study from Dowsey et al (1999) [105], four out of 92 CPW patients were readmitted within a follow up period of three months versus nine out of 71 patients following usual care

(P = 0.06). Delaney et al. (2003) found 3 readmissions for the CPW group versus six readmissions for usual care while managing patients with laparotomy and intestinal resection [104]. In a period of 30 days, Gomez et al. (1996) reported three readmissions for both 50 intervention pathway patients as well as for 50 patients in the usual care group [23]. Roberts et al. (1997) observed five re-hospitalizations for 82 pathway patients versus four readmission events from 83 individuals managed with usual care within an eight-week period [115]. When combined, the effect estimate showed an OR favouring CPW group of OR 0.74 (95% CI 0.48 to 1.15; P = 0.18; Analysis 1.2) with low heterogeneity, I^2 = 13%. There was low-certainty of evidence (Summary of findings table 1).

3.12.3 *In-hospital complications*

In-hospital complications were assessed by eight studies [65, 66, 101, 104, 105, 110, 112, 120]. There was variation in the type of complications assessed following the use of a CPW. All studies reported improvements associated with use of a CPW. Choong et al. (2000) listed postoperative confusion, infection and deep vein thrombosis as complications for patients with a fractured neck of femur and reported 10 events for 55 patients in the CPW group versus 14 events for 56 patients in the usual care (P = 0.40) [120]. Delaney et al. (2003) listed postoperative infection and uncontrolled bleeding as complications for patients following intestinal resection and reported 7 events for 31 patients in the CPW group versus 10 events for 33 patients in the usual care group (P = 0.58) [104].

With respect to adverse drug reactions, Carratala et al. (2012) reported 9 events in 200 patients managed with a CPW versus 32 events out of 201 patients following usual care (P < 0.001) [65]. Kiyama et al. (2003) listed surgery-site problems as complications for patients following gastrectomy and reported 3 events for 47 patients in the intervention group versus 5 events for 38 patients in the control group [110]. Marelich et al. (2000) listed ventilator-associated pneumonia as a complication for patients requiring mechanical ventilation and reported 11 events for 166 patients in the CPW group versus 20 events for 169 patients in the usual group (P = 0.06) [112]. Process et al. (2014) found 23 adverse events out of 439 patients following a CPW versus 37 events out of 456 patients in the usual care group (P = 0.32) [66]. Aizawa et al. (2002) did not describe specific complications for patients following transurethral resection of the prostate and reported 1 event for 32 patients in the intervention group versus 2 events in 37 patients in the control group [101]. Dowsey et al. (1999) listed

wound infection, chest infection, deep vein thrombosis, joint dislocation, pressure areas, failure to cope at home and decreased range of motion post discharge as complications for patients following knee or hip arthroplasty up to three months' post-surgery and reported 10 events for 92 patients in the intervention group, versus 20 events for 71 patients in the control group (P = 0.01) [105]. The combined odds ratio showed an effect estimate favouring the CPW group OR 0.46 (95% CI 0.33 to 0.64; P < 0.0001; Analysis 1.3). There was low-certainty of evidence (Summary of findings table 1).

3.12.4 *Length of hospital stay*

Length of stay (LOS) was the most commonly reported secondary outcome and majority of [120] studies reporting reduced LOS following the use of CPW. Out of the 32 studies categorized as single pathway interventions, 22 (56.4%) randomised trials examined the effect of CPWs on LOS [23, 25, 26, 64-68, 97, 101, 102, 104, 105, 107, 109, 110, 113, 115, 120, 121, 123-125, 128], 14 studies reported on reductions in LOS [24, 64, 65, 101, 102, 105, 107, 109, 110, 113, 115, 120, 121] while three studies [66, 123, 124] found no difference in LOS between the groups after the use of a CPW. Using an ITS approach, Rotter et al. (2014) reported no change in the LOS after the use of a CPW for prostate patients undergoing RLP [97]. Conversely, Falconer et (1993); Bernard et al. (2011); Trombetti et al (2013). and Sulch et al. (2002) reported increased LOS associated with CPWs in the management of type 2 diabetes, management of malnourished elderly patients and stroke rehabilitation [25, 26, 67, 68]. Due to poor reporting, all the LOS data was missing in one study [128] and the investigators did not provide sufficient information on the uncertainty measures. The MD for the combined studies was -0.83 days (95% CI -1.21 to -0.45; P < 0.00001; Analysis 1.4.1). There was substantial heterogeneity, $I^2 = 81\%$ and we found very low-certainty of evidence (Summary of findings table 1).

3.12.4.1 **Subgroup analyses**

Length of hospital stay: study design

Using a random effects model, we compared randomized studies and non-randomized studies to examine the effects of CPW on LOS based on the study designs used in the primary studies. We observed further reduction in LOS for non-randomized studies group with an effect estimate of MD of -1.85 days (95% CI of -2.74, -0.95; P < 0.0001; Analysis 1.4.2) with

I^2 of 0% compared to randomized studies MD of -0.84 days (95% CI of -1.21, -0.47; P < 0.00001) with I^2 of 79% (Analysis 1.4.3).

Length of hospital stay: country

We examined the effects of market forces from countries where the studies were conducted, on the effect of hospital LOS. A larger reduction in LOS was found among Japanese studies and studies conducted in Spain with a pooled reduction in LOS by approximately three and two days respectively (MD of -3.01 days (95% CI -5.35, -0.67; P = 0.01; Analysis 1.4.4) and -2.09 days (95% CI -3.06 to -1.11; P < 0.0001; Analysis 1.4.5), followed by studies conducted in Australia with a MD -1.45 days (P = 0.0005; 95% CI -2.02 to -0.56; P = 0.0005; Analysis 1.4.6). Studies conducted in the USA constituted majority of the studies included in this update, but those studies combined, led to LOS with a MD of -0.60 days (95% CI -1.08 to -0.11; P = 0.02; Analysis 1.4.7). An increase in LOS was observed for pooled studies conducted in UK, MD of 1.29 days (95% CI -3.22, 5.81; P = 0.57; Analysis 1.4.8).

Length of hospital stay: setting

Emergency department

Seven studies [65, 66, 68, 109, 113, 115, 123] conducted in the emergency department reported on the LOS for 2117 patients managed with a CPW. Only one study [68], focusing on management of diabetes mellitus reported no differences between the CPW group and those following usual care; (5.4 hours (SD 1.8) for the CPW group versus 4.9 hours (SD 1.9) for usual care, P = 0.06). When statistically combined, the MD for the combined LOS was -0.66 days (95% CI -1.12 to -0.20; P < 0.005; Analysis 1.4.9)

Acute care

Eleven studies with 2090 patients [23, 64, 67, 101, 105, 107, 110, 113, 120, 121, 125] reporting on the LOS were conducted in acute care settings with the use of a CPW compared to usual care. Only one study [67] reported an increase in the LOS after the use of a CPW for malnourished elderly patients. When all eleven studies were statistically combined, we observed a reduction in the LOS with an effect estimate of MD equal to -1.37 days (95% CI of -1.87 to -0.87; P <0.00001; Analysis 1.4.10) and I^2 value of 88%.

Extended care

Three studies [25, 26, 104] with 337 patients were conducted in extended sections (rehabilitation units) of the hospital. Delaney et al. (2003) reported no differences in the LOS for patients undergoing surgical rehabilitation with the use of a CPW (5.2 days (SD 2.5) for CPW group versus 5.8 days (SD 3) for usual care (P = 0.12). After statistical pooling, we observed an increase in the effect estimate with a MD of 1.46 days (95% CI -2.14 to 5.05; P = 0.43; Analysis 1.4.11).

Intensive care unit

Two studies [102, 124] with 1440 participants were conducted in the intensive care unit (ICU) hospital. Brook et al. (1999) found a reduction in the LOS after using a CPW for managing sedation during mechanical ventilation (5.7 days (SD 5.9) for CPW group versus 7.5 (SD 6.5) for usual care, P = 0.013). Doig et al. (2008) reported an eight-hour reduction in LOS after using a CPW for the management of malnourished patients in the ICU ward (9.1 days (SD 11.5) for CPW group versus 9.9 (13.3) for usual care, P = 0.42). The combined effect for length of stay for the two studies revealed no difference between the CPW group and usual care group; MD -5.18 days (95% CI -12.94 to 2.57; P = 0.19; Analysis 1.4.12)

Surgical unit

Two studies[101, 110] with 154 participants were conducted in the surgical unit of a hospital. Aizawa et al. (2003) reported a two-day reduction in LOS when a CPW was used in the management of patients with benign prostatic hyperplasia (12.7 days (SD 2.8) for CPW group versus 14.7 (SD 5.2) for usual care, P = 0.04). Kiyama et al. (2003) reported a 10-day reduction in LOS after a CPW was used in the management of patients undergoing gastrectomy in the surgical ward (18.1 days (SD 9.5) for CPW group versus 28.2 (22.3) for usual care, P = 0.009). The combined effect for length of stay for the two studies revealed no difference between the CPW group and usual care group; MD -2.86 days (95% CI -7.77 to 2.04; P = 0.25; Analysis 1.4.13)

Study year

22 studies (3001 patients) were published in years ranging from 1993 to 2014, and reported on LOS, were ordered in forest plots by year of publication. The combined effect resulted in

a MD of -0.98 days (95% CI -1.35 to -0.60; P < 0.00001; Analysis 1.4.14). Association with the impact of CPW on LOS or other outcomes and the study year could not be identified.

Length of hospital stay: clinical condition

There were five conditions which were addressed by more than one study. Three studies [65, 113, 121] evaluated pathway management for pneumonia, two studies each for stroke rehabilitation [25, 26], suspected myocardial infarction [23, 115], malnutrition [67, 124], asthma care in children [107, 123]. Further conditions within this subgroup of single pathway interventions were transurethral resection of the prostate [101], deep vein thrombosis [64], septic shock [66], type 2 diabetes mellitus [68], heart failure [125], menorrhagia and urinary incontinency [117], femoral neck fracture [120], laparotomy and intestinal resection [104], asthma care [118], hip and knee arthroplasty [105], atrial fibrillation [109], gastrectomy [110], chronic obstructive pulmonary disease or COPD [128] and a pathway instrument designed for the better identification of female victims of domestic violence [96]. Due to the variation in the clinical conditions targeted by the various clinical pathways, we report on subgroup analysis per pathway condition.

Pediatric asthma care

Cunningham et al. (2008) reported no differences in reduction of LOS for pediatric patients with asthma (1.6 days (SD 1.1) in the CPW group versus 1.7 days (SD 1.1) in the usual care group, P = 0.83). also found a decrease in the LOS for hospitalized asthmatic pediatric patients when managed with a CPW (1.6 days (SD 1.1) for CPW group vs 2.2 days (SD 1.1) for usual care group, P < 0.01), The combined effect for LOS for these studies (351 patients) revealed no differences between the CPW group and usual care group, MD of -0.31 days, (95% CI -0.72 to 0.09; P = 0.13; Analysis 1.4.15).

Stroke rehabilitation

Falconer et al. (1993) and Sulch et al. (2002) both reported increased LOS associated with CPWs used for stroke rehabilitation units [25, 26]. Falconer et al. (1993) reported a LOS of 35.6 (SD 15.5) days in the CPWs group versus 32.3 (SD 15.4) days in the control group (OR 3.30; 95% CI -2.25 to 8.85). Sulch et al. (2002) reported a LOS of 50 (SD 19) days in the CPWs group versus 45 (SD 23) days in the control group (OR 5.00; 95% CI -1.71 to 11.71).

The combined odds ratio for the two studies was OR 3.99 (95% CI -0.29 to 8.27; P =0.07; Analysis 1.4.16).

Pneumonia

Marrie et al. (2002) and Usui et al. (2004) both reported reductions in LOS and duration of intravenous antibiotic infusion when CPWs was implemented for inpatient management of pneumonia [113, 121]. Marrie et al. (2002) reported a LOS of 8.2 days (SD 1.9) in the CPWs group versus 9.6 days (SD 2.1) in the control group (MD -1.40 days; 95% CI -1.94 to -0.86) whilst duration of intravenous antibiotic infusion was also significantly less in the CPWs group, 4.6 days (SD 0.9) versus 6.3 days (SD 1.4); (MD -1.70 days; 95% CI -2.01 to -1.39). Usui et al. (2004) reported a LOS of 8.0 days (SD 4.2) in the CPWs group versus 10.8 (SD 4.2) days in the control group (MD -2.74 days; 95% CI -4.84 to -0.64), whilst duration of intravenous antibiotic infusion was also significantly less in the CPWs group, 6.5 days (SD 3.5) versus 8.2 days (SD 3.5); (MD -1.75 days; 95% CI -3.52 to 0.02) [121]. Similarly, Carratala et al. (2012) reported reduction in the LOS during the management of hospitalized adults with community acquired pneumonia (3.9 days (SD 6.3)) for CPW group versus 6.3 (SD) for usual care; (MD of -2.10 days; 95% CI -3.33, -0.87) [65]. When the three studies were combined, the LOS decreased with a MD of -1.64 days (95% CI -2.24, -1.05; P < 0.00001; Analysis 1.4.17).

Malnutrition

Doig et al. (2008) reported reductions in LOS for malnourished hospitalized elderly patients managed with the use of CPW, (9.1 days (SD 11.5) for CPW group versus 9.9 (SD 13.3) for the usual care group, P = 0.24) [124]. Conversely, Trombetti et al. (2013) found an increase in the LOS for malnourished patients after the use of a clinical pathway (38 days (SD 34) for CPW group versus 37 days (SD 32) for usual care, P = 0.613) [67]. The combined effect resulted in no differences between both groups with a MD of -0.67 days (95% CI -2.07 to 0.74; Analysis 1.4.18).

Suspected myocardial infarction

Gomez et al (1996) [23] and Roberts et al. (1997) [115] both reported reductions in LOS for CPWs implemented in emergency departments for suspected myocardial infarction. Gomez 1996 reported a reduced LOS in the CPW group (0.64 days (SD 0.51) versus 2.28 days (SD

5.25); P = 0.0001). Roberts et al. (1997) reported a LOS of 1.38 days (SD 1.18) in the CPWs group versus 1.84 days (SD 1.33; P = 0.08) in the control group (MD -0.49 days; -0.87, -0.11). The combined LOS for the Gomez et al. (1996) and Roberts et al. (1997) studies was MD -0.90 days (95% CI -1.98 to 0.18; P = 0.10; Analysis 1.4.19).

Length of hospital stay: invasive versus non-invasive conditions

Fourteen primary studies [24-26, 64-68, 107, 109, 113, 121, 123, 124] reporting on LOS focused on the use of a CPW for non-invasive procedures and eight studies [23, 101, 102, 104, 105, 110, 115, 120] used a CPW for invasive procedures (surgery, mechanical ventilation, coronary angiography). According to health economic theories, invasive procedures should be standardized more easily than non-invasive procedures due to variation during treatment [134]. However, the combined effect estimate showed a minimal reduction in the overall length of hospital stay for invasive conditions versus non-invasive conditions respectively (MD -1.39 days, 95% CI -2.17 to -0.60; P = 0.0006 (Analysis 1.4.20) versus MD -0.81 days, 95% CI -1.25 to -0.37; P < 0.00001, Analysis 1.4.21).

Length of hospital stay*:* implementation strategies

(≤ 3 evidence-based implementation strategies)

Seven studies [65-67, 102, 109, 115, 121] employed less than four implementation strategies (Table 3) during the implementation of a CPW. After combining the seven primary studies based on LOS, we observed a reduction in the LOS with a MD of -1.42 days (95% CI -2.40 - 0.43; P = 0.005; Analysis 1.4.22) with high variation among the pooled studies; I^2 = 66%. Sensitivity analysis excluding studies at high risk and unclear risk of bias from the analysis shows a reduction with a MD of -2.61 days (95% CI -8.13 to 2.91; P = 0.35; Analysis 1.4.23).

(4 to 6 evidence-based implementation strategies)

Twelve studies [23, 26, 64, 68, 101, 104, 105, 110, 113, 120, 123, 125] employed four to six implementation strategies. The combined effect estimate resulted in reduction in the LOS with a MD of -0.98 days (95% CI -1.48 to -0.47; P = 0.00001; Analysis 1.4.24).

(≥ 7 evidence-based implementation strategies)

Two studies [25, 107] reported the use of seven or more implementation strategies. The combined effect resulted in no real increase in LOS with a MD 1.17 days (95% CI -3.87 to 6.22; P = 0.65; Analysis 1.4.25).

3.12.5 Oncology Pathways

With regards to the implications of using a CPW that directly related to oncology care, only one study [135] was found; therefore, statistical pooling was unable to be conducted. Costantini et al. (2014) examined the effectiveness of a CPW on the quality of end-of-life care for patients with cancer in hospitals and for their family members in an Italian medical context [135]. A post intervention assessment involved interviews with 232 family members of patients who had died from cancer approximately 107 days after death. No significant difference for the overall quality of care was determined between wards in which the CPW program was implemented and the control wards.

By comparison, one study [110] conducted in a Japanese medical context that indirectly related to oncology care found several positive implications of using a CPW. Kiyama et al. (2003) examined gastrectomy patients with either gastric cancer or gastrointestinal stromal tumors (malignant or benign tumor not specified) to determine the clinical and cost-effectiveness of a standardized CPW in comparison to traditional consultations [110]. Regarding patient outcomes, the target achievement at 24 hours ($P < 0.005$), 4 days ($P < 0.05$), 7 days ($P < 0.05$), and 14 days ($P < 0.001$) were significantly improved for the CPW group in comparison to the control. In terms of the length of time in hospital, preoperative stays were significantly reduced ($P < 0.001$) in the CPW group (MD 9 days, SD 3.2) versus control group (MD 12.6 days, SD 6.0). A reduction was also reported for postoperative stays ($P < 0.01$) in the CPW group (MD 18.1 days, SD 9.5) in comparison to the control group (MD 28.2 days, SD 22.3). However, the length of postoperative stay did not differ between groups for patients with postoperative complications (MD 25.5 days, SD 4.8 for CPW group versus MD 33.9, SD 10.2 for control group). The reduction in length of hospital stay for patients in the CPW group resulted in a 22% decrease in medical costs as measured by a cost-consequences study.

3.12.6 Hospital costs and charges

Out of 32 primary investigations grouped as single pathway interventions, eight of the included studies (1264 patients) reported on a highly varying set of cost/ charge measures. All eight studies [23, 24, 101, 107, 110, 115, 121, 132] found lower hospitalization costs/ charges or insurance points for CPW groups. We reported all hospital charges and cost in US dollars.

Five studies reported on hospital costs [109-111, 115, 132]. While professional fees were included in the hospital costs reported by Kiyama et al. (2003) and Roberts et al. (1997), Kim et al. (2002) excluded them from the cost estimates. Three [109-111] out of the four studies used indirect hospital costs and only one study [115] reported on direct and indirect hospital costs. Only two studies [110, 115] reported on reductions in hospital costs; Kiyama et al. (2003) reported full hospital cost (direct and indirect costs) of USD 13069.36 (SD 1822) for CPW group vs USD 16,806 (SD 5072), $P<0.001$, for patients undergoing gastrectomy at a medical school hospital. Roberts et al. (1997) also reported full hospital cost of USD 2,344 (SD 1145) for patients managed on a CPW vs USD 3,214 (SD 919) for patients following usual care ($P<0.01$). Verdu et al. (2009) reported an estimated cost savings of around EUR 21,393.18 (EUR 60,391.90 - EUR 38,998.72) in 2004 in comparison cost incurred in 2002 after the implementation of a clinical pathway to manage patients with lower deep vein thrombosis in an academic tertiary Spanish hospital [132].

Within the subgroup of hospital charges, three studies [23, 107, 125] reported hospital charges associated with the use of CPWs for patients with varying clinical conditions. All three studies [23, 107, 125] reported reductions in the hospital charges for patients managed via CPW as compared to usual care and one study found difference between both groups. Gomez et al. (1996) reported 30 day-hospital charge of USD 1,424 (SD 1,735) for myocardial ischemic patients following a CPW vs USD 5,860 (SD 14,638) for the usual care group ($P = 0.0001$) [23]. Johnson et al. (2000) reported hospital routine charges (room charge) of USD 2407 (SD 1151.9) for asthmatic patients following a CPW vs USD 3116 (SD 1151.9) for those following usual care ($P<0.001$) [107]. Panella et al. (2009) reported hospital charges for patients hospitalized with heart failure following a CPW to be Euros 2125 (SD 843.52) while Euros 2211 (SD 917) was estimated for patients following usual care ($P = 0.11$) [125].

Types of hospital costs and charges reported in included studies are provided in Appendix 2. Table 3 provides data as reported whereas Table 4 provides price data adjusted to US dollars standardized to the year 2016. Two studies [101, 121] used surrogate cost outcomes in form of the Japanese insurance points and they reported reductions in charges and surrogates for the pathway groups. Aizawa et al. (2002) reported 48424.2 insurance points for patients (n = 32) managed with a CPW and 55365.5 insurance points for patients (n= 37) managed with usual care, Usui et al. (2004) reported 24.338 insurance points for patients (n = 30) managed with a CPW and 34.048 insurance points for patients (n= 31) managed with usual care, P = 0.0031. Taken together, the MD was USD 1171.52 (95% CI -1835.86 to 507.1; P < 0.00001; Analysis 1.5). There was substantial heterogeneity, I^2 = 88% and we found very low-certainty of evidence (Summary of findings table 1).

3.12.7 Adherence to recommended practice

Three studies [25, 89, 96] measured the impact of CPWs on the adherence to recommended practice by healthcare professionals using a CPW, and all three reported positive findings for the use of CPWs. Adherence to recommended practice was measured by the quantity of documentation conducted by healthcare professionals while managing patients on a CPW. Doherty et al. (2006a) reported a 54% improvement in documentation of severity of asthma in the study hospitals compared to a 3% improvement in the control hospitals. Sulch et al. (2002) measured documentation of team goals for stroke patients and reported compliance in 75 of 76 cases in the intervention versus 56 of 76 cases in the control group (OR 26.79, 95% CI 3.49 to 205.58).

Tilden et al. (1987) measured documented identification of female victims of domestic violence in the emergency department and found no change when time series analysis was utilized. Due to insufficient number of comparable studies, we did not conduct any meta-analysis for this outcome.

Other professional practice outcomes reported by three studies [25, 117, 123] include: provider knowledge, patient contact, and provider-patient communication (Table 4; Table 7; Table 10; Table 11) reported a reduction in the number of inappropriate uses of urodynamics for urological patients managed with a CPW (43% for the CPW group and 45% for usual care) and increase in the compliance score regarding recommendations for initial hospital

assessment for urinary incontinence (3.5 points for CPW and 3.0 for usual care). Cunningham et al. (2008) reported: an increase in the number of medical contacts with asthmatic patients during the first 12 hours of care (6 contacts for the CPW group versus 5.5 contacts for usual care, P = 0.04); increase in the number of nursing contacts with patients (22 contacts for the CPW group versus 19.2 contacts for usual care, P = 0.001); and increase in the number of clinician contacts with all patients (16 contacts for the CPW group versus 13.8 contacts for usual care, P = 0.001). Sulch et al. (2002) found an increase in the proportion of communications with general practitioners following death/discharge within a 24-hour time (80% for the CPW group and 45% for usual care, P < 0.001). However, Chadha et al. (2000) found a 2% reduction in the percentage of appropriate first-line treatments for urological patients (81% for the CPW group and 83% for usual care).

3.13 ITS studies

Three ITS studies [95-97] are included in this review.

Brattebo et al. (2002) investigated the effect of a scoring system and protocol for sedation on duration of patients' need for ventilator support in a surgical intensive care unit. Measures (LOS and ventilator time) were taken 11 months before and after the introduction of the sedation protocol at the ICU department of the hospital. Using a time series analysis, Brattebo et al. (2002) found a 2.1-day (95% CI 0.65 to 3.55) reduction in mean ventilator time, demonstrated by a decrease from 7.4 days to 5.3 days after the implementation of the sedation protocol for ventilating ICU patients. Brattebo 2002 also reported a 1 day (95% CI -0.89 to 2.89) reduction in mean LOS demonstrated by a reduction from 9.3 days to 8.3 days after the introduction of the intervention.

Rotter et al. (2014) reported on the effects of a CPW for 254 prostate patients undergoing radical laparoscopic prostatectomy at a surgical ward of medical facility. Data was collected using at six time points every 4-week before (n = 123) and after (n = 131) the implementation of the intervention. Mixed results were reported from this study. Rotter et al. (2014) reported no change when comparing LOS before (9 days) and after (9 days) CPW implementation. There was no difference in slope (P = 0.472) or change in mean (P = 0.910). Rotter et al. (2014) also reported a reduction in the number of admissions to ICU with 11 admissions pre-intervention and 4 admissions post intervention (P =0.041). Further, Rotter et al. (2014) found an increase in the number of re-operations after pathway implementation (n = 4 pre-

pathway and n = 5 post-pathway P = 0.539) and a decrease in the number of transfusions of blood products after pathway implementation (n= 4 pre-pathway and 3 post-pathway, P = 0.465). Finally, Rotter et al. (2014) reported an increase in the number of patients requiring readmissions within 30 days (n= 8 pre-pathway vs n = 23 post pathway implementation, P= 0.006).

Tilden et al. (1987) investigated the effect of a nursing protocol in identifying battered women receiving care in the ED of a hospital. The goal of the protocol is to increase the rate of identification of battered women presenting to the ED of the hospital. The intervention was introduced in May 1984 and data was collected at four time points prior to (n = 72) and after (n = 74) the implementation of the intervention (June to September 1983 and June to September 1984). Tilden et al. (1987) found an increase in the post treatment rate of positive battering during the study period (7 cases pre-intervention vs 17 cases post-intervention, P = 0.03).

Table 3–4. **Summary of findings table 2**

Multifaceted clinical pathway compared to usual care						
Patient or population: hospitalised patients **Setting:** hospital **Intervention:** multifaceted intervention (including clinical pathway) **Comparison:** usual care						
Outcomes	**Anticipated absolute effects*** **(95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with usual care	**Risk with Multifaceted intervention (including clinical pathway)**				
90-day mortality	Study population		-	227 (2 RCTs)	⊕⊖⊖⊖ Very low[1, 2, 3]	Statistical pooling was not conducted due to insufficient number of studies
	See comment	See comment				
Hospital readmission up to six months	Study population		-	1569 (2 RCTs)	⊕⊕⊖⊖ Low[1, 3]	Statistical pooling was not conducted due to insufficient number of comparable studies
	See comment	See comment				
In-hospital complications	Not reported		-	-	-	Outcome not reported

Multifaceted clinical pathway compared to usual care						
Length of hospital stay	See comment	See comment	-	292 (2 RCTs)	⊕⊕⊖⊖ Low[1, 4]	Random-effects analysis: MD -0.71 (95% CI -1.84 to 0.42)
Hospital costs and charges	See comment	See comment	-	371 (2 RCTs)	⊕⊖⊖⊖ Very low[1, 4, 5]	Statistical pooling was not conducted due to insufficient number of comparable studies
Adherence to recommended practice	Not reported		-	-	-	Outcome not reported

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **MD**: mean difference; **RT**: randomised trial

GRADE Working Group grades of evidence
High-certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate-certainty: we are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low-certainty: our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low-certainty: we have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[1]Downgraded one level due to risk of bias (concealment, randomisation, contamination, dissimilar baseline characteristics).

[2]Downgraded one level due to imprecision (small sample size).

[3]Downgraded one level due to publication bias (difficult to assess owing to insufficient studies).

[4]Downgraded one level due to imprecision (confidence interval contains benefit and harm).

[5]Downgraded one level due to inconsistency (excluding the outlier study, visual inspection suggests inconsistency).

3.14.1 *90-day mortality*

Two studies [114, 129] measured in-hospital mortality up to 90 days and reported no evidence of a reduction in mortality after the use of a CPW. The time to follow-up was not documented by Cole et al. (2002) who found no difference in mortality between intervention and control groups (22.1% versus 19.3%). Philbin et al. (2000) reported no difference in heart failure-related or all-cause mortality at six months. Due to insufficient number of comparable studies, we did not pool the effect estimates. There was very low-certainty of evidence (Summary of findings table 2).

3.14.2 *Hospital readmissions up to six months*

The effect of a CPW on hospital re-admission up to six months was investigated in two studies [108, 114], which looked at the use of a CPW for children with asthma and elderly patients with heart failure respectively. Philbin et al. (2000) reported 169 readmission events for heart failure up to six months for 840 experimental patients vs. 141 readmissions for 664 patients in the control group (P = 0.97) during the management of heart failure patients with a CPW. Readmissions for all causes up to six months were 363 events for 840 patients in the experimental group vs. 293 events for 664 control patients (P = 0.93). Kampan 2006 reported a reduction in six month readmissions for hypoglycemia in patients with diabetes (6% for CPW group versus 34% for usual care; P = 0.04). Studies were not combined due to differences in patient characteristics and insufficient number of studies. There was low-certainty of evidence (Summary of findings table 2).

3.14.3 *Length of hospital stay*

Out of the seven primary studies categorized as multifaceted interventions including a CPW element, three studies [108, 114, 129] reported LOS measures. All studies reported no difference between CPW and usual care groups and Kampan et al. (2006) employed a small sample size. Studies were not combined due to differences in insufficient number of comparable studies. There was low-certainty of evidence (Summary of findings table 2).

Subgroup analyses

3.14.3.1 Length of hospital stay- country

There was an insufficient number of studies to examine country effect on multifaceted intervention including a CPW.

3.14.3.2 Length of hospital stay- condition or intervention

Seven disparate conditions were reported by seven primary studies in this group thus subgroup analysis was not feasible. The different pathway conditions (Table 2) were bipolar disorder [106], palliative care [116], mechanical ventilation [95], asthma in children [103], delirium in older medical patients [129], diabetic patients admitted with hypoglycemia [108] and heart failure [114].

3.14.4 *Hospital costs and charges*

Three [106, 108, 114] out of seven studies grouped as multifaceted interventions including a CPW element reported on hospital costs/charges. Bauer et al. (2006) reported on a set of cost measures stratified on several criteria: three year mean intervention costs, variable outpatient costs, hospital inpatient costs, psychiatric inpatient costs and medical / surgical inpatient costs. None of these three studies reported on differences between the groups in terms of cost/ charge outcomes whilst Kampan et al. (2006) employed only a very small sample size available for analysis. Both studies compared the same sort of variable hospital costs included for each study in the pooled analysis, although it remains unclear if the term "mean costs" used in the Kampan et al. (2006) study refers only to variable costs as further information was not able to be elicited from the chief investigator. Studies were not combined due to insufficient number of comparable studies. There was very low-certainty of evidence due to risk of bias, imprecision and inconsistency (Summary of findings table 2).

3.8 Discussion

3.8.1 Summary of main results

Clinical pathways are implemented in various hospital settings for the management of different clinical conditions. After applying the inclusion criteria to approximately 13,000 search hits, thirty-nine studies with 15911 patients from thirteen countries were included in the final analysis and synthesis. This review included a broad range of clinical conditions using invasive and non-invasive procedures, for which a clinical pathway was implemented in a specific setting of a hospital in addressing the medical condition. Overall, mixed results were reported on the effects of CPWs on patient, professional, length of stay and cost outcomes. The high level of heterogeneity in the clinical conditions and settings examined precluded meaningful meta-analysis of many outcomes and therefore limited our certainty in some of the pooled estimates. Despite the limitations in this review, some of the findings may be valuable to policy makers, managers, researchers, teams and clinicians working with clinical pathways in hospital settings.

The overall findings show that stand-alone clinical pathways implemented in hospitals may reduce in-hospital complications and hospital costs (low certainty evidence). It is uncertain whether stand-alone clinical pathways reduce the length of stay in hospitals or improve the adherence to recommended practice among health care providers in hospital settings because

the certainty of evidence is very low. For multifaceted interventions including a CPW, the use of a CPW may make little or no difference to the hospital length of stay (low certainty evidence) and it is uncertain whether the use multifaceted interventions including a CPW reduce hospital costs because of the certainty of evidence is very low. However, the results must be interpreted with caution, recognizing the variation in hospital settings and clinical conditions, as well as clinical outcomes examined within the studies included in this review. We found a limited number of well-designed study designs evaluating the effects of hospital clinical pathways on other outcomes.

3.8.2 Patient outcomes

Several patient groups were included in this synthesis reflecting the breadth of the review. 90-day mortality, hospital readmissions up to six months and In-hospital complications were reported as direct patient outcomes examined by more than one study. Stand-alone and multifaceted CPW interventions implemented in hospitals make little or no difference in hospital readmissions up to six months (low certainty evidence). A significant reduction in the in-hospital complications assessed was found in the CPW group compared to usual care and the evidence was rated at low certainty implying that stand-alone CPWs may reduce in-hospital complications in hospitals (low certainty evidence). The meta-analytic comparison includes about 1007 patients in the experimental, as well as 1005 patients in the control groups and we observed a reduced effect with an odds ratio of 0.46 (CI 95% 0.33 to 0.64). The results are not unexpected owing to the different clinical conditions examined in the meta-analysis summary. Examining mortality among hospitalized patients on a clinical pathway should likewise be interpreted with caution as other meaningful indicators such as LOS, re-admissions should be considered.

3.8.3 Length of hospital stay

Majority of the studies (27) examining the effects of clinical pathways on hospital length of stay reported beneficial effects while four studies reported increased LOS after CPW implementation. Lack of study power may be responsible for the beneficial effects on LOS without achieving statistical significance. Overall, the variation in the effects of clinical pathways on length of hospital stay may be due to different clinical conditions examined by the individual studies reporting on the length of stay. Patients with comorbidity may require longer hospitalization compared to those without comorbidities. Hence, it is worth noting that

longer LOS does not automatically imply bad care or failed clinical pathway implementation, but provides room for further investigation and suggested changes to the pathway design if necessary. Other important indicators such as re-hospitalization or re-admission rates, mortality rate or rate of complications may be may need to be evaluated in conjunction with LOS to investigate the effect of CPWs thoroughly.

In this review, there was significant reduction in LOS when looking at single clinical pathway interventions compared to multifaceted interventions. The results from the multifaceted intervention showed that there were no differences between groups. The lack of difference between study groups may be due to the number and sample size of the included studies investigating the effects of multifaceted CPW interventions on length of stay. Based on the results, it is uncertain whether stand-alone CPWs reduce length of hospital stay, because the certainty of this evidence is very low. In addition, multifaceted CPW interventions may reduce length of hospital stay (low-certainty evidence). However, the results should be interpreted with caution, and associated factors such as clinical condition, comorbidity, hospital policies, and healthcare systems should be considered.

3.8.4 Hospital costs

Majority of the included studies reporting on cost outcomes or indicators found reductions in hospital cost for patients managed on a CPW compared to usual care. These costs include hospital charges, variable and fixed cost associated with patient hospitalization. Studies utilizing insurance points as cost surrogates also reported reductions due to the use of a clinical pathway in patient management. We found that stand-alone clinical pathways may reduce hospital costs compared to usual care (low certainty evidence), while multifaceted CPW interventions may make little or no difference to hospital costs (low certainty evidence). It is also imperative to examine other factors (e.g., the effect of case mix or Diagnostic related groupings reimbursement systems) that may influence cost outcomes for hospitalized patients but this was beyond the scope of this review.

3.8.5 Professional practice outcomes: adherence to recommended practice

All three included studies reporting on adherence to recommended practice were conducted in stand-alone CPW hospital settings. The three studies reported improvement in the quantity of documentation by healthcare providers using a clinical pathway for patient management as

compared to usual care. However, owing to the risk of bias inherent in the included studies, it is uncertain whether stand-alone CPWs improve the quantity of documentation by healthcare providers in the hospital because the certainty of this evidence is very low. Improved professional documentation may not be directly associated with favorable patient outcomes, but it may increase patient safety because of improved team functioning and communication during care delivery.

There were insufficient numbers of comparable studies to draw other meaningful conclusions to examine the effects of CPWs in hospitals for other primary and secondary outcomes.

3.8.6 CPW Implementation strategies

Several strategies used for implementing CPWs were identified by this review (Table 3-2). All included studies reported the use of a multifaceted approach for clinical pathway implementation in different sections of the hospital. Out of the 39 included studies, clinician involvement was the most common implementation strategy (31 studies) reported by all included studies while few studies (8 studies) reported on the identification of barriers to change before CPW implementation. Based on LOS data and after examining seven studies utilizing less than three implementation strategies, we observed minimal reductions in the pooled effects on LOS. The result was not consistent after conducting a sensitivity analysis. Interestingly, studies utilizing four to six number of implementation strategies did not result in further reductions in hospital LOS. The pooled estimates for studies that used seven or more implementation strategies did not show differences between the CPW group and usual care. Our overall finding of no difference between multifaceted and single intervention strategies to implement CPWs in hospital contexts conforms with the conclusion of a recent systematic review by Squires et al. (2014) [136]. Overall, the high level of variation in all the pooled estimates and the insufficient number of studies reporting on the use of seven or more implementation strategies probably accounted for differences between the groups and further limited meaningful conclusions on the relationship between using clinical pathways and improvement in LOS. For this review, we only evaluated the number of implementation strategies used in each study and not the degree to which any given strategy was implemented.

3.8.7 **Overall completeness and applicability of evidence**

This review update included 39 studies and was limited to single and multifaceted clinical pathways mostly implemented in urban hospital settings. We investigated the effects of single and multifaceted CPWs interventions on the patient outcomes, length of stay, cost and professional practice outcomes. Due to the broad scope of the review questions and certainty of evidence of the results, we are unable to draw firm conclusions on any of the results. Thus, the applicability and generalization of the review findings are a concern. Apart from the statistical pooling of similar studies to answer specific review questions, we conducted subgroup analyses where feasible to further explore heterogeneity in the pooled estimates. To further investigate heterogeneity in the combined effects, where possible, we examined the context and disease-specific variances that may explain our results and meaningful to the review conclusions.

For single CPW interventions implemented in emergency departments, seven studies were sufficiently similar and used for meta-analysis to investigate the impact of CPWs on emergency department LOS. Initially, we observed a reduction in LOS, but the results were invalidated upon conducting a sensitivity analysis by excluding studies with high and unclear risk of bias. Hence, preliminary analysis suggests that CPW implementation may lead to reduced LOS in emergency departments. However further research tailored to this hospital setting with an increased number of similar studies may be required to answer this specific question.

For general acute hospital admissions, eleven studies were comparable and valid results favoring a reduction in LOS was observed from the pooled estimates. However, a sensitivity analysis was not feasible to examine the robustness of our findings thus limiting the applicability of our evidence in this practice setting. A similar approach with three studies for extended hospital care and two studies for intensive care units did not point to any difference between both groups.

One of the recommendations from the previous version of this review Rotter et al. (2010) is the exploration of disease-specific pathways with the hope of reducing heterogeneity after grouping studies by disease conditions. Based on three similar studies from the sub-group analysis, we observed a reduction in the LOS with the use of a CPW for pneumonia

management in the hospital. However, the external validity of this finding was limited because of the risk of bias inherent in the pooled studies thus requiring further investigation with a sufficient number of studies. There was insufficient number of studies focused on other clinical conditions or procedures (asthma, mechanical ventilation, myocardial infarction, malnutrition and stroke rehabilitation). The combined estimates for these investigations also yielded different effect sizes and statistical significance.

With the notion of clinical pathways' potential to reduce variation in care delivery by standardization of care processes, we also explored the effects of CPWs on invasive and non-invasive hospital procedures using twelve and eight similar studies respectively. Based on LOS data, we found reductions in LOS for both categories of hospital procedures with minimal difference between both groups (non-invasive vs invasive procedures) in absolute effect (1.39 days vs 0.81 days respectively). The results were not robust enough to draw meaningful conclusions for non-invasive and invasive procedures due to methodological bias in the primary studies. This interesting although limited finding warrants further investigation that may be meaningful to future use of hospital resources. Such investigations will also be useful for hospital managers to prioritize future areas of clinical pathway development and implementation while balancing patient and health system goals.

3.8.8 **Certainty of the evidence**

3.8.8.1 Stand-alone CPWs

Most studies had methodological issues with study designs and protocol implementation, resulting in high or unclear risk of bias which affected the certainty of evidence. Also, the high level of statistical (I^2 value) and clinical variation in the different conditions and practice settings examined affected the degree of inconsistency and imprecision in the overall results. We evaluated the certainty of the seven reported outcomes (90-day mortality, hospital readmissions up to six months, in-hospital complications, LOS, hospital costs and adherence to recommended practice) using the GRADE system. For stand-alone CPW interventions compared to usual care, we found low and very-low levels of certainty evidence for mortality rates reported up to 90 days due to imprecision and publication bias.

We also graded the certainty of evidence for hospital readmissions up to six months for stand-alone CPW interventions as low due to concerns over the risk of bias and imprecise

estimates. We ranked the certainty of evidence for in-hospital complications as low due to concerns about the risk of bias and imprecise estimates. We graded the certainty of evidence for LOS as very low due to considerations of risk of bias and high-level inconsistency inherent in the pooled studies. Finally, we found very-low level certainty of evidence for adherence to recommended practice due to concerns about the risk of bias and imprecision.

3.8.8.2 Multifaceted CPWs

We found low and very-low levels of certainty of evidence for 90-day mortality in multifaceted CPW interventions compared to usual care due to concerns about imprecision and publication bias. We downgraded the certainty of evidence for six-month hospital re-admissions for multifaceted CPW intervention from high to low due to concerns over the risk of bias and imprecise estimates. In-hospital complications and adherence to recommended practice were not reported by multifaceted CPW interventions. Also, we found low certainty of evidence for LOS for multifaceted CPW interventions due to concern with the risk of bias and imprecision of study results. We graded the certainty of evidence for hospital costs for multifaceted CPW interventions as very-low due to issues around inconsistency, risk of bias and imprecision in the pooled estimates. The certainty of the body of evidence suggests that specific outcomes may be improved by the implementation of CPWs in different hospital settings.

3.8.9 **Potential biases in the review process**

To avoid publication bias, we employed an extensive and highly sensitive search strategy for study identification owing to the complex nature of clinical pathways and the broad review questions investigated in this review. We developed and used our refined working definition on CPWs due to the high variation in the terminologies used to describe a clinical pathway. The validated checklist on what constitutes a clinical pathway helped to include CPW interventions irrespective of the terminology used in the study. Two people independently screened all search results in the screening and full-text stage. We used imputation techniques to approximate missing data where applicable and for non-respondent primary authors during the contact process. Although imputation was conducted for a low number of studies, there is a likelihood of this procedure distorting the overall clinical and or statistical significance.

3.8.10 **Agreements and disagreements with other studies or reviews**

To date, this review remains the only comprehensive systematic review investigating the effects of clinical pathways on length of stay, professional practice outcomes, patient outcomes and costs in hospitals. This review update adds new data to the previous Cochrane systematic review on this topic by Rotter et al. (2010). The conclusions from this systematic review update are in line with the first version published. However there is a low certainty of evidence found for most of the primary outcomes examined in this update. Following the Cochrane EPOC review methods, Rotter 2010 included 11,398 participants from 26 studies and reported that clinical pathways are associated with a decrease in in-hospital complications and an increase in documentation by healthcare professionals in the hospitals. Rotter 2010 did not examine the certainty of evidence.

We found a very-low level certainty of evidence for an increase in adherence to recommended practice following the use of stand-alone clinical pathways in hospitals. Rotter 2010 also saw a decrease in the in-hospital complications after examining five studies using stand-alone clinical pathways in hospital settings. We similarly observed a reduction in the in-hospital complications after combining seven studies. We found low certainty of evidence for in-hospital complications using stand-alone CPW compared to usual care. ALso, for stand-alone CPWs compared to usual care, we found very-low and low levels of certainty of evidence in the reduction of hospital length of stay and hospital costs respectively. These additional findings are consistent with a non-Cochrane systematic review investigating the impact of clinical pathways on hospital length of stay and hospital costs [137].

Conversely, multifaceted CPW intervention may make little or no difference to the length of stay in hospitals (low certainty evidence). Finally, it was uncertain if multifaceted CPW intervention reduces hospital costs because the certainty of this evidence is very low. Other systematic reviews [138, 139] on this topic are disease-specific and reported mixed results. We do not have the sufficient number of studies from this review to test and replicate their review findings.

3.9 Authors' conclusions

3.9.1 Implications for practice

This review provides evidence based on included primary studies conducted in 13 countries (Australia, Canada, Germany, Italy, Spain, Switzerland, United Kingdom, United States, Japan, Taiwan, Thailand, New Zealand, Norway). The low certainty of evidence associated with the majority of the primary outcomes investigated in this review does not permit robust evidence-based conclusions. Although significant variation exists in the direction of effects reported by primary studies, this may be due to the differences in health systems, clinical conditions and other context-specific factors. However, stand-alone clinical pathways may reduce in-hospital complications and hospital cost compared to usual care (low certainty evidence). It is uncertain whether stand-alone clinical pathways reduce hospital length of stay or improve adherence to recommended practice by healthcare providers because the certainty of this evidence is very low.

Multifaceted clinical pathway interventions implemented in hospitals compared to usual care makes little or no difference in hospital readmissions up to six months and length of stay (low certainty evidence). It is uncertain if multifaceted clinical pathway interventions reduce 90-day mortality and hospital costs because the certainty of this evidence is very low.

Overall, there is an association between stand-alone CPWs and a reduction in hospital complications, reduced length of stay, reduced costs and adherence to recommended practice. However, there is no association between stand-alone CPWs and mortality and readmissions. For Multifaceted CPW interventions implemented in hospitals, there is no association between CPW as part of a multifaceted approach and mortality, readmissions, length of stay and costs.

It is worth noting that the review conclusions are limited to the country where the included studies are carried out. The limitations in evidence for effects of clinical pathways in hospital care previously mentioned and the heterogeneity in healthcare systems of the primary studies suggest careful interpretation and application of the evidence into different hospital jurisdictions. Large numbers of adequately powered and rigorous primary studies are required to investigate each sector of hospital care adequately. Due to the costs associated with the implementation and sustainability of complex interventions such as clinical

pathways, a careful prioritization among stakeholders, including patients should be considered.

Also, many studies showed no differences between the pathway group and usual care which may suggest a lack of study power in the design of the study, a relatively high level of care provided in those settings, or low uptake of the pathway intervention by healthcare professionals. Thus, it is imperative for clinical managers to pay close attention to implementation strategies that are more likely to lead to successful patient outcomes.

3.9.2 **Implications for research**

Study designs

Majority of the included studies were randomized patient studies and are prone to the serious risk of bias of contamination of healthcare professionals that may distort the certainty of evidence. We recommend the use well powered cluster-randomized designs on a hospital level to reduce the threats to internal validity posed by patient-RCTs conducted in the same institution or ward. Interrupted time series design with sufficient time points and well-designed controlled before-and-after study design with at least two intervention and two control groups can also be considered. However, it is difficult to eliminate contamination during the evaluation of social complex interventions such as CPWs. Thus, we recommend the use of realist designs which considers contextual factors that modulate patterns of outcomes observed at the level of reality.

Intervention reporting

The development and implementation of the clinical pathways were poorly reported in most studies. This poor reporting hampered our ability to assess implementation and other contextual factors that may translate to successful patient and health system outcomes. These assessments are imperative and will aid program implementers to utilize scare healthcare resources judiciously. It will also enable them to choose the best strategies that are evidence-informed and tailored to the local context. Based on the evidence generated in this review and the findings by Squires et al. (2014) on implementation strategies for complex interventions, we recommend future evaluators to select and prioritize their implementation strategies carefully.

Clinical pathway definition

Owing to the lack of consensus for a clinical pathway definition, identification of primary studies for thorough evaluation of the effects of clinical pathways remain an on-going challenge. We overcame this barrier by refining and pilot testing an operational or working definition for clinical pathways that was subsequently applied to identify important studies. We recommend future researchers or evaluators to use and refine our working definition as they deem fit to their clinical context when synthesizing evidence on this topic. Further research such as concept analysis is required to address the variation in the definition of this complex intervention.

Outcome reporting

The quality of reporting of the study outcomes in many studies was problematic. Primary and secondary outcomes alongside their uncertainty measures should be completely assessed and reported by authors of primary studies. Complete reporting will enable a thorough analysis of the study outcomes, as imputation limits the external validity of the evidence generated. To ensure meaningful interpretation of patient-important measures such as hospital length of stay or mortality rate, associated measures such as rehospitalization or readmissions should likewise be reported.

Cost evaluations

There is an urgent need for robust economic analysis and economic evaluations of clinical pathway interventions in healthcare. This chasm, if filled, will aid policymakers and clinical managers to make evidence-informed decisions to develop, implement and sustain clinical pathways in hospitals. Until this evidence is available, it is difficult to ascertain the return on investment of healthcare dollars.

3.10 Author Contribution

Thomas Rotter (TR) and Leigh Kinsman (LK) conceptualized the study. TR, AL, LK planned the review process in consultation with the Australasian Cochrane Centre. Adegboyega Lawal (AL) managed the data acquisition process in collaboration with the UK Cochrane Centre. AL, TR, LK, Phil Woods (PW), Andreas Machotta (AM) screened records for titles and abstracts. AL and Christopher Plishkha (CP) reviewed and extracted data from eligible full text articles and TR acted as an arbitrator to resolve any disagreement. AL took the

leadership of the review and led the writing, data analysis and final conclusions of the review. TR, LK, Ulrich Ronellenfitsch (UR), Shannon Scott (SS), Donna Goodridge (DG), Gary Groot (GG) provided comments and approved the final draft of the review to be published.

3.11 Differences between protocol and review

In consultation with the Australasian Cochrane centre, the following changes were made to the update review since the protocol was published in 2007.

1.) We refined the working definition for the definition of a clinical pathway (CPW). The following four criteria for clinical working definition derived include:

- the intervention was a structured multidisciplinary plan of care;
- the intervention was used to translate guidelines or evidence into local structures;
- the intervention detailed the steps in a course of treatment or care in a plan, pathway, algorithm, guideline, protocol or other 'inventory of actions' (i.e. the intervention had time-frames or criteria-based progression; and
- the intervention aimed to standardize care for a specific population.

An intervention meeting all four criteria was considered to be a clinical pathway

2.) Since the protocol was published in 2007, we split the review into two separate reviews; this review focusing on secondary care and the other on primary care. For literature searching purposes, we removed the colon and changed the title from 'Clinical pathways: effects on professional practice, patient outcomes, length of stay, and hospital costs' to 'Clinical pathways for secondary care and the effects on professional practice, patient outcomes, length of hospital stay and costs'.

3.) 'Adverse event' was listed as a separate secondary outcome in the protocol. However, due to the overlap with another outcome 'in-hospital complications', we recorded 'adverse events' as a type of in-hospital complication.

4.) We initially planned a fixed-effect and random-effects meta-analysis, however we only conducted random-effects meta-analyses owing to the assumption of the variation in the effect estimates across the included studies.

5.) The first version of this review did not include a 'Summary of findings' table. For this update, we incorporated a few changes to ensure the review complies with updated

MECIR standards by including two 'Summary of findings' tables with six patient relevant outcomes that were defined posthoc.

6.) To conform with the EPOC taxonomy for outcomes reported in EPOC reviews, we changed 'adherence to evidence-based practice' to 'adherence to recommended practice'.

7.) To avoid duplication in outcome reporting, we reported 'inpatient mortality' and 'mortality at longest follow-up' as '90-day mortality'.

TRANSITION FROM CHAPTER 3 TO CHAPTER 4

The Cochrane systematic review (update) on the effects of clinical pathways in hospitals showed that clinical pathways have potentials to reduce hospital length of stay, hospital costs, in-hospital complications and improve adherence to recommended practice. Apart from the equivocal results on the primary and secondary outcomes from the systematic review update, the following gaps were also identified from the review update:

1. Lack of a coherent theory on how clinical pathways work in hospitals
2. Limited research on costing studies and economic evaluations on clinical pathways utilizations in hospitals
3. Lack of contextual factors and mechanisms for successful implementation of CPWs in hospitals

To address some of the limitations of the systematic review update and to adequately address the research questions asked by this thesis, the next manuscript is a realist review protocol that aims to describe a method for developing a realist program theory for clinical pathways in hospitals. Using Pawson's approach for conducting realist reviews and recognizing the role of contextual factors, the protocols describes a five-step process to create the first realist program theory for clinical pathways in hospitals.

CHAPTER 4: DEVELOPMENT OF A PROGRAM THEORY FOR CLINICAL PATHWAYS IN HOPSITALS: PROTOCOL FOR A REALIST REVIEW (MANUSCRIPT 3)

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4.1 Abstract

Background: Despite the increased utilization of clinical pathways (CPWs) as a strategy to improve patient and system outcomes in hospitals, there remain ongoing challenges with their conceptualization, implementation and evaluation. Theories that explain how CPWs work in hospitals are lacking, making it difficult to identify important factors for sustaining changes arising from CPWs implemented in hospitals.

Methods: This is a protocol for a realist review following the approach proposed by Pawson et al. (2005) for realist synthesis and adapted by Molnar et al. (2015). The review will use a six-step iterative process to develop a program theory for CPWs in hospitals.

Discussion: Overall, the review aims to develop a program theory for CPWs in hospitals and to explore how, why, to what extent and in what contexts does the effective implementation of CPWs in hospitals contribute to better patient and system outcomes. As a result, the review will provide a theoretical evidence base on how CPWs work in hospitals.

Systematic review registration: CRD42018103220

Keywords: Clinical pathways, Realist review, Hospitals, Mechanisms, Implementation, Evaluation, Theory

4.2 Background

In this era of increasingly scarce resources, administrators and healthcare providers are tasked continually with the responsibility of providing high-quality patient-centered care [140, 141]. Hospitals play a vital role in patient management by providing acute and specialist services, which constitutes a core feature of well-functioning health systems [142]. Many health systems have turned to new ways of delivering patient care to maximize clinical efficiency [143]. Robust quality improvement initiatives to improve quality of patient care has been trialed across different health systems to improve the quality of the care delivered [143]. Examples of these hospital initiatives include the use of Six Sigma, Lean management and so on [143]. Despite the conscientious effort by healthcare systems to enhance patient outcomes, the adoption and sustainability of improvement initiatives remain an ongoing challenge. Communication and variation of clinical processes have been identified as crucial factors that impact patient care in several hospitals [144, 145].

Clinical pathways (CPWs), also known as care maps, algorithms or protocols are evidence-based multidisciplinary care plans that detail a stepwise approach to the management of patients with a specific disease [40, 146]. CPWs are used to translate universal clinical guidelines into local protocols to influence clinical practice [147]. Originating in the United States in the 1980s [16], CPWs have been implemented across many health systems and are primarily used in hospitals to reduce clinical variation by standardizing care processes, promoting interprofessional teamwork, containing costs and improving patient outcomes [21, 39]. CPWs are commonly implemented as web-based tools to support clinical decision-making processes.

Despite the widespread use of CPWs in healthcare settings, evidence on their effectiveness in hospital settings has been equivocal [21]. A Cochrane systematic review on effects of clinical pathways in hospitals by Rotter et al. (2010) [3] concluded that CPWs have the potential to reduce in-hospital complications and improve documentation among healthcare providers, although there was no evidence of differences in hospital readmissions or mortality rates [3]. Conversely, Doig et al. (2008) and Process et al. (2014) reported increased mortality within a period of 90-days after using CPWs to manage stroke and septic shock patients respectively [66, 124]. A systematic review by Deneckere et al. (2012) on the effects of CPWs on

teamwork found little evidence of improvement in staff knowledge, interprofessional documentation, team communication or team-relations [39].

The conceptualization, implementation and evaluation of CPWs in healthcare settings is an on-going challenge for program managers and CPWs researchers [16, 148]. Several problems plaguing this area of investigation includes a lack of a unified definition for CPWs in healthcare, scarcity of evidence-based strategies for effective implementation and the use of weak evaluative designs [16]. One of the common challenges facing CPWs in hospitals is the lack of explicit theories on how CPWs work in these practice settings [149]. Hospitals are complex healthcare environments with diverse stakeholders and structures interwoven to achieve different and common goals [150]. Adoption of interventions with multifaceted components (complex interventions), such as CPWs in hospitals, require a broader perspective and understanding of the hierarchical layers within the hospital environment [55, 151]. When poorly implemented, CPWs have been portrayed as "cookbook medicine" with little or no adherence by care providers at healthcare facilities including hospitals [41].

The use of theory in implementing evidence-based interventions is vital to the operationalization, adoption and replication of new knowledge in hospitals. Additionally, interventions underpinned by theories are more likely to provide meaningful information on the sequence of events and how they relate to the intended program outcomes [55]. This information can, in turn, be used to improve the overall program or be adapted for a different setting or purpose. Similar to other complex interventions, CPWs can have influence at the micro (individual), meso (healthcare teams) and macro (policy) levels of the health system and a thorough understanding of the relationship between these levels is required for system-wide success [152]. This protocol focuses on the effects of CPWs at the macro health system level, particularly on how effective implementation impacts health-system outcomes.

Factors such as leadership commitment, healthcare provider engagement, information technology, staff empowerment and patient engagement have been identified to influence implementation of CPWs in hospitals [153]. However, there is a lack of understanding of how these critical factors interact to influence patient care in hospitals [77]. Furthermore, unknown critical factors may negatively impact the implementation process and ultimately lead to poor outcomes. Hence, it is timely to develop a testable theory that can explain how,

why, to what extent and in what contexts effective implementation of CPWs in hospitals contributes to better health system outcomes.

A theoretical lens of how CPWs work in hospitals will uncover the essential determinants of effective implementation that can translate to better outcomes. Due to the methodological constraints posed by randomized controlled trials and systematic reviews of randomized controlled trials to control for contextual factors in CPWs research, it is difficult to unravel contextual factors that impact successful adoption of CPWs in healthcare environments. This is due to the difficulty in capturing the reality of healthcare professional environment with these evaluation designs. Therefore, we intend to conduct a realist review to develop a program theory for CPWs in hospital care.

Realist philosophy acknowledges that the world is "real" and humans interact with reality which limits or constructs their interpretation [154]. Thus, realist methodology considers multiple layers of interpretations within a social context as a function of reasoning and resources provided by the social environment [57]. This notion is important in our review because there is a likelihood of variation in the level of understanding or purpose of a CPW for different groups of care providers within the same hospital. Furthermore, our rationale for adopting a realist approach is due to the equivocal results from the preliminary results of our ongoing systematic review update on the effects of CPWs in hospitals [155]. The first version of the ongoing systematic review [3] was limited due to inadequate reporting of included studies and the methodical approach of conducting systematic reviews with explicit inclusion and exclusion criteria. This approach hindered the addition of narrative studies that might have been useful for identifying essential elements of implementation that are associated with intended outcomes.

Realist reviews aim to examine "what works for whom under what circumstances, how and why?" [60] Originally developed by Ray Pawson, a realist review utilizes multiples sources of information and relevant study designs linked to the program theory to explain causal relationships between contexts, mechanisms and outcomes with the goal of refining the program theory [57]. A program theory is an expression of how of an intervention or its components lead to intended outcomes [60]. The program theory seeks to provide decision-makers with an in-depth understanding of an intervention and how it works or does not work

in different contexts, thus making it appropriate for evaluating complex interventions such as CPWs.

While contexts are conditions that an intervention operates in (not necessarily settings), mechanisms in simple terms are "what causes things to happen." [57] Thus realists assert that the interaction between the context(s) and mechanisms can shed light on the patterns of outcomes observed. This theory based synthesis will utilize a context-mechanism-outcome (CMO) configuration to develop a program theory for implementing CPWs in hospitals [57]. CMO configurations will permit the formation of testable hypotheses that can be used for confirmation or refinement of an initial program theory [60]. For example, the identification of a hypothesis for implementing CPWs in hospitals that value "interprofessional collaboration" may provide valuable information that can be used to confirm or refute this aspect of the program theory. The proposed realist review will permit the development of testable hypotheses that can improve our understanding of CPWs in healthcare and how they contribute to better health system outcomes.

4.3 Review objectives and questions

The objective of this realist review is to develop a final program theory for CPWs in hospitals that can be subsequently tested in the real world for further refinement.

The primary review question is: "How, why, to what extent and in what contexts does the effective implementation of clinical pathways in hospitals contribute to better health system outcomes?" To ensure a sizeable scope of the review and allow for comparison with our ongoing systematic review on the effects on CPWs in hospitals, we will focus on the following health system outcomes: length of hospital stay, costs, in-hospital mortality, adherence to recommended practice and in-hospital complications.

The secondary review questions are as follows:

I. What contexts facilitate or hinder the implementation of clinical pathways in hospitals?
II. What mechanisms support the implementation of clinical pathways in hospitals?

4.4 Methods

With content and clinical expertise and librarian support, our team will review the CPWs literature with the aim of developing a program theory. We will adopt the approach by Molnar et al. (2015) [156], developed initially by Pawson for conducting realist review [57], to develop a program theory for CPWs in hospitals. The steps involves (1) development of a preliminary program theory; (2) search strategy and literature search; (3) study selection and appraisal; (4) data extraction; (5) data analysis and synthesis [156]. This review will be conducted following the RAMESES quality standard guidelines for realist synthesis [60]. For this review, we will adopt the working definition for a CPW originally developed by Rotter et al. (2013) and refined by Lawal et al. (2016): (1) the intervention was a structured multidisciplinary plan of care; (2) the intervention was used to translate guidelines or evidence into local structures; (3) the intervention detailed the steps in a course of treatment or care in a plan, pathway, algorithm, guideline, protocol or other 'inventory of actions' (i.e., the intervention had time-frames or criteria-based progression); and (4) the intervention aimed to standardize care for a specific population [146, 157]. An intervention meeting all four criteria will be considered to be a CPW.

4.5 Initial program theory development

In addition to examining the grey literature, the initial program theory will be derived by examining all articles retrieved from the literature search of the on-going systematic review update on the effects of CPWs in hospitals [155]. We will identify and group the processes, strategies, resources and outcomes resulting from the implementation of CPWs in hospitals based on the objective and theoretical accounts of the authors. The review team will construct the preliminary program theory by generating hypotheses of "how," "to what extent" and in "what contexts" does the effective implementation of clinical pathways in hospitals contribute to better health system outcomes. This process will be carried out in close consultation with a realist methodologist, Dr. Gill Westhorp. With support from the Saskatchewan Ministry of Health and the Saskatchewan Health Quality Council's Variations and Appropriateness Working Group, we will consult with a group of multidisciplinary content experts including physicians, nurses, researchers, project managers and other relevant frontline users of CPWs based in Saskatchewan, to provide critical insights to refine the preliminary program theory.

4.6 Search strategy and literature search

To develop an initial understanding of how effective implementation of CPWs in hospitals translates to better health system outcomes, we will conduct a focused examination of the CPWs literature. As recommended by the RAMESES guidelines, our search strategy and search terms will be guided by hypotheses developed from the preliminary program theory [60]. We will start with the initial search terms identified from the on-going systematic review update of CPWs effects in hospitals. Search terms will include: "clinical pathways," "care pathways," "critical pathways," "clinical protocol," "implementation," "effective," "hospital," "patient," "physician(s)," "treatment," "theory," "models," "strategy(s)." The review team will examine these search terms in consultation with an information scientist and expanded as necessary. The search process will commence with Medline and Google scholar and be further expanded to other databases and other sources of information related to our review objectives.

Additionally, we will search grey literature and websites of organizations involved with the implementation of CPWs, such as Intermountain Healthcare [158], European Pathway Association [159], The National Institute for Health and Care Excellence, [160] etc. We will contact authors of included primary articles for other relevant publications. We will use a snowball sampling method [161] to examine references of retained articles during the initial screening phase. We will follow an iterative approach for searching the literature to refine or refute the preliminary program theory. Overall, the initial development and refinement of the search strategy and conducting the literature search will follow an iterative process. Since CPWs emerged in the 1980s, we will search for studies from 1980 to the present. See Appendix 5 for an example of the initial Medline search strategy used for the on-going Cochrane systematic review on the effects of CPWs in hospitals.

4.7 Study selection and appraisal

Two review members will independently screen all retrieved studies from the search process using the following inclusion criteria: (1) intervention meets the following definition for a clinical pathway ((i) the intervention was a structured multidisciplinary plan of care; (ii) the intervention was used to translate guidelines or evidence into local structures; (iii) the intervention detailed the steps in a course of treatment or care in a plan, pathway, algorithm, guideline, protocol or other 'inventory of actions' (i.e. the intervention had time-frames or

criteria-based progression); and (iv) the intervention aimed to standardize care for a specific population. An intervention meeting all four criteria will be considered a CPW); (2) study was conducted in a hospital; (3) availability of information on implementation strategy(s) employed; (4) at least one health system outcome reported - length of hospital stay, costs, in-hospital mortality, adherence to recommended practice and in-hospital complications. We will exclude studies on CPWs that are not focused on hospital interventions. To ensure that the credibility and trustworthiness of the review is maintained, we will assess the rigor and relevance of each study's potential contribution to the development of the program theory. Iteratively, we will use a two-step process to screen all retrieved studies beginning with the abstracts, followed by full-text assessment of the included abstracts. We will manage the literature process using Endnote software and code all included and pending studies. Where applicable, a third review member will resolve any disagreement during the screening process. Following a similar approach, we will assess grey literature and other sources of information relevant during the review process.

4.8 Data extraction

Two review authors will independently extract data from all included primary studies using a piloted draft proposition sheet to extract explanatory accounts propositions (EAPs) about the program theory for CPWs implementation in hospitals. The EAPs are explanatory statements that may support, refine or refute judgments about an aspect or the program theory in its entirety [60]. Areas of data extraction will include:

- Study characteristics: title, author, publication year, country, participants, study focus (hospital interventions)
- Intervention: relevance to the program theory, implementation strategies
- Program theory: explanatory accounts in C-M-O configuration, aspect(s) of program theory supported, refined or refuted, other notes
- Methodology: relevance, study rigor

Relevance and rigor are dimensions of 'fitness for purpose' in realist synthesis [53]. EAPs will be extracted from primary studies using an adapted format ("If-then-because") for extracting propositions in realist inquiries [162]. "If-then-because" propositions assume that "outcome - y" will occur because "z mechanism" fire in context "x." We will identify EAPs

focused on the implementation and outcomes of CPWs in hospital settings. Subsequently, we will attempt to identify the CMOs from the extracted EAPs. Additionally, we will identify middle-range theories which are demi-regularities emerging from the data and are observable as a testable hypothesis to refine, support or refute the program theory [60]. Where feasible, the extracted middle-range theories will be supported by formal theories identified from our ongoing systematic review update or additional sectors apart from healthcare, where CPWs have been implemented. This step will be supported by the review teams' theoretical and content expertise. All extracted data will be managed using Microsoft Excel. See Appendix 5 for the draft data extraction sheet to be used for the review.

4.9 Data analysis and synthesis

Two review authors will extract the EAPs from the data extraction stage. Where necessary the team will consult with a review team to resolve any disagreement to improve the consistency and validity of the evidence generated. We will group the EAPs statements based on emerging themes, for example, "leadership support" or "staff empowerment." Retroductively, we will identify the emerging CMOs configurations from thematic groupings of EAPs. Because the emerging themes from EAPs are not mutually exclusive, EAPs can be grouped into more than one thematic category. Where appropriate, we will juxtapose, reconcile, adjudicate, consolidate and situate the evidence created within the framework of the program theory.

We will then identify the CMOs configuration existing within each thematic grouping and attempt to form CMOs configurations at middle range theory level. Middle range theories explain the regularities of social behavior that can be explored further by hypothesis testing [60]. The CMOs at the middle range theory level will be used to revise our initial program theory to form the initial revised program theory. All hidden and explicitly stated mechanisms [163] will be elicited with the support of content and theoretical expertise within the review team. Due to the focused scope of the review, we will only utilize fundamental mechanisms in developing and refining the program theory; we will use mechanisms that yielded the most substantial impact on the outcomes of interest based on different contexts. This approach also makes the breadth and depth of the review manageable and tangible for translation and implementation. This process will be conducted in consultation with content specialists and other frontline users of CPWs in hospitals to refine the program theory.

4.10 Stakeholder consultation and refinement of the program theory

To ensure the relevance of the program theory, we will consult with a CPW stakeholder advisory group comprising of content experts, realist methodologist, patient representative, policy makers, program managers, healthcare providers and other CPWs frontline users. Our content experts may include authors of primary studies focused on CPW implementation in hospitals or researchers who have successfully implemented CPWs in hospital settings. We will present the initial revised program theory and other study findings to the advisory group for their perspectives and to confirm, refine, or refute the initial revised program theory. The stakeholder engagement sessions will be delivered via facilitated discussion in a semi-structured format comprising of face-to-face and remote sessions to accommodate international participants. The engagement sessions will follow the guiding principles described by Mazano 2016 for conducting approach for realist inquiry [164]. The goal of the engagement sessions is to ensure the appropriateness of all aspects of the program theory and to make suggested changes where necessary. This process will further improve our understanding of the program theory for CPWs in hospitals and ultimately lead to the development of the final revised program theory.

4.11 Discussion

Overall, the realist review aims to assess "how, why, to what extent and in what contexts does the effective implementation of clinical pathways in hospitals contribute to better health system outcomes?" As such, the review will create an evidence-based and theoretical framework to support key decision makers involved with the implementation of CPWs in hospitals. Building on the contextual attributes, successful implementation factors and key mechanisms identified via the program theory, we anticipate an improvement in the uptake of CPWs in hospitals. However, it is important to note that the steps described in this protocol will be conducted iteratively as opposed to a linear process which does not capture the complexities and iterations associated with realist reviews and complex interventions. The review will be disseminated via peer-reviewed journals, academic conferences and as part of a graduate thesis. Finally, we anticipate an increase in beneficial effects from the future implementation of CPWs in hospitals, particularly those focused on the outcomes of interest in this review; length of hospital stay, costs, in-hospital mortality, adherence to recommended practice and in-hospital complications.

7. CHAPTER 5: GENERAL DISCUSSION & CONCLUSIONS

Clinical pathways (CPWs) have been used across health systems to bridge the evidence-practice gap, reduce clinical variation, improve patient-centered care and reduce cost [21, 165]. CPWs are predominantly implemented in hospitals and have evolved in healthcare as part of the ongoing effort to improve the quality of healthcare services. Also, CPWs are complex interventions that aim to translate the best available evidence to practice for specific health conditions [14]. They are multidisciplinary care plans that support the clinical decision-making process during the delivery of patient care.

Traditionally, systematic reviews and more recently, realist reviews have been used to synthesize evidence on complex interventions such as CPWs [148, 166]. The aim is to translate research findings from several sources into a portable format that is useful for clinical practice on time. Despite the upward trend in the use of CPWs in hospitals due to their promising potentials to reduce clinical variation, improve patient outcomes, reduce associated healthcare cost in healthcare, there still exists issues that affect their effectiveness and uptake in hospitals [3]. To date, there is no consensus on the definition of a CPW in healthcare and studies evaluating the effects of CPWs have produced variable results [3]. Furthermore, there is no theoretical framework on how CPWs work in hospitals and evidence on strategies to best implement pathways in hospitals are lacking.

The primary objective of this thesis was to examine the effects of clinical pathways (CPWs) in hospitals specifically on professional practice, patient outcomes, length of hospital stay and hospital cost. The secondary objective is to propose and describe a scientific method to develop a program theory for CPWs in hospitals as a starting point towards a theoretical framework for hospital pathways. The objectives were addressed via three manuscripts that form the core of this thesis: 1) a study that describes the process of refining an operational definition for CPWs; 2) a systematic review on the effects of CPWs in hospitals, and 3) a realist review protocol that describes a scientific approach to develop a program theory for CPWs in hospitals.

The following overarching research questions were addressed:

1.) What is a clinical pathway (manuscript 1)?
2.) What are the effects of clinical pathways in hospitals on professional practice, patient outcomes, length of stay and hospital costs (manuscript 2)?
3.) How can we develop a program theory for hospital-based clinical pathways (manuscript 3)?

A brief synopsis and analysis of the three manuscripts will be provided in this chapter. An overall discussion that integrates the findings from all manuscripts and how they contribute to the current body of evidence, future research considerations, and implications for practice and policy will also be provided.

5.1 Synopsis of Manuscripts

5.1.1 Manuscript 1: What is a clinical pathway? Refinement of an operational definition to identify clinical pathway studies for a Cochrane systematic review

The first manuscript (chapter 2) was a methods paper that builds on the work of Kinsman et al. 2010 [16]where a minimum set of criteria was developed to identify CPW studies in hospital settings for appraisal. The five-criteria checklist was used in conducting the first Cochrane systematic review on the effects of CPWs in hospitals in 2010 [14].

However, due to poor reporting of CPWs interventions by authors of primary studies, it was problematic in applying the minimum criteria (operational definition) developed by Kinsman et al. 2010 to CPWs studies conducted across broader healthcare settings, e.g. primary care [157]. Hence, a four-criteria checklist (operational definition) for the definition of a CPWs was proposed as a more inclusive definition to capture CPW studies for literature synthesis. This thesis began by rigorously testing the refined operational definition for a CPW using reliability analysis.

Twenty randomly selected articles focused on CPWs research were selected and independently appraised by two review team members using the four-criteria checklist for the definition of a CPW. Reliability analysis for qualitative variables was estimated using the kappa statistic. The pilot testing process generated 85% observed and 75% expected

agreement respectively with a kappa statistic of 0.99 (P value < 0.001), implying perfect agreement between the two reviewers.

Henceforth a CPW was defined as an intervention that contained all four criteria; 1) a structured multidisciplinary care plan (2) used to channel the translation of guidelines or evidence into local structures (3) it details the steps in a course of treatment or care in a plan, pathway, algorithm, guideline, protocol or other 'inventory of actions' (i.e. the intervention had time frames or criteria based progression) (4) it aims to standardize care for a specific clinical problem, procedure or episode of care in a specific population [15]. The refinement and validation of the operational definition for a CPW permitted us to objectively investigate the current evidence on the effects of CPWs in hospitals via a Cochrane systematic review update.

5.1.2 Manuscript 2: Clinical pathways for secondary care and their effects on professional practice, patient outcomes, length of stay and hospital costs: A Cochrane systematic review update

The systematic review update to assess the current evidence on the effects of CPWs in hospitals followed the approach recommended by the Cochrane Effective Practice and Organisation of Care group for evaluating complex interventions. Due to the sensitivity of the search filters applied to various databases searched from August 7, 2008 to March 1, 2017 and broad scope of the review, over 8000 search hits were screened with 12 additional identified during the updated search. In addition to the previously included 27 studies in the first version of the systematic review, the total number of included studies in the review update is 39 involving 15,911 participants.

The review spanned across a broad range of hospital contexts from 13 countries and examined several clinical conditions involving diverse patient groups with 28 studies focused on non-invasive interventions. Thirty-two studies used a CPW as a single intervention (stand-alone) to manage patient care while seven studies utilized a CPW as part of a multifaceted intervention to deliver patient care. In terms of study designs, four types of study designs (randomized controlled trials, non-randomized controlled trials, interrupted time series study and controlled before and after study) were considered for analysis. Overall, the direction of

effect estimates observed from the individual studies examined range from beneficial to non-beneficial.

Length of hospital stay (LOS) was the most frequent outcome reported among the included studies. LOS was reported more by studies evaluating stand-alone CPW interventions compared to multifaceted CPW interventions. Majority (22 studies) of the individual studies reported a reduction in hospital length of stay for patients managed with a CPW. Statistical pooling of the estimates from individual studies reporting on the length of hospital stay showed an overall reduction in length of stay of 0.83 days (95% CI -1.21 to -0.45) for stand-alone CPW interventions and there were no differences in the LOS for patients managed with multifaceted CPW intervention compared to usual care. See (Table 3-3 and Table 3-4).

In terms of hospital cost, seven studies reported on a highly diverse set of hospital cost or charge measures. All seven studies found lower hospitalization cost/charges or insurance points after the use of a stand-alone CPW for managing different clinical conditions. Meta-analysis showed a cost savings of USD 1171.52 (95% CI -1835.86 to -507.18). There were no differences in cost savings for patients managed with multifaceted CPW intervention compared to usual care See (Table 3-3 and Table 3-4).

Concerning patient outcomes, mortality at 90 days was examined by six studies from the stand-alone CPW intervention perspective. Meta-analysis revealed no differences between the CPW group and usual care group with an odds ratio of 0.83 (95% CI 0.62 to 1.12). For multifaceted CPW interventions, only two studies examined the effects of CPWs on mortality at 90 days and both studies found no statistical difference between the CPW group and usual care. Meta-analysis of seven studies using stand-alone CPW interventions to assess in-hospital complications showed a significant reduction in in-hospital complications with an odds ratio of 0.46 (95% CI 0.33 to 0.65). There were no differences in hospital readmission rates up to six months after the use of stand-alone CPW interventions in managing patient care. See (Table 3-3 and Table 3-4).

Adherence to recommended practice particularly documentation was the only professional practice outcome identified and examined. We found evidence for an increase in the number of documentation by healthcare providers using a CPW for clinical management purposes

compared to usual care. The combined odds ratio from two non-randomised studies was 11.95 (95% CI 4.72 to 30.58). See (Table 3-3 and Table 3-4).

Due to poor reporting of the primary studies examined we were only able to explore the number of implementation strategies used in implementing CPWs in hospitals and limited in assessing the degree with which the implementation strategies were effective. Clinician involvement was the most frequently reported strategy used by authors of included studies during the implementation of a CPW in the hospital (Table 3-2). Overall, the systematic review found evidence of improved outcomes when multiple implementation strategies are used.

In terms of the quality of the evidence, all included studies had an inherent risk of bias that could have impacted the individual and pooled estimates. Sensitivity analyses of different effect estimates of the outcomes assessed by this review revealed equivocal results (Appendix 3). Apart from the broad scope of the review, the indefinite results observed from most of the outcomes examined may be due to the high-level of statistical and clinical heterogeneity. Following the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework for developing and presenting summaries of evidence, the strength of the evidence of the review conclusions range from low certainty to very-low certainty (Table 3-3 and Table 3-4).

The systematic review identified gaps in the literature; lack of a theoretical framework for CPWs in hospitals, no consensus on the definition of a CPW, lack of robust costing studies and a paucity of studies focused on the implementation process of CPWs in hospitals. These gaps allowed us to identify the next step in advancing the evidence base for CPWs in hospitals by attempting to describe a scientific process to develop a program theory for hospital-based pathways.

5.1.3 Manuscript 3: Development of a program theory for clinical pathways in hospitals: protocol for a realist review

The lack of a theoretical framework on how CPWs work in hospitals and the shortfall of systematic reviews to rigorously examine the relationship between contextual factors and observed outcomes has been documented in the literature [167]. A realist review aims to

develop a program theory by eliciting the interaction between context and mechanisms that can explain the pattern(s) of outcomes; a critical piece for implementing CPWs in hospitals [53]. The third manuscript, a realist review protocol describes a six-step process to developing a realist program theory for hospital-based CPWs with a focus on "how, why, to what extent and in what contexts does the effective implementation of CPWs in hospitals contribute to better health system outcomes?"

Following Pawson's approach for conducting realist reviews and in a non-iterative manner, the review will follow the following steps depicted in the figure below to arrive at the first draft of a program theory for CPWs in hospitals:

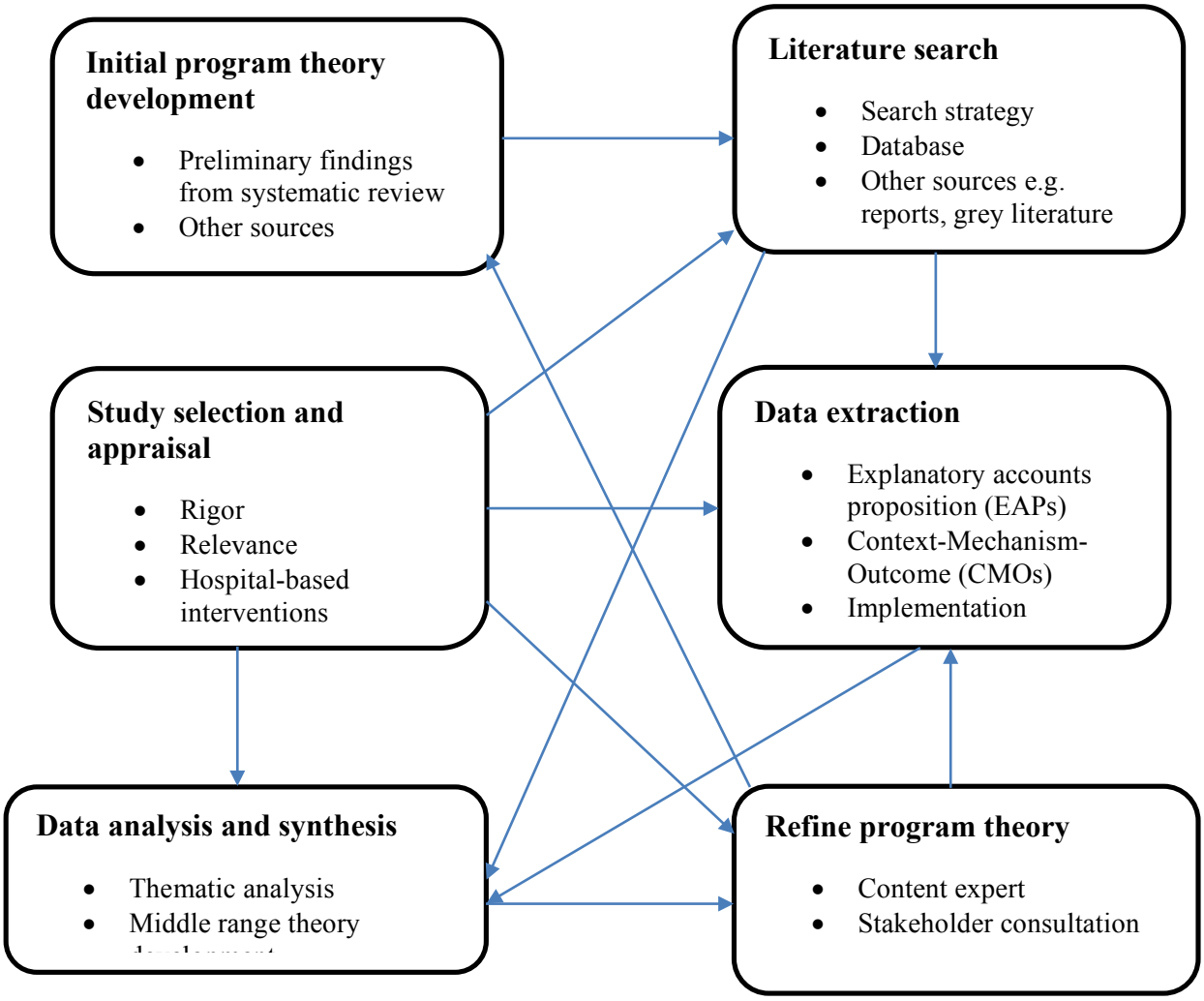

Figure 3-3: Non-iterative steps to conducting realist review. Adapted from Molnar et. al (2015)

To our knowledge, the realist review will be first to elicit a program theory for CPWs in hospitals considering the influence of contextual factors on desired outcomes. This step can fill the void on a theoretical framework for hospital-based pathways and support implementation efforts in hospital settings.

What is a clinical pathway?

Historically, several definitions have been used to describe a clinical pathway and to date, there is still a lack of international consensus on what constitutes a clinical pathway [15]. This notion was evidenced via the systematic review on the effects of CPWs in hospitals where several terms such as protocols, care maps, algorithms, etc. used to refer to a clinical pathway were identified [14]. This finding is not surprising because CPWs are purported as complex interventions requiring a collaborative effort between different stakeholders to advance patient care. With variation in stakeholder interests especially in a hospital setting, CPWs may mean or serve different purposes for different groups of care providers and patients. Variation in CPW definition can negatively impact the strength of the evidence base for CPWs due to inconsistent and unobjective identification of pathway studies.

However, this thesis was able to circumvent this problem by empirically testing a working (operational) definition for CPWs developed by Kinsman et al. (2010) [16] that is more inclusive of other healthcare settings including hospitals [15]. The refined definition comprising of four-criteria checklist for a CPW was subsequently used to update the evidence base on the effects of CPWs in hospitals via a Cochrane systematic review. A similar approach to developing and refining working definitions described in manuscript 1 can be adopted by researchers aiming to objectively create a set of criteria to identify studies reporting on interventions that lack a standard definition.

Implementation of clinical pathways in hospitals

Globally, the prevalence of CPWs in hospitals is on the horizon [36]. CPWs are often developed by care teams who adapt clinical guidelines and often supplemented with local evidence to suit clinical need or policy purposes. The implementation process is a vital step to ensure stakeholders clearly understand intended outcomes and expectations. Single or multiple implementation strategies have been reported in the literature [136]. Apart from poor reporting, the Cochrane EPOC study designs are quantitative thus making it difficult to assess

the relationship between CPW implementation strategies and the outcomes reported by primary studies in the systematic review update. This vital piece of the review is probably located in qualitative literature that has been excluded from the review thus justifying the use of a realist approach for future synthesis.

All included studies in the review used multifaceted implementation strategies during the implementation of a CPW in various hospital context (Table 3-2). Clinician involvement was the most frequently used implementation strategy during the implementation process of a CPW on a ward, unit or hospital level (Table 3-2). This finding may be due to the key role clinicians play in driving pathway usage in hospital settings.

The systematic review update also found no difference between the use of a single implementation strategy and multiple implementation strategies. This finding conforms with a recent systematic review by Squires et al. (2014) [136]. It could also imply that CPWs are less likely to affect outcomes in high functioning care teams in hospital although we found no evidence of this notion in our review. Overall, the evidence base on the best approach to implement CPWs to maximize intended outcomes is still weak as most reviews focused on the number of strategies as opposed to their influence on outcomes, a pivotal piece to successful implementation.

Effects of clinical pathways in hospitals

With the surge in the use of CPWs in hospitals and several healthcare systems intending to develop more pathways in various areas to address health system needs, it was timely to assess the evidence base on the effects of CPWs in hospitals. Equivocal results on the effects of CPWs in hospital settings have been documented by several studies in the literature [14]. To our knowledge, this systematic review update is the most comprehensive evidence base on the effects of hospital-based CPWs. The review builds on the first version of the Cochrane systematic review with new insights and findings [14].

The updated review concluded that there is an association between stand-alone CPWs and a reduction in in-hospital complications, reduced length of hospital stay, reduced costs and adherence to recommended practice. However, there is no association between stand-alone CPWs and mortality and readmissions. For multifaceted CPW interventions implemented in hospitals, there is no association between a CPW that is part of a multifaceted approach and

mortality, readmissions, length of stay and costs. The strength of the evidence range from low certainty to very weak certainty. Due to the small number of studies (39 studies) included in the review from 13 countries with a high degree of statistical and clinical heterogeneity, the conclusions should be applied with caution. It was problematic in assessing disease-specific outcomes that may be more meaningful due to the insufficient studies reporting on similar outcomes or group of patients.

Evaluation of clinical pathways in hospitals

A key finding from the systematic review update is still the prevalence of weak study designs in evaluating the effects of CPWs in hospital contexts. Majority of the studies excluded from the review is due to the use of pre-post study designs which are prone to bias e.g. confounding bias. The use of randomized trials, non-randomized trials, interrupted time series design and controlled before-after designs as suggested by the Cochrane EPOC group ensured that only rigorous evaluations were considered for analysis [31]. Majority of the meta-analysis conducted in the review showed that weak study designs tend to overestimate the effects of CPWs in individual studies (Appendix 3). The use of Cochrane EPOC study designs aims to limit bias but are resource intensive and may limit the sample size of included studies that might have resulted in different conclusions.

Despite the use of systematic reviews in providing information in a portable format for stakeholders and generating new hypotheses, there still exist gaps when used for complex interventions such as CPWs. This notion was evidenced in our systematic review where we found it difficult to attribute beneficial outcomes reported from individual studies to any aspect of the intervention. Apart from poor reporting in primary studies, the quantitative focus of the systematic review might have led to the exclusion of qualitative articles with contextual information that can inform us better on how CPWs work in hospitals and what pieces contribute to intended outcomes.

A proposed method to bridge the gaps in the field of evaluation research for CPWs is the use of "realist methodology." Realist reviews aim to utilize multiple sources of information to examine "what works for whom under what circumstances, how and why" and with the goal of developing or refining a program theory [53]. This thesis proposed a six-step process for developing a draft program theory for CPWs in hospitals. Due to the complexities associated

with normalizing CPWs in complex environments, it is not surprising there that is variability in the effects reported across various hospital contexts.

Realist methods are more suited than systematic reviews for the evaluation of CPWs because they go beyond examining if an intervention "works or not" to "why," "for whom," "in what context" and "to what extent," which is vital for success. The realist review will attempt to extract all explanatory account statements (EAs) related the initial program theory for implementing CPWs in hospitals and using a context-mechanism-outcome configuration (CMO). Subsequently, emergent themes, e.g. leadership support, team-work, etc. from the EAs will be used to develop key middle-range theories that can be tested at a hypothesis level to support, refute or refine the initial program theory. Apart from a better understanding of for whom or how CPWs work in hospitals, the realist approach will also help to uncover barriers and enablers to CPW implementation in different hospital settings making it a suitable choice for policy and practice.

5.2 Contributions to Research

This thesis started by statistically assessing the reliability of an operational definition for CPWs developed by defined Kinsman et al. (2010) to permit an objective identification of CPW studies (Manuscript 1) [146]. To my knowledge, the four-set CPW criteria validated via reliability analysis is the first of its kind to be used in appraising the literature for evidence synthesis in the field of CPW research. The four-criteria checklist for a CPW can be used to advance discussions towards an international consensus on what constitutes a CPW and further strengthen the evidence base for CPWs research.

The Cochrane systematic review update on the effects of CPWs in hospitals represents the most comprehensive evidence base on this research topic since the first version of the review by Rotter et al. (2010). Other reviews exploring CPW effects in hospitals are limited in scope to assessing effects in a hospital unit or on a single clinical condition and do not focus on implementation strategies. Also, the Cochrane systematic review update is the first of its kind to rank the strength of the evidence which is vital to policymakers, researchers and care providers using CPWs. This step is a key addition to the field of evidence synthesis as methodological bias inherent in included studies tends to overestimate or underestimate

intervention effects and may likely affect policy formulation on hospital-based pathways. The updated systematic review will be published in the Cochrane Library.

Due to resource constraints and scope of my doctoral program, it was not feasible to complete the realist review on CPWs in hospitals in this thesis. However, a significant strength is that this thesis did not only investigate the effects of clinical pathways in hospitals but ended with a comprehensive realist review protocol that lays the foundation for future research. The development of a realist program theory for CPWs in hospitals proposed by this thesis (Manuscript 3) will be the first attempt to derive a coherent theoretical framework on how CPWs work in hospitals. Upon completion of the realist review, the derived program theory for CPWs will advance our knowledge and understanding of CPWs in hospitals and how they contribute to better health system outcomes. The derived program theory can be adapted, refined or refuted with subsequent realist syntheses. To my knowledge, the realist review will be the first literature synthesis to develop a generic realist program theory for CPWs in hospitals. The nuggets of evidence arising from the realist review will be valuable to policymakers, care providers and researchers in optimizing the effects of CPWs in hospitals.

5.3 General Study Limitations

Although we validated a refined operational definition for CPWs via reliability analysis, there is a likelihood that other attributes of a CPW might have been missed by the four-criteria checklist used to define a CPW in this thesis. This is an area that can be explored for future research via concept analysis [168] with an international perspective. Another study limitation is the inherent risk of bias present in the 39 included studies of the systematic review update on the effects of CPWs in hospitals (Fig 3-2). Ten studies had an unclear risk of bias and two studies had a loss to follow up of more than 20%. The risk of bias in the included studies could have impacted the study results reported in the individual studies used in the meta-analysis for estimating CPW effects in hospitals.

The broad scope of the systematic review by attempting to examine CPW effects across all hospital contexts might have contributed to the high degree of statistical and clinical heterogeneity observed in the majority of the meta-analytic comparisons carried out in the review (Appendix 3). Although highly sensitive search filters were used to design the search

strategy for the searching studies for the systematic review and other sources were searched, it is still unlikely to have captured all relevant CPW studies during this process. Also, Imputation techniques were used to account for missing data in some of the included studies particularly on missing measures of uncertainties (standard deviations, p-values, confidence intervals, etc.). The imputed values could have impacted the review estimates and associated meta-analyses in an unknown direction. Statistical summaries generated via systematic reviews are mostly based on averages or medians that may not be representative of the general population.

Lastly, the positivist approach (systematic review) used by this thesis to investigate the effects of CPWs in hospitals was not able to capture the complexities associated with CPWs. Several qualitative studies or methods that could have better inform the current evidence were excluded or not considered. This made it difficult to identify and understand how important contextual factors and mechanisms for CPW effectiveness interact in hospitals to generate intended outcomes. However, this thesis filled this void by proposing an alternative method for future inquiries for CPW effects in hospitals following a realist approach.

5.4 Future Research Recommendations

Future research should focus on addressing the confusion on what constitutes a CPW. The lack of specificity in the definition of a CPW hinders the objective examination of CPW effects in healthcare. The four-criteria used to to define a CPW by this thesis operationally can be a starting point for international consensus. This task requires a joint effort by researchers, methodologist, health providers, patients, healthcare organizations and governmental bodies associated with the development, implementation and evaluation of CPWs in healthcare.

The broad scope of the systematic review update on the effects of CPWs in hospitals contributed to the clinical and statistical heterogeneity observed in majority of the meta-analytic summaries included in the review. To limit the impact of these variations in future reviews, authors should focus on investigating disease-specific pathways in hospitals. This approach may help to increase the number of primary studies available for possible analysis with higher statistical power and increased precision in the effect estimates.

Based on the complexities associated with normalizing CPWs in hospitals and the limited evidence generated by the systematic reviews in evaluating complex interventions, future evaluative designs with policy and practice implications should consider using realist methods for evidence synthesis. Realist approaches have the potential to elicit "who," "for whom," "how," "in what contexts" and "to what extent" are CPWs effective in hospitals. Conducting the realist review described by the protocol in this thesis can serve as a starting point to form a theoretical framework on how CPWs work in hospitals which can be further explored by other researchers.

With the global rise in the cost of healthcare, it is imperative to fill the void on the economic evidence for CPW interventions in hospitals. This issue can be addressed by conducting economic evaluations or robust costing studies that can objectively present the cost benefit of using CPWs in hospitals. Also, economic studies can provide additional information on the resources required for the effective implementation of CPWs. Finally, robust economic designs can aid the decision-making process for policy makers and hospital managers regarding the key decision to implement a pathway for a clinical condition or not- an exploration of value for money.

5.5 Implications for Practice and Policy

CPWs are continually developed in hospital settings to bridge evidence-practice gaps and support clinical decision making processes to maximize patient and health system outcomes. With the reported increase in the global prevalence of CPWs across many health systems, more CPWs are likely to be developed in the future for patient management. The information presented in this thesis on the effects of CPWs in different hospitals settings can support the decision-making process for healthcare providers using CPWs for managing patients with different clinical conditions.

With the conflicting evidence and low confidence associated with the outcomes examined by the systematic review conducted in this thesis, it is essential for policymakers and health administrators to carefully consider the cost versus quality implications and where possible utilize alternative interventions. Additionally, the evidence on implementation strategies for CPWs in hospitals generated by this thesis is valuable to health administrators who are challenged with the best approach to roll out CPWs in hospital units.

5.6 Conclusion

Globally, health systems are continuously searching for effective ways to provide patient care without a comprise of quality and costs. CPWs are quality improvement strategies that can reduce variation in care processes during an episode of care thus optimizing patient and health system outcomes. This thesis has shown via a Cochrane systematic review on the effects of CPWs in hospitals, that stand-alone CPW interventions have the potential to reduce hospital length of stay and in-hospital complications, improve documentation by care providers and reduce associated healthcare costs for patients. These findings should be interpreted and extrapolated with caution due to the low certainty of evidence associated with the review conclusions.

To our knowledge, this is the most comprehensive evidence base for assessing the effects of CPWs in hospitals. Due to the study limitations, experience and challenges faced using the systematic review methodology to assess CPW effects, we recommend a realist approach for future syntheses of complex interventions including CPWs. A realist synthesis helps to identify and unpack critical factors within different hospital contexts that may influence the patterns of outcomes observed after the implementation of a CPW. These nuggets of information are vital for the understanding, implementation, evaluation and sustainability of CPW in hospitals.

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APPENDICES

APPENDIX A

MEDLINE Search Strategy for Manuscript 2: Effects of CPWs in Hospital Care
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present

No.	Search terms
1	Critical Pathways/
2	((clinical or critical) adj2 (pathway? or path)).timba.
3	((care adj2 algorithm?) or clinical algorithm?).ti,ab.
4	(care adj2 pathway?).ti,ab.
5	(treatment adj3 algorithm?).ti,ab.
6	(structured care or intensive management).ti,ab.
7	(standardi$ adj3 (treatment? or care or patient care or plan$)).ti,ab.
8	(care adj2 (plan? or map or maps or protocol? or algorithm?)).ti,ab.
9	(protocol? adj4 (nursing or treatment or management or directed or guided)).ti,ab.
10	((local or locally) adj2 adapt$ adj5 guideline?).ti,ab.
11	(treatment model? adj10 standardi$).ti,ab.
12	(standardi$ adj3 (template or templates)).ti,ab.
13	or/1-12 [Pathways]
14	Clinical protocols/
15	Algorithm/ and (di.fs. or (treatment or care or patient?).ti. or diagnos$.ti,ab.)
16	Practice Guidelines as Topic/ or Guideline Adherence/ or Guidelines as topic/
17	((guideline or guidelines) adj2 (adher$ or implement$)).ti,ab.
18	(guideline? adj4 (compliance or complying)).ti,ab.
19	or/16-18 [PGL or GL Adherence]
20	(adherence or care or compliance or comply$ or implement$ or impact or plan? or standardi?ed or pathway or (treatment adj3 (protocol? or algorithm?))).ti,ab.
21	19 and 20 [GL]
22	*Guidelines as topic/ or *Practice Guidelines as topic/
23	*Guideline Adherence/
24	or/22-23 [Focussed MeSH Guideline]
25	Primary health care/ or Primary Care Nursing/
26	Family practice/ or General Practice/
27	General Practitioners/ or Physicians, Family/ or Physicians, Primary Care/
28	((general or family) adj2 (practice? or practitioner? or physician? or doctor?)).ti,ab.
29	(primary adj2 (care or health care or healthcare or medical care or patient care)).ti,ab.
30	(primary care or family medic$ or general practice or family practi$).jn.
31	GP.ti.
32	or/25-31 [Primary Care]
33	Ambulatory Care/ or Community medicine/ or community health nursing/ or community health services/ or home care services/ or Community mental health services/ or Community Pharmacy Services/
34	Ambulatory Care Facilities/ or Community Health Centers/
35	(community or communities).ti,ab,hw.
36	(((ambulatory or walk-in or neighbo?rhood or community) adj2 (clinic? or care centre or care centres or care center? or health$ centre or health$ centres or health$ center?)) or public clinic?).ti,ab.
37	((urban or rural) adj3 health).ti,ab.

38 or/33-37 [Community Care]

39 13 and 32 [Pathway terms & PC]

40 (and/13,38) not 39 [Pathways & Community-Ambulatory Care]

41 (and/24,32) not (or/39-40) [Focussed GL & PC]

42 (and/24,38) not (or/39-41) [Focussed GL & Community-Ambulatory Care]

43 (21 and (or/32,38)) not (or/39-42) [GL & PC/Amb Care]

44 ((or/14-15) and ((or/26-31,38) or *Primary health care/ or *Primary Care Nursing/)) not (or/39-43) [Clinical Protocols/Algorithms Mesh & PC/Community Care-combine with RCT filter only]

45 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.

46 exp animals/ not humans.sh.

47 45 not 46 [Cochrane RCT Filter 6.4.d Sens/Precision Maximizing]

48 intervention?.ti. or (intervention? adj6 (clinician? or collaborat$ or community or complex or DESIGN$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv$ or individuali?e? or individuali?ing or interdisciplin$ or multicomponent or multi-component or multidisciplin$ or multi-disciplin$ or multifacet$ or multi-facet$ or multimodal$ or multi-modal$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib$ or prescription? or primary care or professional$ or provider? or regulatory or regulatory or tailor$ or target$ or team$ or usual care)).ab.

49 (pre-intervention? or preintervention? or "pre intervention?" or post-intervention? or postintervention? or "post intervention?").ti,ab. [added 2.4]

50 (hospital$ or patient?).hw. and (study or studies or care or health$ or practitioner? or provider? or physician? or nurse? or nursing or doctor?).ti,hw.

51 demonstration project?.ti,ab.

52 (pre-post or "pre test$" or pretest$ or posttest$ or "post test$" or (pre adj5 post)).ti,ab.

53 (pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).ti,ab.

54 trial.ti. or ((study adj3 aim?) or "our study").ab.

55 (before adj10 (after or during)).ti,ab.

56 ("quasi-experiment$" or quasiexperiment$ or "quasi random$" or quasirandom$ or "quasi control$" or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab,hw.

57 ("time series" adj2 interrupt$).ti,ab,hw.

58 (time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month$ or hour? or day? or "more than")).ab.

59 pilot.ti.

60 Pilot projects/

61 (clinical trial or controlled clinical trial or multicenter study).pt.

62 (multicentre or multicenter or multi-centre or multi-center).ti.

63 random$.ti,ab. or controlled.ti.

64 (control adj3 (area or cohort? or compare? or condition or design or group? or intervention? or participant? or study)).ab. not (controlled clinical trial or randomized controlled trial).pt.

65 evaluation studies as topic/ or prospective studies/ or retrospective studies/ [Added Jan 2013]

66 (utili?ation or programme or programmes).ti. [Added Jan 2013]

67 (during adj5 period).ti,ab. [Added Jan 2013]

68 ((strategy or strategies) adj2 (improv$ or education$)).ti,ab. [Added Jan 2013]

69 "comment on".cm. or review.pt. or (review not "peer review$").ti. or randomized controlled trial.pt. [Changed Jan 2013]

70 (rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti.

71 exp animals/ not humans.sh.

72 (or/48-68) not (or/69-71) [EPOC Methods Filter 2.5-added Evaluation Studies line forward--Jan 20130 Medline]
73 (or/39-44) and 47 [RCT Results]
74 (39 and 72) not 73 [EPOC Filter Results Set 1 : Pathways & PC]
75 (40 and 72) not (or/73-74) [EPOC Filter Set 2: Pathways & Community-Ambulatory Care]
76 (41 and 72) not (or/73-75) [EPOC Filter Set 3: Focussed GL & PC]
77 (42 and 72) not (or/73-76) [EPOC Filter Set 4: Focussed GL & Ambultory]
78 (43 and 72) not (or/73-77) [EPOC Filter Set 5: GL & PC/Amb care]
79 or/74-78 [EPOC Filter Results]
80 73 or 79
81 limit 80 to yr="2015 -Current"

2016 update: 30/08/2016

No. Search terms

1 Critical Pathways/
2 ((clinical or critical) adj2 (pathway? or path)).ti,ab.
3 ((care adj2 algorithm?) or clinical algorithm?).ti,ab.
4 (care adj2 pathway?).ti,ab.
5 (treatment adj3 algorithm?).ti,ab.
6 (structured care or intensive management).ti,ab.
7 (standardi$ adj3 (treatment? or care or patient care or plan$)).ti,ab.
8 (care adj2 (plan? or map or maps or protocol? or algorithm?)).ti,ab.
9 (protocol? adj4 (nursing or treatment or management or directed or guided)).ti,ab.
10 ((local or locally) adj2 adapt$ adj5 guideline?).ti,ab.
11 (treatment model? adj10 standardi$).ti,ab.
12 (standardi$ adj3 (template or templates)).ti,ab.
13 or/1-12 [Pathways]
14 Clinical protocols/
15 Algorithm/ and (di.fs. or (treatment or care or patient?).ti. or diagnos$.ti,ab.)
16 Practice Guidelines as Topic/ or Guideline Adherence/ or Guidelines as topic/
17 ((guideline or guidelines) adj2 (adher$ or implement$)).ti,ab.
18 (guideline? adj4 (compliance or complying)).ti,ab.
19 or/16-18 [PGL or GL Adherence]
20 (adherence or care or compliance or comply$ or implement$ or impact or plan? or standardi?ed or pathway or (treatment adj3 (protocol? or algorithm?))).ti,ab.
21 19 and 20 [GL]
22 *Guidelines as topic/ or *Practice Guidelines as topic/
23 *Guideline Adherence/
24 or/22-23 [Focussed MeSH Guideline]
25 Primary health care/ or Primary Care Nursing/
26 Family practice/ or General Practice/
27 General Practitioners/ or Physicians, Family/ or Physicians, Primary Care/
28 ((general or family) adj2 (practice? or practitioner? or physician? or doctor?)).ti,ab.
29 (primary adj2 (care or health care or healthcare or medical care or patient care)).ti,ab.
30 (primary care or family medic$ or general practice or family practi$).jn.

31 GP.ti.

32 or/25-31 [Primary Care]

33 Ambulatory Care/ or Community medicine/ or community health nursing/ or community health services/ or home care services/ or Community mental health services/ or Community Pharmacy Services/

34 Ambulatory Care Facilities/ or Community Health Centers/

35 (community or communities).ti,ab,hw.

36 (((ambulatory or walk-in or neighbo?rhood or community) adj2 (clinic? or care centre or care centres or care center? or health$ centre or health$ centres or health$ center?)) or public clinic?).ti,ab.

37 ((urban or rural) adj3 health).ti,ab.

38 or/33-37 [Community Care]

39 13 and 32 [Pathway terms & PC]

40 (and/13,38) not 39 [Pathways & Community-Ambulatory Care]

41 (and/24,32) not (or/39-40) [Focussed GL & PC]

42 (and/24,38) not (or/39-41) [Focussed GL & Community-Ambulatory Care]

43 (21 and (or/32,38)) not (or/39-42) [GL & PC/Amb Care]

44 ((or/14-15) and ((or/26-31,38) or *Primary health care/ or *Primary Care Nursing/)) not (or/39-43) [Clinical Protocols/Algorithms Mesh & PC/Community Care-combine with RCT filter only]

45 (randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.

46 exp animals/ not humans.sh.

47 45 not 46 [Cochrane RCT Filter 6.4.d Sens/Precision Maximizing]

48 intervention?.ti. or (intervention? adj6 (clinician? or collaborat$ or community or complex or DESIGN$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv$ or individuali?e? or individuali?ing or interdisciplin$ or multicomponent or multi-component or multidisciplin$ or multi-disciplin$ or multifacet$ or multi-facet$ or multimodal$ or multi-modal$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib$ or prescription? or primary care or professional$ or provider? or regulatory or regulatory or tailor$ or target$ or team$ or usual care)).ab.

49 (pre-intervention? or preintervention? or "pre intervention?" or post-intervention? or postintervention? or "post intervention?").ti,ab. [added 2.4]

50 (hospital$ or patient?).hw. and (study or studies or care or health$ or practitioner? or provider? or physician? or nurse? or nursing or doctor?).ti,hw.

51 demonstration project?.ti,ab.

52 (pre-post or "pre test$" or pretest$ or posttest$ or "post test$" or (pre adj5 post)).ti,ab.

53 (pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).ti,ab.

54 trial.ti. or ((study adj3 aim?) or "our study").ab.

55 (before adj10 (after or during)).ti,ab.

56 ("quasi-experiment$" or quasiexperiment$ or "quasi random$" or quasirandom$ or "quasi control$" or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab,hw.

57 ("time series" adj2 interrupt$).ti,ab,hw.

58 (time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month$ or hour? or day? or "more than")).ab.

59 pilot.ti.

60 Pilot projects/

61 (clinical trial or controlled clinical trial or multicenter study).pt.

62 (multicentre or multicenter or multi-centre or multi-center).ti.

63 random$.ti,ab. or controlled.ti.

64 (control adj3 (area or cohort? or compare? or condition or design or group? or intervention? or participant? or study)).ab. not (controlled clinical trial or randomized controlled trial).pt.
65 evaluation studies as topic/ or prospective studies/ or retrospective studies/ [Added Jan 2013]
66 (utili?ation or programme or programmes).ti. [Added Jan 2013]
67 (during adj5 period).ti,ab. [Added Jan 2013]
68 ((strategy or strategies) adj2 (improv$ or education$)).ti,ab. [Added Jan 2013]
69 "comment on".cm. or review.pt. or (review not "peer review$").ti. or randomized controlled trial.pt. [Changed Jan 2013]
70 (rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti.
71 exp animals/ not humans.sh.
72 (or/48-68) not (or/69-71) [EPOC Methods Filter 2.5-added Evaluation Studies line forward--Jan 20130 Medline]
73 (or/39-44) and 47 [RCT Results]
74 (39 and 72) not 73 [EPOC Filter Results Set 1 : Pathways & PC]
75 (40 and 72) not (or/73-74) [EPOC Filter Set 2: Pathways & Community-Ambulatory Care]
76 (41 and 72) not (or/73-75) [EPOC Filter Set 3: Focussed GL & PC]
77 (42 and 72) not (or/73-76) [EPOC Filter Set 4: Focussed GL & Ambultory]
78 (43 and 72) not (or/73-77) [EPOC Filter Set 5: GL & PC/Amb care]
79 or/74-78 [EPOC Filter Results]
80 73 or 79
81 limit 80 to yr="2015 -Current"

2017 update: 08/02/2017

No. Search terms

1 (clinical adj2 pathway?).ti.
2 critical pathways/
3 ((clinical or critical) adj1 (pathway? or path?)).ti,ab.
4 ((care adj2 algorithm?) or clinical algorithm?).ti,ab.
5 (care adj1 pathway?).ti,ab.
6 (treatment adj3 algorithm?).ti,ab.
7 (management protocol? or treatment protocol?).ti,ab.
8 (care adj1 (plan? or map?)).ti,ab.
9 (protocol? adj1 (nursing or directed or guided)).ti,ab.
10 ((local or locally) adj2 adapt* adj5 guideline?).ti,ab.
11 (treatment model? adj10 standardi*).ti,ab.
12 (standardi* adj3 protocol?).ti,ab.
13 systematic detection.ti,ab.
14 or/2-13
15 clinical protocols/
16 (treat* or therap*).ti,ab.
17 15 and 16
18 practice guidelines as topic/
19 (implement* or pathway or protocol?).ti,ab.
20 18 and 19
21 (guideline? adj1 (implement* or pathway or protocol?)).ti,ab.
22 or/20-21

23 14 or 17 or 22
24 (hospital or hospitals or hospitalis* or hospitaliz*).ti,ab.
25 exp hospital units/
26 exp hospitals/
27 exp hospital departments/
28 hospitalization/
29 or/24-28
30 1 or (23 and 29)
31 randomized controlled trial.pt.
32 controlled clinical trial.pt.
33 multicenter study.pt.
34 pragmatic clinical trial.pt.
35 (randomis* or randomiz* or randomly).ti,ab.
36 groups.ab.
37 (trial or multicenter or multi center or multicentre or multi centre).ti.
38 (intervention? or effect? or impact? or controlled or control group? or (before adj5 after) or (pre adj5 post) or ((pretest or pre test) and (posttest or post test)) or quasiexperiment* or quasi experiment* or pseudo experiment* or pseudoexperiment* or evaluat* or time series or time point? or repeated measur*).ti,ab.
39 non-randomized controlled trials as topic/
40 interrupted time series analysis/
41 controlled before-after studies/
42 or/31-41
43 exp animals/
44 humans/
45 43 not (43 and 44)
46 review.pt.
47 meta analysis.pt.
48 news.pt.
49 comment.pt.
50 editorial.pt.
51 cochrane database of systematic reviews.jn.
52 comment on.cm.
53 (systematic review or literature review).ti.
54 or/45-53
55 42 not 54
56 30 and 55
57 limit 56 to yr="2008 -Current"

APPENDIX B

Table B.1: Costing method and cost/charges for included studies

Study ID	Costs measure	Country	Costing method	Costs/ charges included	Costs/ charges excluded
Comparison 1: single CPW intervention versus usual care					
Aizawa 2002	Insurance data (points)	Japan	Hospital charges: including variable & fixed costs	Dosage, injection, treatment, operation and anaesthesia, examination, diagnostic, room, medical care	Not reported
Falconer 1993	Hospital charges to proxy costs of rehabilitation	USA	Hospital charges	Charges for hospital bed days, medical and rehabilitation services (including professional fees), equipment, drugs and procedures (radiographs, laboratory tests, injections)	Not reported
Gomez 1996	Hospital charges	USA	Hospital charges	Room, nursing care, laboratory, therapeutic and tests	Physician fees
Johnson 2000	Hospital charges	USA	Hospital charges	Room, medication, laboratory tests and respiratory therapy	Physician fees
Kim 2002	Hospital costs	USA	Variable costs	Remains unclear, only "total direct costs" reported	Professional fees
Kiyama 2003a	Hospital costs	Japan	Variable costs	Total medical costs including medication and examination (physician fees)	Fixed costs
Kollef 1997	Hospital costs	USA	Not reported	Not reported	Physician fees
Roberts 1997	Hospital costs	USA	Variable & fixed costs	Professional fees	Not reported
Usui 2004	Insurance data (points)	Japan	Hospital charges: including variable costs	Treatment (antibiotic infusion), laboratory and radiography tests	Fixed costs
Verdu 2009	Hospital charges	Spain	Hospital charges	Cost per day of hospital stay	Not reported
Panella 2009	Hospital charges	Italy	Activity-based costing	Cost of hospital care (admission)	Not reported
Comparison 2: Multifaceted intervention including a CPW versus usual care					
Bauer 2006	Hospital costs	USA	Variable costs	Not reported	Not reported
Kampan 2006	Hospital costs	Thailand	Remains unclear, only "mean costs" reported	Not reported	Not reported
Philbin 2000	Hospital charges	USA	Hospital charges	Not reported	Professional fees

Table B.2: Original reported costs / charges data

Study ID	Country	Price year / study period	Cost / charges measure	Original currency	Pathway	E-N (SD)	Usual care	C-N (SD)
(Comparison 1: single CPW intervention versus usual care								
Aizawa 2002	Japan	2000	hospital charges (insurance points)	insurance points	48424	32 (4438)	55366	37 (16805)
Falconer 1993	USA	87-91	(median) hospital charges bed days	US $	14440	53	14420	68
Falconer 1993	USA	87-91	(median) hospital charges services	US $	11249	53	9579	68
Falconer 1993	USA	87-91	(median) hospital charges drugs	US $	1130	53	1015	68
Falconer 1993	USA	87-91	(median) hospital charges; other charges	US $	2397	53	1871	68
Gomez 1996	USA	1994	hospital charges initial stay	US $	1279	50 (1677)	5719	50 (14668)
Gomez 1996	USA	1994	hospital charges at 30 days	US $	1424	50 (1735)	5860	50 (14638)
Johnson 2000	USA	95-97	hospital room charges	US $	2407	55 (1099)	3116	55 (1099)
Johnson 2000	USA	95-97	hospital medication charges	US $	129	55 (107)	153	55 (107)
Johnson 2000	USA	95-97	hospital lab tests charges	US $	21	55 (66)	42	55 (66)
Johnson 2000	USA	95-97	hospital charges respiratory therapy	US $	42	55 (322)	250	55 (322)
Kim 2002	USA	2000	direct variable mean hospital costs (excluding professional fees)	US $	870	9 (394)	1706	9 (1512)
Kiyama 2003a	Japan	2001	direct variable mean hospital costs (including medication and professional fees)	Jen	1502587	47 (282489)	1932197	38 (786185)
Kiyama 2003a	Japan	2001	direct variable mean costs medication	Jen	190339	47 (112760)	270631	38 (176643)
Kiyama 2003a	Japan	2001	direct variable mean daily costs	Jen	58383	47 (8575)	55651	38 (15573)
Kollef 1997	USA	1995	hospital costs (poor reporting: seems to be direct variable costs	US $	27680	179 (26823)	27439	178 (25873)
Panella 2009	Italy	2004	Cost of hospital care (admission)	Euros	2125	214 (534)	2211	215 (580)
Roberts 1997	USA	1993	total hospital costs (doctors & nurse fees included)	US $	1528	82 (1012)	2095	83 (2095)
Usui 2004	Japan	2002/ 2003	hospital charges (insurance points)	insurance points	24338	30 (12291)	34048	31 (12291)
Usui 2004	Japan	2002/ 2003	hospital charges antibiotic infusion	insurance points	3285	30 (2027)	3928	31 (2027)
Usui 2004	Japan	2002/ 2003	hospital charges laboratory costs	insurance points	3220	30 (3097)	5785	31 (3097)
Usui 2004	Japan	2002/ 2003	hospital charges radiology costs	insurance points	1438	30 (1194)	2471	31 (1194)
Verdu 2009	Spain	2002-2004	Cost of hospital stay	Euros	38998.72	40	60391.9	48
Comparison 2: Multifaceted intervention including a CPW versus usual care								
Bauer 2006	USA	2004	3 years mean intervention costs (direct variable costs)	US $	61398	157 (63129)	64379	149 (58118)

Study ID	Country	Price year / study period	Cost / charges measure	Original currency	Pathway	E-N (SD)	Usual care	C-N (SD)
Bauer 2006	USA	2004	direct outpatient costs (direct variable costs)	US $	20740	157 (15825)	20091	149 (15825)
Bauer 2006	USA	2004	hospital inpatient costs (direct variable costs)	US $	40658	157 (54684)	44288	149 (54684)
Bauer 2006	USA	2004	psychiatric inpatient costs (direct variable costs)	US $	27428	157 (41440)	30665	149 (41440)
Bauer 2006	USA	2004	medical surgical inpatient costs (direct variable costs)	US $	13230	157 (28798)	13523	149 (28798)
Kampan 2006	Thailand	2005	hospital costs (poor reporting: seems to be total hospital costs	BAHT	2744	33 (1473)	3687	32 (3111)
Philbin 2000	USA	1995	hospital charges	US $	-469	840 (17125)	348	664 (17125)

E-N = number of participants in experimental group; C -N = number of participants in control group; (SD) = standard deviation; USA = United States of America

Table B.3: Cost / charges data, standardized to the year 2016 (CCEMG EPPI tool used)

Study ID	Cost / charges measure	Price year used	Deflator used	Exchange rates	Target currency	Experimental	E-N (SD)	Control	C-N (SD)
Comparison 1: single CPW intervention versus usual care									
Aizawa 2002	hospital charges (insurance points)	2000	NONE	insurance points	NON	48424	32 (4438)	55366	37 (168)
Falconer 1993	(median) hospital charges bed days	median (87-91)	GDPD values (IMF)*	PPP values*	USD year 2016	22155.47	53	22124.78	68
Falconer 1993	(median) hospital charges services	median (87-91)	GDPD values (IMF)*	PPP values*	USD year 2016	17259.48	53	14697.18	68
Falconer 1993	(median) hospital charges drugs	median (87-91)	GDPD values (IMF)*	PPP values*	USD year 2016	1733.77	53	1557.33	68
Falconer 1993	(median) hospital charges; other charges	median (87-91)	GDPD values (IMF)*	PPP values*	USD year 2016	3677.75	53	2870.70	68
Gomez 1996	hospital charges initial stay	1994	GDPD values (IMF)*	PPP values*	USD year 2016	1921.51	50 (1858)	8591.95	50 (16251)
Gomez 1996	hospital charges at 30 days	1994	GDPD values (IMF)*	PPP values*	USD year 2016	2139.35	50 (1922)	2606.58	50 (16218)
Johnson 2000	hospital room charges	1997	GDPD values (IMF)*	PPP values*	USD year 2016	3420.22	55 (1152)	4427.67	55 (1152)
Johnson 2000	hospital medication charges	1997	GDPD values (IMF)*	PPP values*	USD year 2016	183.30	55 (112)	217.41	57 (112)
Johnson 2000	hospital lab tests charges	1997	GDPD values (IMF)*	PPP values*	USD year 2016	29.84	55 (70)	59.68	55 (70)
Johnson 2000	hospital charges respiratory therapy	1997	GDPD values (IMF)*	PPP values*	USD year 2016	59.68	55 (338)	355.24	55 (338)
Kim 2002	direct variable mean hospital costs (excluding professional fees)	2000	GDPD values (IMF)*	PPP values*	USD year 2016	1177.73	9 (394)	2382.52	9 (1512)
Kiyama 2003a	direct variable mean hospital costs (including medication and professional fees)	2001	GDPD values (IMF)*	PPP values*	USD year 2016	13069.36	47 (1823)	16806.06	38 (5073)
Kiyama 2003a	direct variable mean costs medication	2001	GDPD values (IMF)*	PPP values*	USD year 2016	1655.55	47 (728)	2353.92	38 (1140)
Kiyama 2003a	direct variable mean daily costs	2001	US $	PPP values*	USD year 2016	507.81	47 (55)	484.05	38 (100)
Kollef 1997	hospital costs (poor reporting: seems to be direct variable costs	1995	US $	PPP values*	USD year 2016	40340.02	179 (29122)	39988.80	178 (28090)
Panella 2009	Hospital charges	2004	GDPD values (IMF)*	PPP values*	US $ year 2016	3356.72	214 (843.52)	3492.57	215 (916.19)
Roberts 1997	total hospital costs (doctors & nurse fees included)	1993	GDPD values (IMF)*	PPP values*	USD year 2016	2344.43	82 (1145)	3214.38	83 (920)
Usui 2004	hospital charges (insurance points)	2002/ 2003	NONE	insurance points	NON	2338	30 (12291)	34048	31 (12291)

Study ID	Cost / charges measure	Price year used	Deflator used	Exchange rates	Target currency	Experimental	E-N (SD)	Control	C-N (SD)
Usui 2004	hospital charges antibiotic infusion	2002/ 2003	NONE	insurance points	NON	3285	30 (2027)	3928	31 (2027)
Usui 2004	hospital charges laboratory costs	2002/ 2003	NONE	insurance points	NON	3220	30 (3097)	5785	31 (3097)
Usui 2004	hospital charges radiology costs	2002/ 2003	NONE	insurance points	NON	1438	30 (1194)	2471	31 (1194)
Verdu 2009	Spain	2002-2004	GDPD values (IMF)*	Euros	US $ year 2016	38998.72	40	60391.9	
Comparison 2: Multifaceted intervention including a CPW versus usual care									
Bauer 2006	3 years mean intervention costs (direct variable costs)	2004	GDPD values (IMF)*	PPP values*	US year 2016	76369.27	157 (57672)		149
Bauer 2006	direct outpatient costs (direct variable costs)	2004	GDPD values (IMF)*	PPP values*	USD year 2016	25797.24	157 (14457)	24989.98	149
Bauer 2006	hospital inpatient costs (direct variable costs)	2004	GDPD values (IMF)*	PPP values*	USD year 2016	50572.04	157 (49957)	55087.18	149
Bauer 2006	psychiatric inpatient costs (direct variable costs)	2004	GDPD values (IMF)*	PPP values*	USD year 2016	34116.04	157 (37857)	38142.35	149
Bauer 2006	medical surgical inpatient costs (direct variable costs)	2004	GDPD values (IMF)*	PPP values*	USD year 2016	16456	157 (26308)	16820.45	149
Kampan 2006	hospital costs (poor reporting: seems to be total hospital costs	2005	GDPD values (IMF)*	PPP values*	USD year 2016	291.58	33 (82)	391.78	32
Philbin 2000	hospital charges	1995	GDPD values (IMF)*	PPP values*	USD year 2016	-690.21	840 (18593)	512.14	664

Legend: E-N = number of participants in experimental group; C -N = number of participants in control group; (SD) = standard deviation; PPP = purchasing power parity; GDPD = gross domestic product deflator index; IMF = International Monetary Fund

Table B.4: Continuous primary study results post-intervention measures

study ID	Outcome	E-mean	E-SD	E-N	C-mean	C-SD	C-N	P-value as far as reported	95% CI as far as reported
Comparison 1: single CPW intervention versus usual care									
Aizawa 2002	LOS (days)	12.70	2.80	32.00	14.70	5.20	37.00		
Aizawa 2002	Duration of catheterization	4.75	1.10	32.00	5.40	2.10	37.00		
Bernard 2011	Final ED blood glucose (mg/dl)	217	71	87.00	257	89	89.0	<0.01	
Bernard 2011	ED Length of stay (days)	0.23	0.1	87.00	0.2	0.1	89.0	0.06	
Bernard 2011	Number of patients treated with insulin	100		87.00	54		89.0		
Bernard 2011	Admission blood glucose level (mg/dl)	184	70	87.00	224	93	89.0	0.01	
Bernard 2011	Hospital length of stay (days)	2.7	2.0	87.0	3.1	1.9	89.0	0.58	
Bernard 2011	Number of admissions	60			61		89.0		
Bittinger 1995	Total satisfaction scores	246.80	17.97	15	233.133	25.357	15	0.100	
Bittinger 1995	Dissatisfaction scores	97.80	11.98	15	90.67	16.39	15	0.184	
Bittinger 1995	Interpersonal scores	77.60	4.405	15	73.47	5.01	15	0.023	
Bittinger 1995	Good impression	71.4	4.52	15	69.0	6.79	15	0.266	
Brook 1999	Duration of mechanical ventilation (in hours)	89.10	133.60	162.00	124.00	153.60	159.00		
Brook 1999	LOS ICU stay (days)	5.70	5.90	162.00	7.50	6.50	159.00		
Brook 1999	LOS hospital stay (days)	14.00	17.30	162.00	19.90	24.20	159.00		
Brook 1999	Number of acquired organ system derangements	2.84	1.40	162.00	2.90	1.50	159.00		
Carratala 2012	length of stay (days)	3.9		200	6.0		201	<0.001	
Carratala 2012	Adverse drug reaction (%)	4.5		200	15.9		201	<0.001	
Carratala 2012	Patient satisfaction (%)	94.6		200	94.3		201	0.60	
Carratala 2012	Number of subsequent hospital admission within 30 days	18		200	15		201	0.59	
Carratala 2012	Number of overall case fatality rate within 30days	4		200	2		201	0.45	
Carratala 2012	Median length of antibiotic IV therapy	2.0		200	4		201	<0.001	
Chadha 2000	Compliance with five recommendations for initial hospital assessment (urinary incontinence).	3.80	1.52	416.00	3.10	1.52	472.00		(0.5 to 0.9)
Choong 2000	LOS (days)	6.60	3.35	55.00	8.00	3.35	56.00	0.0300	
Choong 2000	Days to mobilisation (days)	1.60	1.44	55.00	2.20	1.44	56.00	0.0300	
Costantini 2014	Overall quality of care (scores)	70.5		118	63.0		111	0.12	
Costantini 2014	informing and making decisions	73.5		117	64.3		110	<0.01	
Costantini 2014	Respect, dignity and kindness	78.8		115	70.4		109	<0.01	
Costantini 2014	Family emotional support	46.6		117	38.6		109	0.09	

study ID	Outcome	E-mean	E-SD	E-N	C-mean	C-SD	C-N	P-value as far as reported	95% CI as far as reported
Costantini 2014	Coordination of care	81.4		115	76.8		110	0.04	
Costantini 2014	Family self-efficacy	48.9		116	44.4		110	0.01	
Cunningham 2008	Mean time from arrival at ED to achieve oxygen saturation >=94% (hrs)	9.3		136	10.3		115	0.30	
Cunningham 2008	Time to achieve 4-hr spacing of multidose spacer delivered salbutamol (1000mg) in hrs	23.1		136	23.6		115	0.83	
Cunningham 2008	Length of stay (days)	37.6		136	40.7		115	0.07	
Cunningham 2008	Number of additional visits	16		136	19		115	0.27	
Cunningham 2008	Number of prescribing errors	10.4		136	14.8		115	0.02	
Cunningham 2008	Number of medical contacts with patient during the first 12 hrs	6		136	5.5		115	0.04	
Cunningham 2008	Number of nursing contacts	16		136	13.8		115	0.002	
Cunningham 2008	Number of clinical contacts with patients	22		136	19.2		115	0.0004	
Doig 2008	LOS in hospital (days)	24.2		561	24.3		557	0.97	
Doig 2008	LOS in ICU (days)	9.1		561	9.9		557	0.42	
Doig 2008	Renal dysfunction days/10 patient days	1.54		561	2.12		557	0.04	
Doig 2008	Pulmonary dysfunction days/10 patient days	8.28		561	7.79		557	0.18	
Doig 2008	Hepatic dysfunction days/10 patient days	1.43		561	1.41		557	0.91	
Doig 2008	Coagulation dysfunction days/10 patient-days	1.13		561	0.97		557	0.25	
Doig 2008	Cardiovascular dysfunction days/10 patient days	1.04		561	1.09		557	0.72	
Doig 2008	Multiple organ dysfunction days/ 10 patient days	3.26		561	3.41		557	0.77	
Doig 2008	Organ system dysfunction, no/patient day	1.34		561	1.34		557	0.94	
Doig 2008	Witnessed aspiration/1000 fed pt. days	2.19		561	4.33		557	0.28	
Doig 2008	Witnessed aspiration and new pulmonary infiltrates within 24h, events/1000 fed pt. days	0.83		561	0.93		557	0.84	
Doig 2008	Serum albumin <25g/l, days/10 pt. days	4.58		561	4.31		557	0.22	
Doig 2008	Renal replacement therapy/pt. days	0.75		561	0.91		557	0.29	
Doig 2008	Invasive mechanical ventilation/10 pt. days	7.69		561	7.21		557	0.70	
Doig 2008	Deaths at hospital discharge N (%)	172		561	153		557	0.75	
Doig 2008	Systemic antibiotics/10 pt. days	7.41		561	7.19		557	0.47	
Delaney 2003	LOS days (primary LOS until discharge)	5.20	2.50	31.00	5.80	3.00	33.00		
Delaney 2003	Total LOS days including time spent in readmission	5.40	2.50	31.00	7.10	4.80	33.00		

study ID	Outcome	E-mean	E-SD	E-N	C-mean	C-SD	C-N	P-value as far as reported	95% CI as far as reported
Delaney 2003	Pain score at two days' post-op	3.30	1.90	31.00	3.40	1.50	33.00		
Delaney 2003	QOL at ten days' post-op	5.60	1.80	31.00	6.30	2.10	33.00		
Delaney 2003	Satisfaction with hospital stay at 30 days	8.20	2.20	31.00	8.40	1.60	33.00		
Delaney 2003	Happiness to be discharged	8.00	1.90	31.00	8.00	1.90	33.00		
Dowsey 1999	Los (days)	7.10	3.67	92.00	8.60	3.67	71.00		(1.03-1.30)
Dowsey 1999	Days to sitting out of bed	1.94	2.80	92.00	3.42	2.80	71.00	0.0010	(1.05-1.95)
Dowsey 1999	Days to Ambulation	2.19	3.83	92.00	3.61	3.83	71.00	0.0200	(0.94-1.98)
Falconer 1993	Los (days)	35.60	15.50	53.00	32.30	15.40	68.00		
Falconer 1993	Patient satisfaction	7.70	2.60	53.00	8.8	1.70	68.00		
Falconer 1993	Functional status	40.90	15.80	53.00	40.2	17.40	68.00		
Gomez 1996	LOS (days)	0.64	0.51	53.00	2.28	5.25	68.00		
Gomez 1996	LOS (hours)	15.40	12.20	50.00	54.6	126.00	50.00		
Johnson 2000	LOS (days)	1.68	1.12	50.00	2.24	1.12	50.00		
Johnson 2000	LOS (hours)	40.30	26.80	55.00	53.7	26.80	55.00	0.0100	
Johnson 2000	Number of nebulizations during hospitalisation every 2 hours	4.50	4.44	55.00	6.5	4.44	55.00	0.0200	
Johnson 2000	Number of nebulizations during hospitalisation every 3 hours	3.70	3.64	55.00	5.9	3.64	55.00	0.0020	
Johnson 2000	Number of nebulizations during hospitalisation every 4 hours	3.50	3.09	55.00	4.7	3.09	55.00	0.0440	
Johnson 2000	Number of nebulizations during hospitalisation every 6 hours	1.40	1.60	55.00	2.2	1.60	55.00	0.0100	
Johnson 2000	Number of nebulizations during hospitalisation every 8 hours	0.10	-0.52	55.00	0	-0.52	55.00	0.3200	
Kim 2002	Los (days)	0.25	0.15	9.00	2.1	2.30	9.00		
Kiyama 2003a	Los (days) pre-operative hospital stay	9.00	3.20	47.00	12.6	6.00	38.00	0.0010	
Kiyama 2003a	Los (days) post-operative hospital stay	18.10	9.50	47.00	28.2	22.30	38.00	0.0100	
Kollef 1997	Duration of mechanical ventilation (in hours) following commencement of weaning	69.40	123.70	179.00	102	169.10	178.00	0.2900	
Marrie 2000	SF-36 2 weeks after cessation of antibiotics	16.00	3.70	716.00	16.50	4.70	1027.00		
Marrie 2000	SF-36 6 weeks after cessation of antibiotics	30.30	1.50	716.00	29.9	1.60	1027.00		
Marrie 2000	Bed days per patient managed (product of average LOS/admission rate) surrogate for direct costs	4.4	1.50	716.00	6.1	2.10	1027.00	0.0400	
Marrie 2000	LOS (days)	8.20	1.90	716.00	9.60	2.10	1027.00		
Marrie 2000	Duration intravenous antibiotics (days)	4.60	0.90	716.00	6.30	1.40	1027.00		
Marelich 2000	Duration of mechanical ventilation (medical ICU) median values reported	3.25	11.32	82.00	9.67	11.32	88.00	0.0003	
Marelich 2000	Duration of mechanical ventilation (combined ICUs) median values reported	2.83	5.42	166.00	5.17	5.42	169.00	0.0001	

study ID	Outcome	E-mean	E-SD	E-N	C-mean	C-SD	C-N	P-value as far as reported	95% CI as far as reported
Panella 2009	Death (in-hospital mortality)	5.6		214	15.4		215	0.001	
Panella 2009	Transferred to another hospital	0.5		214	1.5		215	0.30	
Panella 2009	Appropriateness of the stay (%)	76.2		214	72.1		215	0.30	
Panella 2009	Rate of unscheduled readmissions	7.9		214	13.9		215	0.053	
Panella 2009	LOS (days)	10.4		214	11.4		215	0.028	
Panella 2009	Cost of admission (Euros)	2125		214	2211		215	0.11	
Panella 2009	Patient satisfaction score	8.5		214	8.14		215	0.50	
ProCess 2014	In hospital death after 60 days, n (%)	21		439	18.9		456	0.83	
ProCess 2014	Death by 90 days	31.9		405	33.7		412	0.66	
ProCess 2014	Cardiovascular failure in the first week (%)	61.3		439	56.1		456	0.06	
ProCess 2014	Respiratory organ failure (%)	38.0		434	32.4		451	0.19	
ProCess 2014	Renal failure (%)	3.1		382	2.8		397	0.04	
ProCess 2014	Duration of cardiovascular support (days)	2.6	1.6	439	2.5	1.6	456	0.52	
ProCess 2014	Respiratory support (days)	6.4	8.4	439	6.9	8.2	456	0.41	
ProCess 2014	Renal support (days)	7.1	10.8	439	8.8	13.7	456	0.92	
ProCess 2014	Admission to ICU (%)	91.3		439	86.2		456	0.01	
ProCess 2014	Stay in ICU among admitted patients (days)	5.1	6.3	439	4.7	5.8	456	0.63	
ProCess 2014	Stay in hospital (days)	11.1	10	439	11.3	10.9	456	0.25	
ProCess 2014	Serious ADR N (%)	5.2		439	8.1		456	0.32	
Roberts 1997	LOS (days)	1.38	1.18	82.00	1.87	1.33	83.00		
Roberts 1997	LOS (hours)	33.10	28.40	82.00	44.8	31.80	83.00		
Rotter 2014	LOS (days)	9.16	0.9	123	9.11	1	131	0.91	
Rotter 2014	Duration of operation (min)	241.99	14.5	123	272.86	28.2	131	0.038	
Rotter 2014	Duration of anaesthesia (min)	323.51	17.89	123	354.06	30.58	131	0.061	
Rotter 2014	No of patients admitted to ICU	4		123	11		131	0.041	
Rotter 2014	Number of patients requiring readmissions within 30 days	23		123	8		131	0.006	
Sulch 2002	LOS (days)	50.00	19.00	76.00	45	23.00	76.00		
Sulch 2002	Physiotherapy: Mean duration of therapy input at 12 weeks	38.00	28.80	76.00	34.8	27.80	76.00		
Sulch 2002	Physiotherapy: Mean duration of therapy input at 26 weeks	42.80	41.20	76.00	39.4	36.40	76.00		
Sulch 2002	Physiotherapy: Mean duration of therapy per patient day	0.80	0.60	76.00	0.7	0.60	76.00		
Sulch 2002	Occupational Therapy: Mean duration of therapy input at 12 weeks	8.00	6.00	76.00	7.5	7.00	76.00		
Sulch 2002	Occupational Therapy: Mean duration of therapy input at 26 weeks	8.50	7.50	76.00	8	705.00	76.00		
Sulch 2002	Occupational Therapy: Mean duration of therapy per patient day	0.20	0.40	76.00	0.2	0.20	76.00		
Trombetti 2013	Proportion of nutrition counselling requests (%)	43		465	32		229	<0.05	
Trombetti 2013	Number of nutritional supplements prescribed (%)	38		465	30		229	<0.05	

study ID	Outcome	E-mean	E-SD	E-N	C-mean	C-SD	C-N	P-value as far as reported	95% CI as far as reported
Trombetti 2013	Proportion of patients receiving an enriched meal (%)	20		465	8		229	0.0001	
Trombetti 2013	LOS (days)	38	34	465	37	32	229	0.613	
Trombetti 2013	Functional independence	6.4	18.6	465	7.2	19.6	229	0.756	
Usui 2004	LOS (days)	8.03	4.18	30.00	10.77	4.18	31.00	0.0130	
Usui 2004	Duration of antibiotic infusion (days) surrogate outcome for costs	6.47	3.53	30.00	8.22	3.53	31.00	0.0580	
Verdu 2009	Mean LOS (days)	4.72	3.83	40	6.78	3.83	48	0.014	
Verdu 2009	Degree of implementation (%)	95.3		40			48		
Verdu 2009	Compliance (%)	65		40			48		
Verdu 2009	Cost savings in euros (2004 vs 2002)	38998.72		40	60391.90		48		
Verdu 2009	Patient satisfaction	67		40			48		
Comparison 2: Multifaceted intervention including a CPW versus usual care									
Chen 2004	Usage rate of the emergency room (surrogate outcome for in-hosp. complications)	0.15	0.37	20.00	0.59	0.50	22.00		
Cole 2002	LOS days	19.70	17.10	113.00	19.10	16.80	114.00		
Kampan 2006	LOS (days)	3.94	1.03	33.00	6.38	4.04	32.00		
Kampan 2006	Number of capillary blood glucose tests	10.03	5.04	33.00	12.34	5.96	32.00		
Philbin 2000	LOS (days) all hospitals pooled	-1.80	17.69	840.00	-0.70	17.69	664.00		(-2.9 - 0.7)

E = experimental; C = control; E-N = number of participants in experimental group; C -N = number of participants in control group; E-mean = mean off outcome in the experimental group; C-mean = mean of outcome in the control group; E-SD = standard deviation in the experimental group; C-SD = standard deviation in the control group

Table B.5: Continuous primary study results (pre-intervention) baseline measures

STUDY ID	Baseline outcome measure	E-Mean baseline	E-Median baseline	E-N baseline	C-Mean baseline	C-Median baseline	C-N baseline
Comparison 1: single CPW intervention versus usual care							
Chadha 2000	Compliance with five recommendations for initial hospital assessment (menorrhagia).	3.7		472	3.4		416
Chadha 2000	Compliance with five recommendations for initial hospital assessment (urinary incontinence).	3.1		416	3.0		472
Smith 2004	LOS days (no values reported)			505			216
Smith 2004	Readmission rate per 100 participant days	0.59			0.56		
Smith 2004	Deaths per 100 patient days	0.20			0.19		
Sulch 2002	Barthel index		5	152 (total both groups)		6	152 (total both groups)
Comparison 2: Multifaceted intervention including a CPW versus usual care							
Philbin 2000	LOS (days) all hospitals pooled	8.0		762	7.7		640

E = experimental; C = control; E-N baseline= number of participants in experimental group at baseline; C -N baseline = number of participants in control group at baseline;

Table B.6: Continuous primary study outcome (more than two study groups/ hospitals): experimental groups/ hospitals

Study ID	Experimental groups baseline outcome	E-N baseline	E-Mean baseline	Experimental groups post intervention	E-N post-intervention	E-Mean post-intervention	pre-post change	P value
Comparison 1: single CPW intervention versus usual care								
Philbin 2000	Hospital A LOS (days)	18	9.2	Hospital A LOS (days)	37	5.8		P= 0.42
Philbin 2000	Hospital B LOS (days)	243	9.1	Hospital B LOS (days)	217	6.9		P= 0.02
Philbin 2000	Hospital C LOS (days)	159	7.2	Hospital C LOS (days)	126	5.2		P= 0.01
Philbin 2000	Hospital D LOS (days)	168	9.0	Hospital D LOS (days)	225	7.5		P= 0.07
Philbin 2000	Hospital E LOS (days)	174	5.7	Hospital E LOS (days)	235	5.7		P= 0.09
Bookbinder 2005	Palliative ward Symptoms assessed	20	7.6	Palliative ward Symptoms assessed	55	10.2	2.6	P<0.001
Bookbinder 2005	Oncology & geriatric wards Symptoms assessed	41	6	Oncology & geriatric wards Symptoms assessed	51	10.5	4.5	P<0.001
Bookbinder 2005	Palliative ward Problematic Symptoms identified	20	4.8	Palliative ward Problematic Symptoms identified	55	3.7	1.1	P=0.014
Bookbinder 2005	Oncology & geriatric wards Problematic Symptoms identified	41	3.5	Oncology & geriatric wards Problematic Symptoms identified	51	3.9	0.4	P=0.386
Bookbinder 2005	Palliative ward Number of Interventions	20	5.1	Palliative ward Number of Interventions	55	4.1	1	P=0.021
Bookbinder 2005	Oncology & geriatric wards Number of interventions	41	4.1	Oncology & geriatric wards Number of interventions	51	4.4	0.3	P=0.484
Bookbinder 2005	Palliative ward Number inpatient consultations	20	1.6	Palliative ward Number inpatient consultations	55	2.2	0.6	P=0.062
Bookbinder 2005	Oncology & geriatric wards Number inpatient consultations	41	4	Oncology & geriatric wards Number inpatient consultations	51	5.1	1.1	p=0.037
Kinsman 2012	Percentage eligible and receiving thrombolytic drugs	25	80	Percentage eligible and receiving thrombolytic drugs	32	78	2	P=0.960
Kinsman 2012	Mean door -to-needle time (mins)	25	46.6	Mean door -to-needle time (mins)	32	47.2	-0.6	P=0.360
Kinsman 2012	Percentage receiving thrombolytic drug within 30 mins	25	40	Percentage receiving thrombolytic drug within 30 mins	32	37	3	P=0.205
Kinsman 2012	Mean door-to-ECG time (mins)	25	6.4	Mean door-to-ECG time (mins)	32	11.4	-5.0	P=0.313
Kinsman 2012	Percentage having ECG within 10 minutes	25	73	Percentage having ECG within 10 minutes	32	72	1	P=0.980

E = experimental; C = control; E-N = number of participants in experimental group; C -N = number of participants in control group; ECG = electrocardiogram; LOS = length of stay

Table B.7: Continuous primary study outcome (more than two study groups/ hospitals): control groups/ hospitals

Study ID	Control groups baseline outcome	Control-N baseline	C-Mean baseline	Control post-intervention outcome	C-N post-intervention	C-Mean post-intervention	pre-post change	P value
Comparison 1: single CPW intervention versus usual care								
Philbin 2000	Hospital F LOS (days)	152	5.7	Hospital F LOS (days)	134	5.2		P= 0.48
Philbin 2000	Hospital G LOS (days)	117	8.0	Hospital G LOS (days)	152	7.3		P= 0.34
Philbin 2000	Hospital H LOS (days)	125	9.4	Hospital H LOS (days)	104	6.7		P= 0.001
Philbin 2000	Hospital I LOS (days)	25	6.5	Hospital I LOS (days)	5	6.8		P= 0.08
Philbin 2000	Hospital J LOS (days)	221	8.9	Hospital J LOS (days)	269	8.9		P= 0.94
Bookbinder 2005	General Medical Wards Symptoms assessed	50	7.9	General Medical Wards Symptoms assessed	50	9.5	1.6	P<0.001
Bookbinder 2005	General Medical Wards Problematic Symptoms identified	50	3.4	General Medical Wards Problematic Symptoms identified	50	2.7	0.7	p=0.124
Bookbinder 2005	General Medical Wards Number of interventions	50	3.9	General Medical Wards Number of interventions	50	3.1	0.8	p=0.109
Bookbinder 2005	General Medical Wards Number inpatient consultations	50	3.3	General Medical Wards Number inpatient consultations	50	4.3	1	p=0.068
Kinsman 2012	Percentage eligible and receiving thrombolytic drugs	26	96	Percentage eligible and receiving thrombolytic drugs	25	84	12	0.191
Kinsman 2012	Mean door -to-needle time (mins)	26	43.8	Mean door -to-needle time (mins)	25	35.9	7.9	0.404
Kinsman 2012	Percentage receiving thrombolytic drug within 30 mins	26	36	Percentage receiving thrombolytic drug within 30 mins	25	62	-26	0.072
Kinsman 2012	Mean door-to-ECG time (mins)	26	7.0	Mean door-to-ECG time (mins)	25	7.4	-0.4	0.817
Kinsman 2012	Percentage having ECG within 10 minutes	26	77	Percentage having ECG within 10 minutes	25	83	-6	0.571

E = experimental; C = control; E-N = number of participants in experimental group; C -N = number of participants in control group; ECG = electrocardiogram; LOS = length of stay

Table B.8: Dichotomous primary study outcomes (pre-intervention) baseline

Study ID	Dichotomous outcome baseline measure	Experimental-events	E-N	%	Control-events	C-N	%
Comparison 1: single CPW intervention versus usual care							
Chadha 2000	Appropriate use of hospital investigations (menorrhagia)	208	472	44%	175	416	42%
Chadha 2000	Appropriate use of hospital investigations (urinary incontinence)	92	416	22%	212	472	45%
Chadha 2000	Inappropriate use of hospital investigations (menorrhagia)	127	472	27%	125	416	30%
Chadha 2000	Inappropriate use of hospital investigations (urinary incontinence)	116	416	28%	38	472	8%
Chadha 2000	Appropriate first-line treatments (menorrhagia)	382	472	81%	345	416	83%
Chadha 2000	Appropriate first-line treatments (urinary incontinence)	262	416	63%	340	472	72%
Chadha 2000	Appropriate pre-surgery assessment (menorrhagia)	90	472	19%	62	416	15%
Chadha 2000	Appropriate pre-surgery assessment (urinary incontinence)	29	416	7%	99	472	21%
Doherty 2006a	Assessment of severity of asthma	4	52	8%	5	46	11%
Doherty 2006a	Use of spirometry	6	52	12%	1	46	2%
Doherty 2006a	Overuse of ipratropium for mild asthma	16	36	44%	15	31	48%
Doherty 2006a	Use of systemic steroids	31	51	61%	22	46	48%
Doherty 2006a	Use of STAMP (Short-term Asthma Management Plan)	4	44	9%	0	32	0%
Doherty 2006a	Inappropriate use of antibiotics	9	43	21%	11	41	27%
Doherty 2006a	Aggregate measures	99	278	36%	74	242	31%

E = experimental; C = control; E-N = number of participants in experimental group; C -N = number of participants in control group

Table B.9: Dichotomous primary study results post-intervention measures

Study ID	Dichotomous outcome post-intervention	E-events	E-N	%	C-events	C-N	%
Comparison 1: single CPW intervention versus usual care							
Aizawa 2002	In-hospital complications	1	32	3%	2	37	5%
Aizawa 2002	Rehospitalisation within 6 months	1	32	3%	0	37	0%
Brook 1999	In-hospital mortality	49	162	30%	57	159	36%
Chadha 2000	Appropriate use of hospital investigations (menorrhagia)	217	472	46%	233	416	56%
Chadha 2000	Appropriate use of hospital investigations (urinary incontinence)	179	416	43%	179	472	38%
Chadha 2000	Inappropriate use of hospital investigations (menorrhagia)	99	472	21%	75	416	18%
Chadha 2000	Inappropriate use of hospital investigations (urinary incontinence)	58	416	14%	64	427	15%
Chadha 2000	Appropriate first-line treatments (menorrhagia)	378	472	80%	324	416	78%
Chadha 2000	Appropriate first-line treatments (urinary incontinence)	241	416	58%	359	472	76%
Chadha 2000	Appropriate pre-surgery assessment (menorrhagia)	203	472	43%	46	416	11%
Chadha 2000	Appropriate pre-surgery assessment (urinary incontinence)	133	416	32%	127	472	27%
Choong 2000	Confusional status (yes-no)	23	55	42%	31	56	55%
Choong 2000	In-hospital complications	10	55	18%	14	56	25%
Choong 2000	Post-discharge complications	3	55	5%	6	56	11%
Choong 2000	Readmission rates (28 days)	2	55	4%	6	56	11%
Costantini 2014	Overall control of pain	100	119	70.7%	89	113	65%
Costantini 2014	Overall control of breathlessness	108	119	54.4%	97	113	36.9%
Costantini 2014	Overall control of nausea or vomiting	102	119	83.9%	91	113	77.2%
Delaney 2003	Hospital readmissions within 30 days	3	31	10%	6	33	18%
Delaney 2003	In-hospital complications	7	31	23%	10	33	30%
Doherty 2006a	Assessment of severity of asthma	29	47	62%	6	42	14%
Doherty 2006a	Use of spirometry	29	47	62%	3	42	7%
Doherty 2006a	Overuse of ipratropium for mild asthma	9	30	30%	13	42	31%
Doherty 2006a	Use of systemic steroids	33	46	72%	8	38	21%
Doherty 2006a	Use of STAMP (Short-term Asthma Management Plan)	10	38	26%	1	38	3%
Doherty 2006a	Inappropriate use of antibiotics	9	42	21%	5	39	13%
Doherty 2006a	Aggregate measures	155	250	62%	71	231	31%
Dowsey 1999	Match/ planned discharge destination	64	92	70%	43	71	61%
Dowsey 1999	hospital readmission at 3 month follow up	4	92	4%	9	71	13%
Dowsey 1999	complication until 3 month	10	92	11%	20	71	28%
Gomez 1996	Rehospitalisation within 30 days	3	50	6%	3	50	6%
Johnson 2000	Number of unplanned interventions within 2 weeks of discharge	1	55	2%	4	55	7%
Kiyama 2003a	Morbidity rate in hospital	3	47	6%	5	38	13%
Kiyama 2003a	In-hospital complications until discharge	3	47	6%	5	38	13%
Kiyama 2003a	Target achievements day 1	41	47	87%	21	38	54%
Kiyama 2003a	Target achievements day 4	46	47	98%	30	38	78%
Kiyama 2003a	Target achievements day 7	43	47	91%	26	38	68%
Kiyama 2003a	Target achievements day 14	43	47	91%	19	38	50%
Kollef 1997	Hospital mortality	40	179	22%	42	178	24%
Marelich 2000	Rate of ventilator assisted pneumonia (medical ICU)	6	82	7%	8	88	9%
Marelich 2000	Rate of ventilator assisted pneumonia (surgical ICU)	5	84	6%	12	81	15%
Marelich 2000	Rate of ventilator assisted pneumonia (combined ICUs)	11	166	7%	20	169	12%
Roberts 1997	Hospital admission rate	37	82	45%	83	83	100%
Roberts 1997	Rehospitalisation after 8 weeks	5	82	6%	4	83	5%

Study ID	Dichotomous outcome post-intervention	E-events	E-N	%	C-events	C-N	%
Smith 2004	Hospital mortality	49	334	15%	30	175	17%
Sulch 2002	Mortality at 26 weeks	10	76	13%	6	76	8%
Sulch 2002	Discharge to home	56	76	74%	54	76	71%
Sulch 2002aa	Process of care (nutritional assessment)	49	66	74%	14	64	22%
Sulch 2002aa	Process of care (documentation of goals)	75	76	99%	56	76	74%
Sulch 2002aa	Process of care (documented death / follow-up)	68	76	89%	53	76	70%
Sulch 2002aa	Process of care (communication with GP)	61	76	80%	34	76	45%
Usui 2004	Treatment success rate	27	30	90%	28	31	90%
Comparison 2: Multifaceted intervention including a CPW versus usual care							
Cole 2002	Mortality at 8 weeks	25	113	0.22	22	114	19%
Cole 2002	Discharged at 8 weeks	65	113	0.58	77	114	68%
Cole 2002	Less dependent at 8 weeks	4	65	0.06	6	77	8%
Kampan 2006	Readmissions with hypoglycaemia within 3 months	2	33	6%	11	32	34%
Philbin 2000	In-hospital mortality	44	840	5%	25	664	4%
Philbin 2000	Quality of life (QOL) following discharge	7	840	1%	7	664	1%
Philbin 2000	QOL (functional)	2	840	0%	2	664	0%
Philbin 2000	Heart failure mortality (6 months)	105	840	13%	84	664	13%
Philbin 2000	All-cause mortality (6 months)	183	840	22%	139	664	21%
Philbin 2000	Readmission for heart failure (6 months)	169	840	20%	141	664	21%
Philbin 2000	Readmission - all causes (6 month)	363	840	43%	293	664	44%
Philbin 2000	Process of care - evaluation	638	840	76%	485	664	73%
Philbin 2000	Process of care - documentation	529	840	63%	511	664	77%
Philbin 2000	Process of care - diet counselling	613	840	73%	518	664	78%
Philbin 2000	ACE inhibitor use at discharge	529	840	63%	438	664	66%
Trombetti 2013	In-hospital mortality	28	465	6%	20.6	229	9%

E = experimental; C = control; E-N = number of participants in experimental group; C -N = number of participants in control group; ICU = intensive care unit; GP = general practitioner; ACE = angiotensin converting enzyme

Table B.10: ITS studies data

Study ID	Tilden, VP (Tilden 1987)	Brattebo, G (Brattebø 2002)	Rotter, T (Rotter 2014)
Outcome measure	Documented identification by nurses of female victims of domestic violence	Ventilation patient days per month	Number of admissions, number of readmissions, LOS, number of re-operations,
N-baseline	447	147	123
N-post-intervention	445	138	131
Number of measures baseline	4	11	6

APPENDIX C

Data analysis and meta-analysis summaries for manuscript 2

Table C.1: Stand-alone clinical pathway versus usual care

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
1.1 90-day mortality	7		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
1.1.1 90-day mortality	7	4341	Odds Ratio (M-H, Random, 95% CI)	0.84 [0.65, 1.08]
1.1.2 90-day mortality: sensitivity analysis	4	2705	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.87, 1.24]
1.2 Hospital readmission (up to 6 months)	8	1647	Odds Ratio (M-H, Random, 95% CI)	0.76 [0.51, 1.12]
1.3 In-hospital complications	8	2123	Odds Ratio (M-H, Random, 95% CI)	0.48 [0.35, 0.65]
1.4 Length of hospital stay	25		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.4.1 Length of hospital stay	22	5931	Mean Difference (IV, Random, 95% CI)	-0.94 [-1.32, -0.55]
1.4.2 Length of hospital stay: non-randomised studies	3	260	Mean Difference (IV, Random, 95% CI)	-1.85 [-2.74, -0.95]
1.4.3 Length of hospital stay: Randomised	22	7351	Mean Difference (IV, Random, 95% CI)	-0.84 [-1.21, -0.47]
1.4.4 Length of hospital stay (country): Japan	3	215	Mean Difference (IV, Random, 95% CI)	-3.01 [-5.35, -0.67]
1.4.5 Length of hospital stay (country): Spain	2	489	Mean Difference (IV, Random, 95% CI)	-2.09 [-3.06, -1.11]
1.4.6 Length of hospital stay (country): Australia	3	1393	Mean Difference (IV, Random, 95% CI)	-1.29 [-2.02, -0.56]
1.4.7 Length of hospital stay (country): USA	9	1981	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.08, -0.11]
1.4.8 Length of hospital stay (country): UK	2	403	Mean Difference (IV, Random, 95% CI)	1.29 [-3.22, 5.81]
1.4.9 Length of hospital stay (hospital area): emergency department	7	2117	Mean Difference (IV, Random, 95% CI)	-0.66 [-1.12, -0.20]
1.4.10 Length of hospital stay (hospital area): acute care	11	2132	Mean Difference (IV, Random, 95% CI)	-1.37 [-1.87, -0.87]
1.4.11 Length of hospital stay (hospital area): extended care	3	337	Mean Difference (IV, Random, 95% CI)	1.46 [-2.14, 5.05]
1.4.12 Length of hospital stay (hospital area): intensive care unit	2	1440	Mean Difference (IV, Random, 95% CI)	-2.86 [-7.77, 2.04]
1.4.13 Length of hospital stay (hospital area): surgical unit	2	154	Mean Difference (IV, Random, 95% CI)	-5.18 [-12.94, 2.57]
1.4.14 Length of hospital stay: study year	22	5815	Mean Difference (IV, Random, 95% CI)	-0.98 [-1.35, -0.60]
1.4.15 Length of hospital stay (clinical condition): paediatric asthma	2	351	Mean Difference (IV, Random, 95% CI)	-0.31 [-0.72, 0.09]
1.4.16 Length of hospital stay (clinical condition): stroke rehabilitation	2	273	Mean Difference (IV, Random, 95% CI)	3.99 [-0.29, 8.27]
1.4.17 Length of hospital stay (clinical condition): pneumonia	3	673	Mean Difference (IV, Random, 95% CI)	-1.64 [-2.24, -1.05]
1.4.18 Length of hospital stay (clinical condition): malnutrition	2	1813	Mean Difference (IV, Random, 95% CI)	-0.67 [-2.07, 0.74]
1.4.19 Length of hospital stay (clinical condition): suspected myocardial infarction	2	286	Mean Difference (IV, Random, 95% CI)	-0.90 [-1.98, 0.18]

1.4.20 Length of hospital stay (procedure type): invasive	8	1099	Mean Difference (IV, Random, 95% CI)	-1.39 [-2.17, -0.60]
1.4.21 Length of hospital stay (procedure type): non-invasive	14	4716	Mean Difference (IV, Random, 95% CI)	-0.81 [-1.25, -0.37]
1.4.22 Length of hospital stay (implementation): low	7	2555	Mean Difference (IV, Random, 95% CI)	-1.42 [-2.40, -0.43]
1.4.23 Length of hospital stay (implementation): low - sensitivity analysis	2	1216	Mean Difference (IV, Random, 95% CI)	-2.61 [-8.13, 2.91]
1.4.24 Length of hospital stay (implementation) moderate	12	1889	Mean Difference (IV, Random, 95% CI)	-0.96 [-1.46, -0.47]
1.4.25 Length of hospital stay (implementation): high	2	252	Mean Difference (IV, Random, 95% CI)	1.17 [-3.87, 6.22]
1.5 Hospital cost and charges	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.5.1 Hospital cost and charges	7	1264	Mean Difference (IV, Random, 95% CI)	-1171.52 [-1835.86, -507.18]
1.5.2 Hospital costs	4	625	Mean Difference (IV, Random, 95% CI)	-1602.52 [-2775.88, -429.15]
1.5.3 Hospital charges	3	639	Mean Difference (IV, Random, 95% CI)	-888.36 [-1920.77, 144.05]
1.6 Adherence to recommended practice	2	241	Odds Ratio (M-H, Random, 95% CI)	11.95 [4.72, 30.30]

Table C.2: Multifaceted intervention (including clinical pathway) versus usual care

Outcome or Subgroup	Studies	Participants	Statistical Method	Effect Estimate
2.1 Length of hospital stay	3	1796	Mean Difference (IV, Random, 95% CI)	-0.71 [-1.84, 0.42]
2.2 Hospital cost and charges	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
2.2.1 Hospital cost and charges	3	1875	Mean Difference (IV, Random, 95% CI)	-53.77 [-120.08, 12.54]
2.2.2 Hospital charges	1	1504	Mean Difference (IV, Random, 95% CI)	-887.03 [-2779.38, 1005.32]
2.2.3 Hospital costs	2	371	Mean Difference (IV, Random, 95% CI)	-52.74 [-119.09, 13.60]

Figure C.1: Analysis 1.1.1 and 1.1.2 90-day mortality

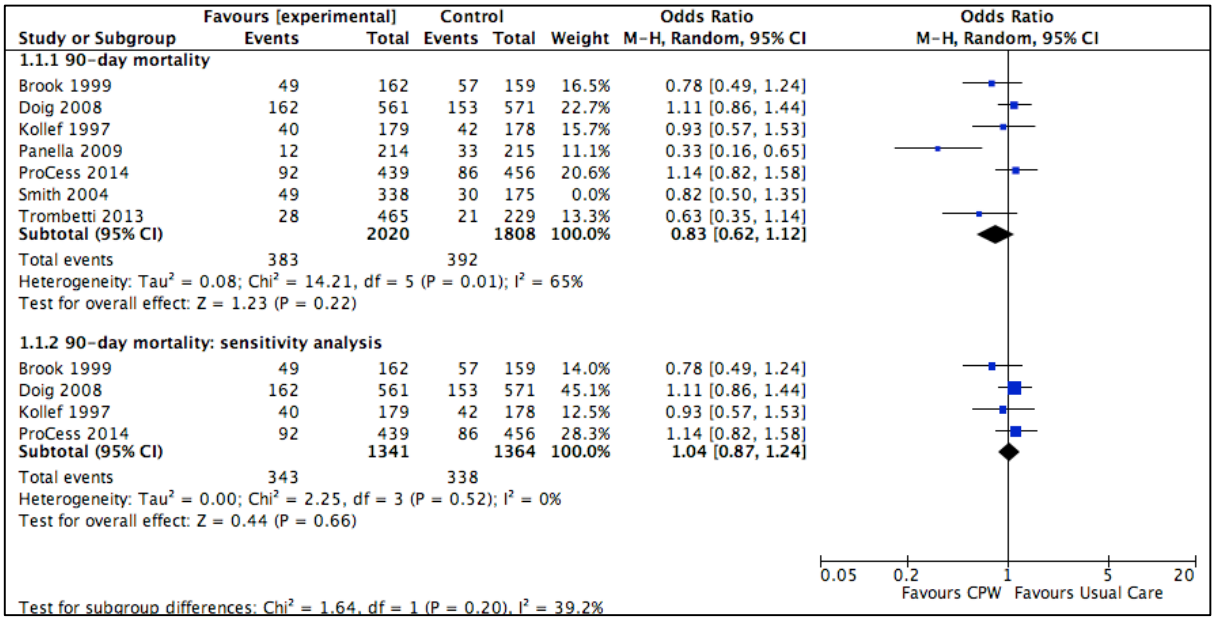


Figure C.2: Analysis 1.2 Hospital readmission (up to 6 months)

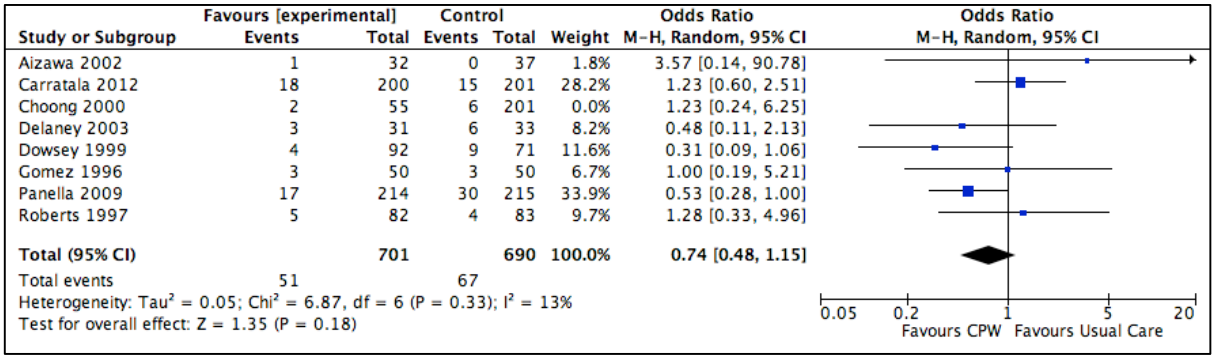


Figure C.3: Analysis 1.3 In-Hospital Complications

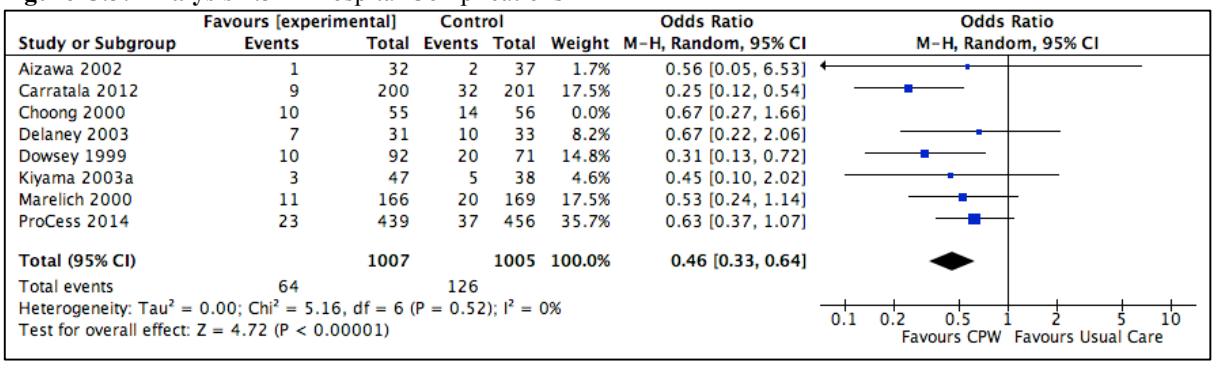


Figure C.4: Analysis 1.4.1 Length of hospital stay Favours CPW Favours UC

Study or Subgroup	Favours [experimental] Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 Length of hospital stay								
Aizawa 2002	12.7	2.8	32	14.7	5.2	37	2.9%	-2.00 [-3.94, -0.06]
Bernard 2011	0.23	0.1	87	0.2	0.1	89	12.0%	0.03 [0.00, 0.06]
Brook 1999	14	17.3	162	19.9	24.2	159	0.6%	-5.90 [-10.51, -1.29]
Carratala 2012	3.9	6.3	200	6	6.3	201	5.3%	-2.10 [-3.33, -0.87]
Cole 2002	19.7	17.1	113	19.1	16.8	114	0.7%	0.60 [-3.81, 5.01]
Cunningham 2008	1.56	1.1	136	1.7	1.15	115	11.3%	-0.14 [-0.42, 0.14]
Delaney 2003	5.2	2.5	31	5.8	3	33	4.8%	-0.60 [-1.95, 0.75]
Doig 2008	9.1	11.5	561	9.9	13.3	558	4.4%	-0.80 [-2.26, 0.66]
Dowsey 1999	7.1	3.67	92	8.6	3.67	71	5.8%	-1.50 [-2.64, -0.36]
Falconer 1993	35.6	15.5	53	32.3	15.4	68	0.5%	3.30 [-2.25, 8.85]
Gomez 1996	0.64	0.51	53	2.28	5.25	68	5.2%	-1.64 [-2.90, -0.38]
Johnson 2000	1.68	1.12	50	2.24	1.12	50	10.4%	-0.56 [-1.00, -0.12]
Kim 2002	0.25	0.15	9	2.1	2.3	9	4.2%	-1.85 [-3.36, -0.34]
Kiyama 2003a	18.1	9.5	47	28.2	22.3	38	0.2%	-10.10 [-17.69, -2.51]
Marrie 2000	8.2	1.9	87	9.6	2.1	124	9.7%	-1.40 [-1.94, -0.86]
Panella 2009	10.4	5.22	214	11.4	6.73	215	5.8%	-1.00 [-2.14, 0.14]
ProCess 2014	11.1	10	439	11.3	10.9	456	4.7%	-0.20 [-1.57, 1.17]
Roberts 1997	1.38	1.18	82	1.87	1.33	83	10.7%	-0.49 [-0.87, -0.11]
Sulch 2002	50	19	76	45	23	76	0.3%	5.00 [-1.71, 11.71]
Trombetti 2013	38	34	465	37	32	229	0.5%	1.00 [-4.17, 6.17]
Usui 2004	8.03	4.18	30	10.77	4.18	31	0.0%	-2.74 [-4.84, -0.64]
Verdu 2009	4.72	3.83	40	6.78	3.83	48	0.0%	-2.06 [-3.67, -0.45]
Subtotal (95% CI)			**2989**			**2793**	**100.0%**	**-0.83 [-1.21, -0.45]**

Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 98.19$, df = 19 ($P < 0.00001$); $I^2 = 81\%$
Test for overall effect: $Z = 4.28$ ($P < 0.0001$)

Figure C.5: Analysis 1.4.2 Length of hospital stay (non-randomised studies) Favours CPW Favours UC

1.4.2 Length of hospital stay: non-randomised studies								
Choong 2000	6.6	3.35	55	8	3.35	56	51.2%	-1.40 [-2.65, -0.15]
Usui 2004	8.03	4.18	30	10.77	4.18	31	18.1%	-2.74 [-4.84, -0.64]
Verdu 2009	4.72	3.83	40	6.78	3.83	48	30.8%	-2.06 [-3.67, -0.45]
Subtotal (95% CI)			**125**			**135**	**100.0%**	**-1.85 [-2.74, -0.95]**

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.26$, df = 2 ($P = 0.53$); $I^2 = 0\%$
Test for overall effect: $Z = 4.06$ ($P < 0.0001$)

Figure C.6: Analysis 1.4.3 Length of hospital stay (randomised studies). Favours CPW Favours UC

1.4.3 Length of hospital stay: Randomised								
Aizawa 2002	12.7	2.8	32	14.7	5.2	37	2.8%	-2.00 [-3.94, -0.06]
Bernard 2011	0.23	0.1	87	0.2	0.1	89	11.7%	0.03 [0.00, 0.06]
Brook 1999	14	17.3	162	19.9	24.2	159	0.6%	-5.90 [-10.51, -1.29]
Carratala 2012	3.9	6.3	200	6	6.3	201	5.1%	-2.10 [-3.33, -0.87]
Cole 2002	19.7	17.1	113	19.1	16.8	114	0.7%	0.60 [-3.81, 5.01]
Cunningham 2008	1.56	1.1	136	1.7	1.15	115	11.0%	-0.14 [-0.42, 0.14]
Delaney 2003	5.2	2.5	31	5.8	3	33	4.6%	-0.60 [-1.95, 0.75]
Doig 2008	9.1	11.5	561	9.9	13.3	558	4.2%	-0.80 [-2.26, 0.66]
Dowsey 1999	7.1	3.67	92	8.6	3.67	71	5.6%	-1.50 [-2.64, -0.36]
Falconer 1993	35.6	15.5	53	32.3	15.4	68	0.4%	3.30 [-2.25, 8.85]
Gomez 1996	0.64	0.51	53	2.28	5.25	68	5.0%	-1.64 [-2.90, -0.38]
Johnson 2000	1.68	1.12	50	2.24	1.12	50	10.1%	-0.56 [-1.00, -0.12]
Kampan 2006	3.94	1.03	33	6.38	404	32	0.0%	-2.44 [-142.42, 137.54]
Kim 2002	0.25	0.15	9	2.1	2.3	9	4.0%	-1.85 [-3.36, -0.34]
Kiyama 2003a	18.1	9.5	47	28.2	22.3	38	0.2%	-10.10 [-17.69, -2.51]
Marrie 2000	8.2	1.9	87	9.6	2.1	124	9.4%	-1.40 [-1.94, -0.86]
Panella 2009	10.4	5.22	214	11.4	6.73	215	5.6%	-1.00 [-2.14, 0.14]
Philbin 2000	-1.8	17.69	840	-0.7	17.69	664	3.1%	-1.10 [-2.90, 0.70]
ProCess 2014	11.1	10	439	11.3	10.9	456	4.5%	-0.20 [-1.57, 1.17]
Roberts 1997	1.38	1.18	82	1.87	1.33	83	10.4%	-0.49 [-0.87, -0.11]
Sulch 2002	50	19	76	45	23	76	0.3%	5.00 [-1.71, 11.71]
Trombetti 2013	38	34	465	37	32	229	0.5%	1.00 [-4.17, 6.17]
Subtotal (95% CI)			**3862**			**3489**	**100.0%**	**-0.84 [-1.21, -0.47]**

Heterogeneity: $Tau^2 = 0.31$; $Chi^2 = 99.66$, df = 21 ($P < 0.00001$); $I^2 = 79\%$
Test for overall effect: $Z = 4.41$ ($P < 0.0001$)

Figure C.7: Analysis 1.4.4 Length of hospital stay (country): Japan Favours CPW Favours UC

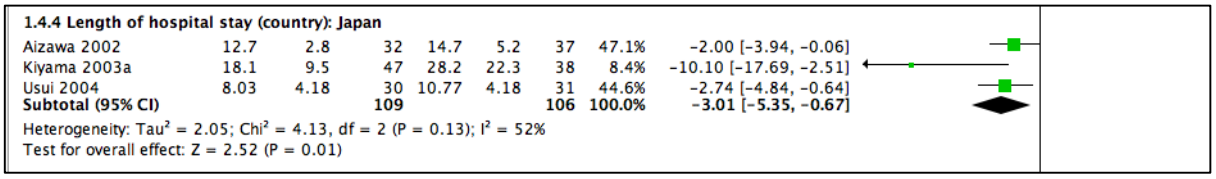


Figure C.8: Analysis 1.4.5 Length of hospital stay (country): Spain Favours CPW Favours UC

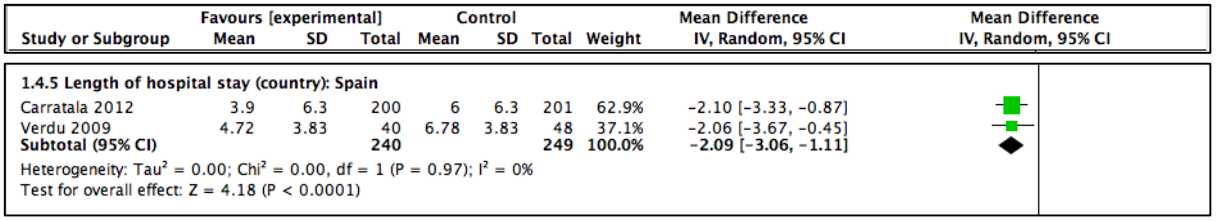


Figure C.9: Analysis 1.4.6 Length of hospital stay (country): Australia Favours CPW Favours UC

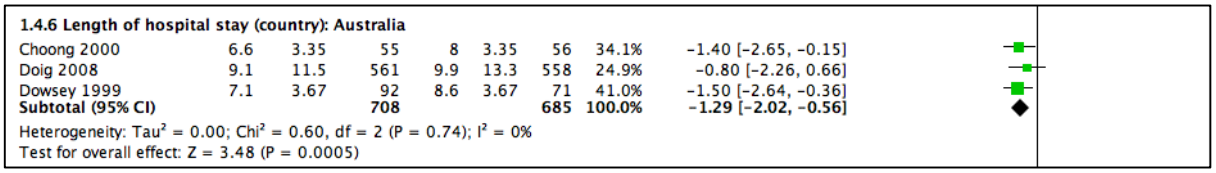


Figure C.10: Analysis 1.4.7 Length of hospital stay (country): USA Favours CPW Favours UC

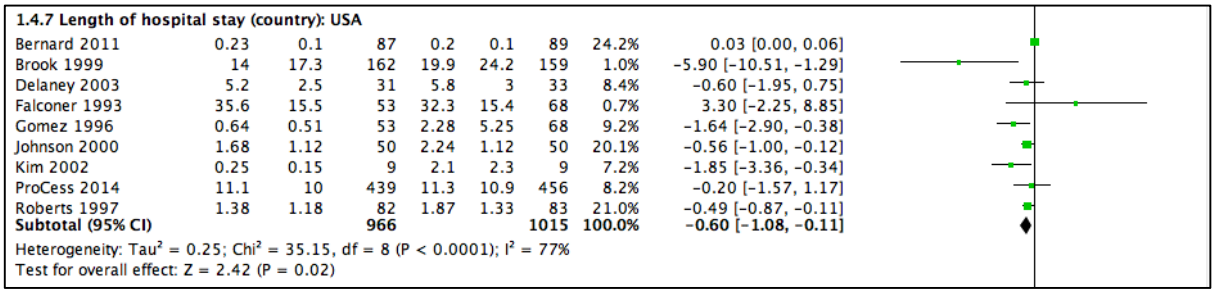


Figure C.11: Analysis 1.4.8 Length of hospital stay (country): UK Favours CPW Favours UC

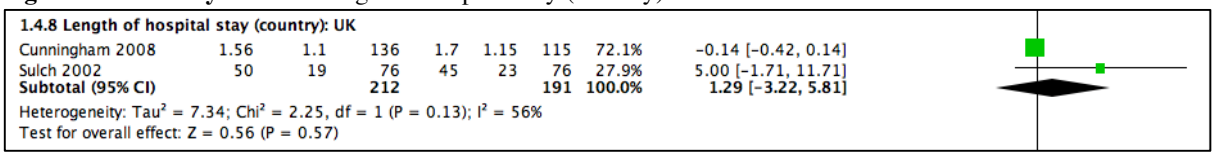
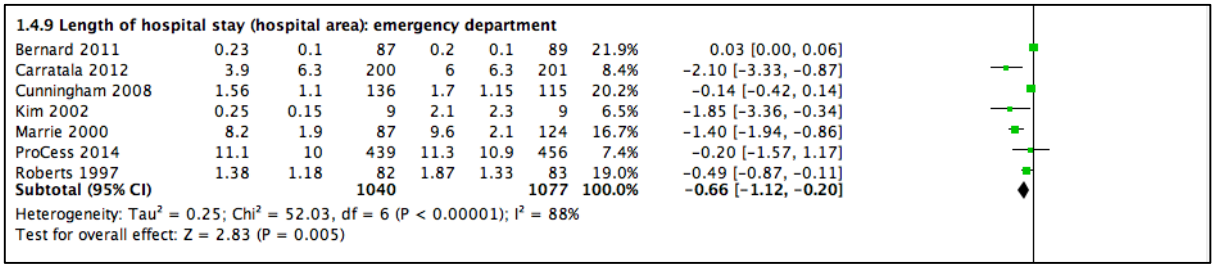


Figure C.12: Analysis 1.4.9 Length of hospital stay (hospital area): ED Favours CPW Favours UC



ED = emergency department

Figure C.13: Analysis 1.4.10 Length of hospital stay (hospital area): acute care Favours CPW Favours UC

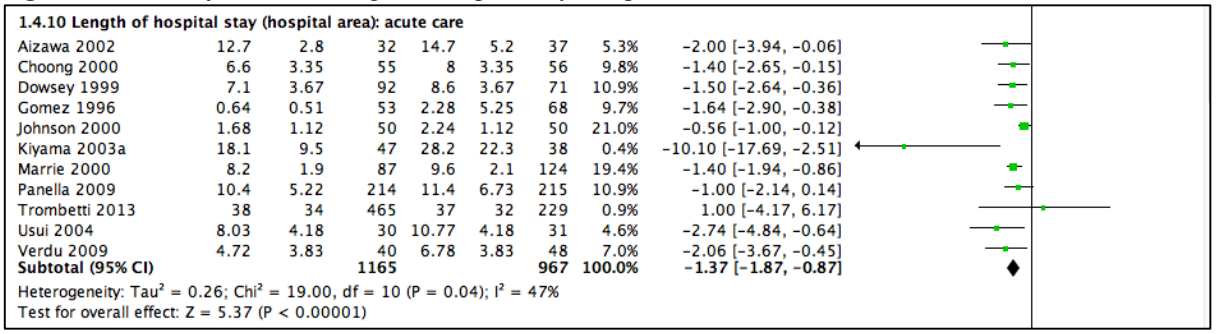
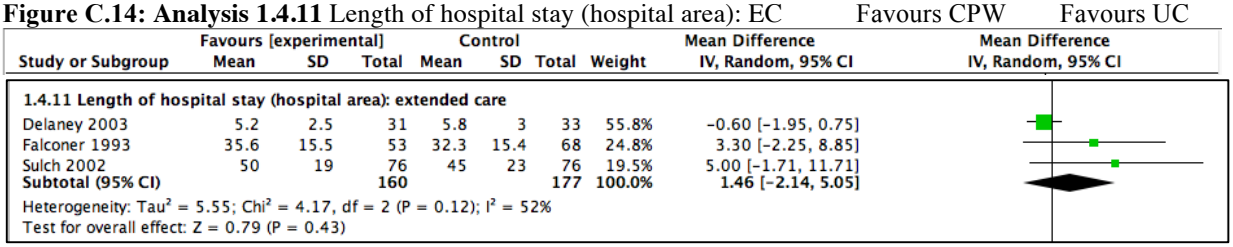
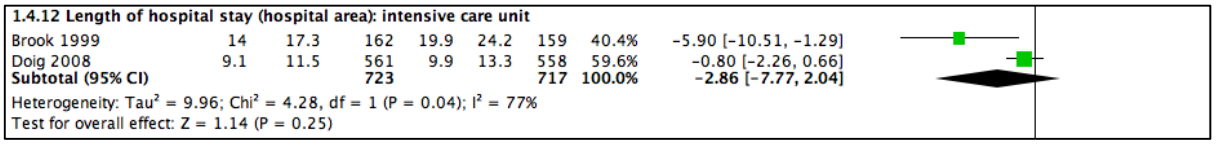


Figure C.14: Analysis 1.4.11 Length of hospital stay (hospital area): EC Favours CPW Favours UC



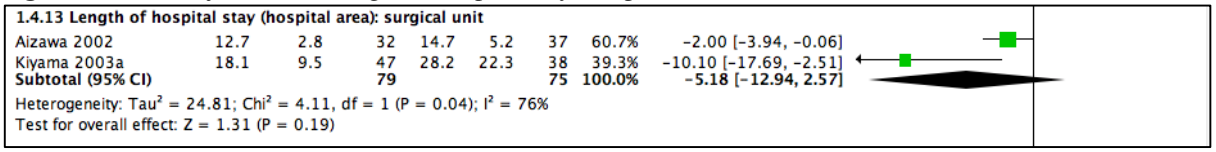
EC = extended care

Figure C.15: Analysis 1.4.12 Length of hospital stay (hospital area): ICU Favours CPW Favours UC



ICU = intensive care unit

Figure C.16: Analysis 1.4.13 Length of hospital stay (hospital area): SU Favours CPW Favours UC



SU = surgical unit

Figure C.17: Analysis 1.4.14 Length of hospital stay (study-year) Favours CPW Favours UC

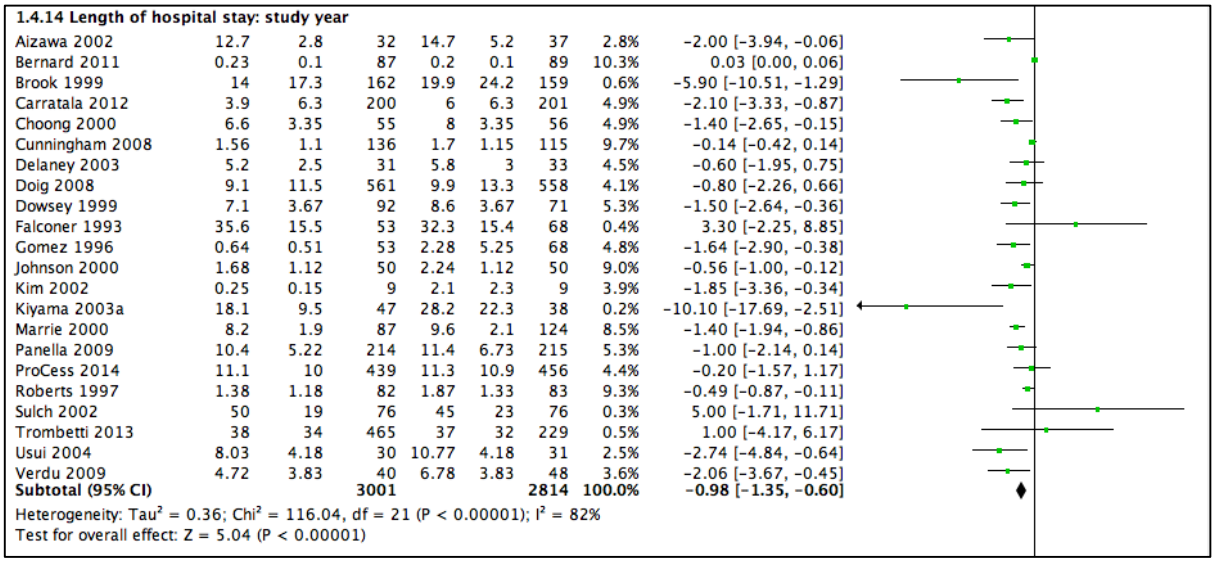
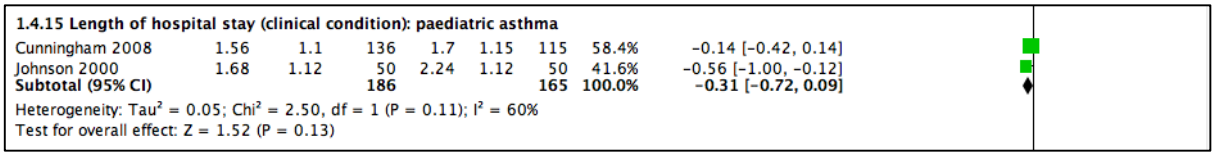
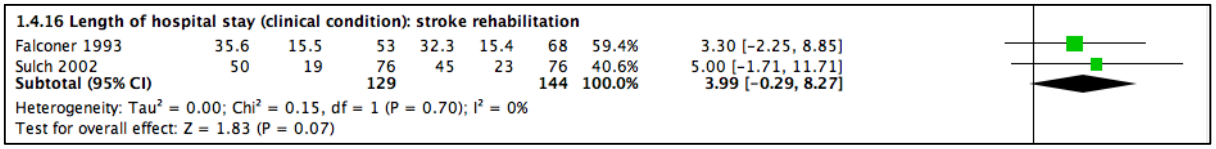


Figure C.18: Analysis 1.4.15 Length of hospital stay (clinical condition): PA Favours CPW Favours UC



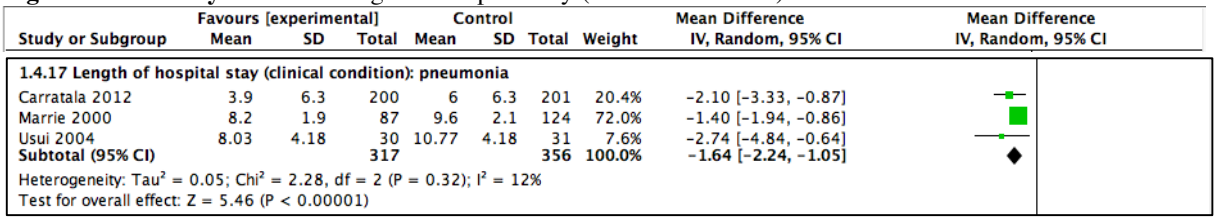
PA = paediatric asthma

Figure C.19: Analysis 1.4.16 Length of hospital stay (clinical condition): SR Favours CPW Favours UC



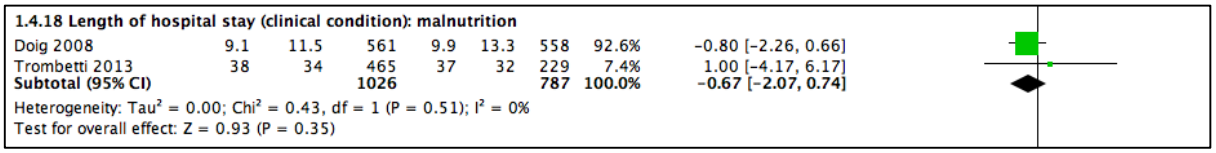
SR = stroke rehabilitation

Figure C.20: Analysis 1.4.17 Length of hospital stay (clinical condition): PN Favours CPW Favours UC



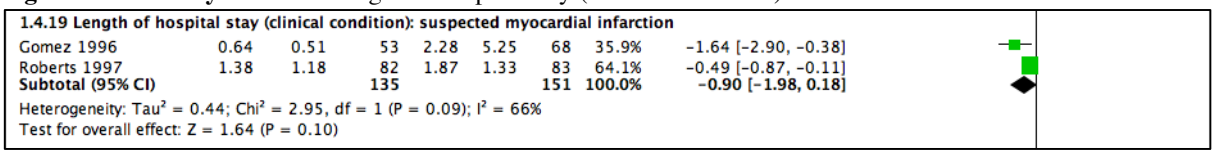
PN = pneumonia

Figure C.21: Analysis 1.4.18 Length of hospital stay (clinical condition): MN Favours CPW Favours UC



MN = malnutrition

Figure C.22: Analysis 1.4.19 Length of hospital stay (clinical condition): MI Favours CPW Favours UC



MI = myocardial infarction

Figure C.23: Analysis 1.4.20 Length of hospital stay (procedure type): invasive Favours CPW Favours UC

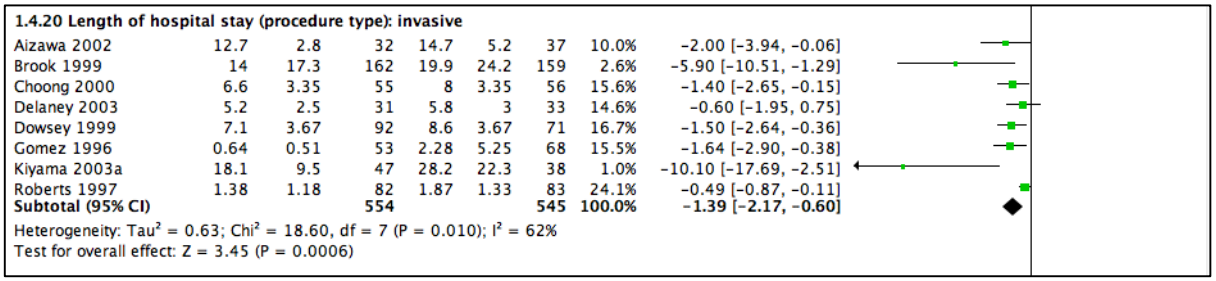
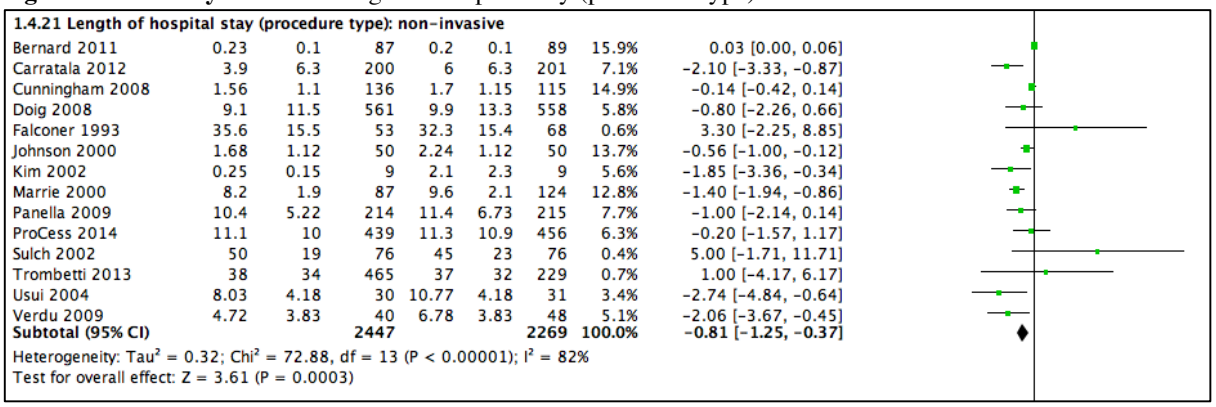


Figure C.24: Analysis 1.4.21 Length of hospital stay (procedure type): NI Favours CPW Favours UC



NI = non-invasive

Figure C.25: Analysis 1.4.22 Length of hospital stay (implementation): low Favours CPW Favours UC

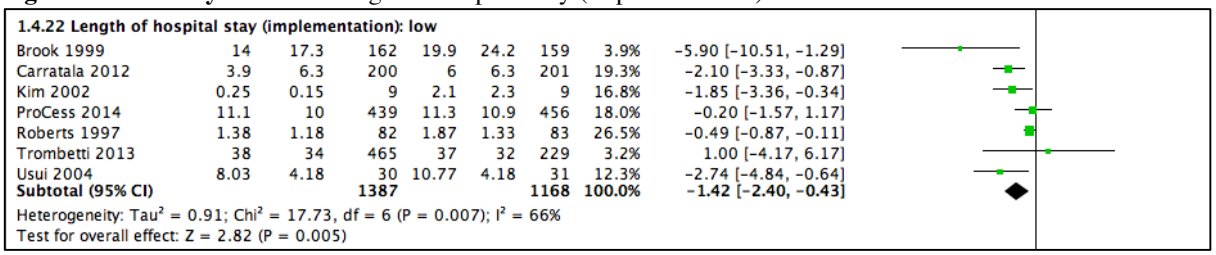
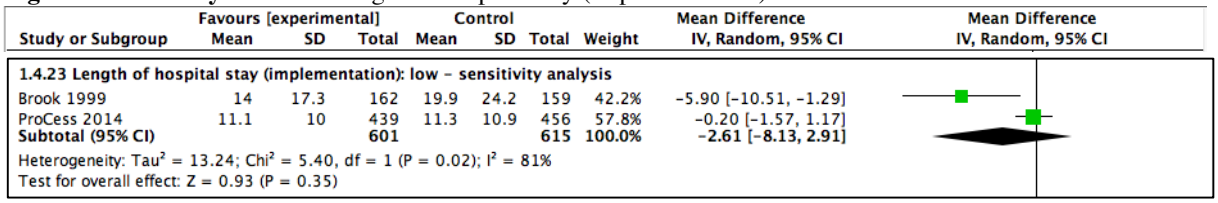


Figure C.26: Analysis 1.4.23 Length of hospital stay (implementation): low-SA Favours CPW Favours UC



SA = sensitivity analysis

Figure C.27: Analysis 1.4.24 Length of hospital stay (implementation): moderate Favour CPW Favour UC

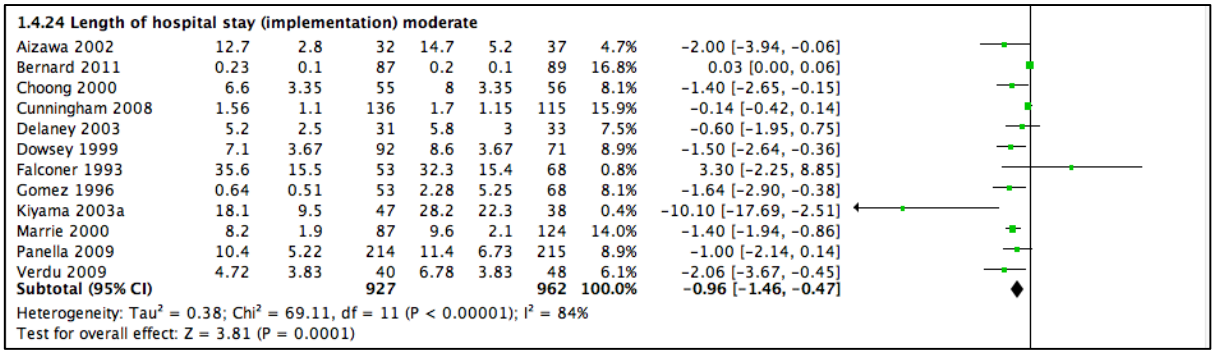


Figure C.28: Analysis 1.4.25 Length of hospital stay (implementation): high Favours CPW Favours UC

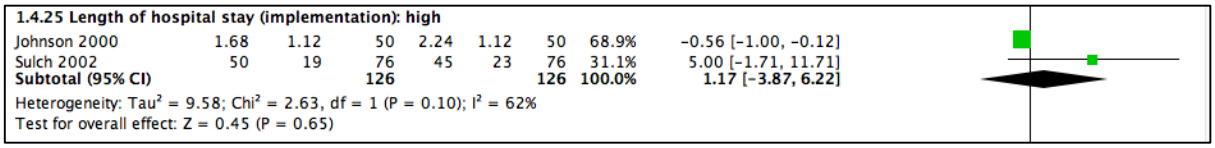
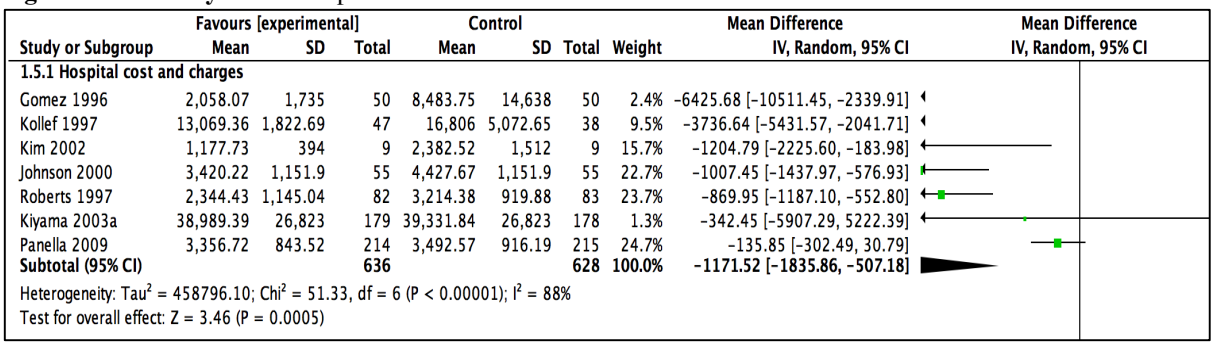


Figure C.29: Analysis 1.5 Hospital costs Favours CPW Favours UC



APPENDIX D

DATA EXTRACTION SHEET FOR MANUSCRIPT 2 and 3

Data Collection Form
Study ID number ……
STUDY STATUS
Pending = Pend
Included = In
Excluded = Ex

Did both reviewers agree on inclusion / exclusion?	**No**
Notes, including source(s) of disagreement.	

Primary Author Email Address for correspondence: Email address

DATA EXTRACTION FORM: Clinical Pathways: Effects on Professional Practice, Patient Outcomes, Length of Stay and Hospital Costs.	
Name of Reviewer:	
MINIMUM CRITERIA FOR A CLINICAL PATHWAY	
1. Is it a structured multidisciplinary care plan?	**YES** **NO** **Can't tell**
2. Is it used to channel the translation of guidelines or evidence into local structures?	**YES** **NO** **Can't tell**
3. Does it detail the steps in a course of treatment or care in a plan, pathway, algorithm, guideline, protocol or other "inventory of actions" (i.e. the intervention had time frames or criteria based progression)?	**YES** **NO** **Can't tell**
4. Does it aim to standardise care for a specific clinical problem, procedure or episode of care in a specific population?	**YES** **NO** **Can't tell**
Source of information for minimum criteria for a clinical pathway (CPW) (page numbers):	
Eligibility: **All 4 Criteria – must be "yes"** **Eligibility: EXCLUDE / CONTINUE**	

STUDY DESIGN	
Type of study (using EPOC criteria): RCT: participants randomly allocated, has a control group NRCTs: participants quasi-randomly allocated, has a control group CBA: participants non-randomly allocated, has a control group ITS: no control group. Must have 3 data points before and after intervention **Record specific method here** (e.g. Multi-centre, cross-over design)**:**	**RCTs** **NRCTs** **CBA** **ITS**
For RCTs, NRCTs or CBA:	
Level of randomisation/allocation? Was randomisation at the level of individual participant (e.g. patient) or were groups randomly assigned (e.g. ward, hospital)?	**Individual level** **Cluster**

Level of analysis Were results analysed as events per hospital?	**Individual level** **Cluster**
If CBA:	
Contemporaneous data collection? The timing of data collection pre-and post-intervention must be the same both study and control sites. DONE = dates mentioned NOT CLEAR = dates not mentioned - STOP DATA EXTRACTION UNTIL CONFIRMED NOT DONE = STOP DATA EXTRACTION	**Done** **Not clear** **Not done**
Appropriate choice of control sites AND at least two control sites? Control and study sites need to be comparable on issues such as reimbursement system, level of care, setting, academic status NOT CLEAR = can't tell if sites are comparable - STOP DATA EXTRACTION UNTIL CONFIRMED NOT DONE = STOP DATA EXTRACTION	**Done** **Not clear** **Not done**
If ITS:	
Clearly defined point in time when the intervention occurred? Intervention must have occurred at a clearly defined point in time. NOT CLEAR = not reported in paper STOP DATA EXTRACTION UNTIL CONFIRMED NOT DONE = STOP DATA EXTRACTION	**Done** **Not clear** **Not done**
At least three data points before and after the intervention? NOT CLEAR = e.g. number of discrete data points not mentioned in table or text - STOP DATA EXTRACTION UNTIL CONFIRMED NOT DONE = STOP DATA EXTRACTION	**Done** **Not clear** **Not done**
Source of information for study design (page numbers):	
Eligibility: If not above design, or have selected NOT DONE then EXCLUDE **Reason for exclusion: _____ or CONTINUE**	

SETTING & PARTICIPANTS	
Geographic location of the hospital Where was the hospital/s situated?	**Remote** **Rural** **Regional** **Urban** **Not clear**
Country Where was the study conducted? Not clear if information is not available	**Not clear** **Specify** _____
Description of health professionals targeted Which health professionals were expected to utilise the CPW? **Provide description here:** (page no.)	**Specialists/Surgeons** **Nurses** **Allied Health** **Multidisciplinary** **Others (specify)** _____ **Not clear** □
Number of health professionals targeted How many health professionals were involved (include both intervention and control sites)	**n =** **not stated**
Demographic characteristics of health professionals Was a description of the health care professionals who were the target of the CPW provided?	**Gender (% male):** **Gender (% female):** **Age range:**

	Not stated
Section of hospital where intervention took place What specific ward or unit was the CPW introduced in to?	**Medical** **Surgical** **Emergency** **Rehab** **Aged care** **Hospital-wide** **Other (specify)** **_____** **Not clear**
Description of patients What were the characteristics of the patients?	**Outpatients** **Presenting to ED** **Hospitalised** **Other (specify)** **_____**
Inclusion criteria for patients Were the inclusion criteria for patients clearly stated and appropriate? **Inclusion criteria for cluster?** For cluster trials, were the inclusion criteria for clusters (e.g. hospitals, wards) clearly stated and appropriate?	**Done** **Not clear** **Not done** **Done** **Not clear** **Not done** **Not applicable**
Number of patients included How many patients were included in the study? How many in intervention and control groups?	**Number of groups** **Intervention** | **Control** **Number of participants** **Intervention** n = **Control** n = **Total number of participants** n =
Characteristics of patients included. What were the demographic characteristics of the patients who were recruited?	**Gender (% male):** **Gender (% female):** **Age range:** **Ethnicity:** **Not stated**
Power calculation: Was a power calculation explicitly stated? **Record specific power calculation here:** (page no.) **For cluster trials, did power calculation allow for effects of clustering?** e.g. do they mention intraclass correlation co-efficient?	**Done** **Not clear** **Not done** **Yes** **No** **Not applicable**
ELIGIBILITY: If setting is not a hospital or patients are not hospitalised then EXCLUDE **Reason for exclusion: -_____ or CONTINUE**	
CLINICAL PATHWAY CHARACTERISTICS	
Type of intervention: Was the CPW combined with any other type of intervention (e.g. electronic medical records, academic detailing) or was it a stand-alone intervention?	**CPW vs usual care** **Intervention including CPW vs intervention without CPW** **Intervention including CPW vs usual care**

	Other (specify) _____
Description of intervention: (page no.)	
Invasive or non-invasive intervention targeted? INVASIVE examples = CPW for gastrectomy; PTCA; laparoscopic cholecystectomy; hip and knee arthroplasty NON-INVASIVE examples = CPW for stroke; pneumonia; asthma	**Invasive** **Non-invasive**
Specify intervention or diagnosis targeted:	
What was the purpose of the CPW? What did the authors state as the main reason the CPW was developed/introduced?	**Appropriate mgmt.** **Cost containment** **Other (specify)** _____ **Not clear**
Was there a multi-faceted implementation process? Was the process of development of the CPW described? **Short description of the collaborative process:** (page no.)	**Done** **Not clear** **Not done**
Was content of the CPW evidence based? DONE = content of CPW based on a systematic review or ≥ one RCT or best practice guidelines NOT CLEAR = not stated NOT DONE = content clearly not evidence-based	**Done** **Not clear** **Not done**
What was the format of the CPW? Was the CPW paper-based and part of a hardcopy medical record or was it electronic?	**Paper** **Electronic** **Other (specify)** _____ **Not clear**
Was the CPW adapted for local use? DONE = format of CPW adapted in collaboration with users / clinicians NOT CLEAR = not stated NOT DONE = no collaboration with users / clinicians on format of CPW	**Done** **Not clear** **Not done**
Was there clinician involvement in development of CPW? DONE = clearly stated that clinicians were involved in content of CPW	**Done** **Not clear** **Not done**
Was there an implementation team?	**Done** **Not clear** **Not done**
Were evidence-practice gaps identified prior to implementation of the CPW? DONE = gaps identified by local audit NOT CLEAR = anecdotal or evidence not local NOT DONE = no audit or identifying of evidence-practice gaps	**Done** **Not clear** **Not done**
Were barriers to change identified? DONE = barriers clearly stated NOT CLEAR = barriers may have been identified NOT DONE = barriers to change not stated	**Done** **Not clear** **Not done**
Were reminder systems incorporated into implementation? DONE = formal reminder system described e.g. posters, computer reminders NOT CLEAR = reminder system may have been used	**Done** **Not clear** **Not done**

NOT DONE = reminder system not described	
Was audit and feedback incorporated into implementation? DONE = audit and feedback process clearly stated NOT CLEAR = audit and feedback may have been used NOT DONE = no description of audit and feedback provided	**Done** **Not clear** **Not done**
Were education sessions used to implement CPW? DONE = education sessions attended by majority of users / clinicians NOT CLEAR = education sessions may have been provided and may have been attended by users / clinicians NOT DONE = no education sessions provided or attended by users / clinicians	**Done** **Not clear** **Not done**
Were local opinions leaders used to implement CPW? DONE = clear identification and utilisation of local opinion leaders NOT CLEAR = local opinion leaders may have been involved NOT DONE = no evidence of utilisation of local opinion leaders	**Done** **Not clear** **Not done**
Evidence-based implementation strategy: A = 7-10 criteria checked as "Done" B = 2-6 criteria checked as "Done" C = 0-1 criteria checked as "Done"	**A (high)** **B (moderate)** **C (low)**
What was the source of funding for the study? Who funded the study?	**Nil** **Govt** **Commercial** **Health service** **Voluntary body** **Charity** **Research** **Other (specify)** **_____** **Not clear**
Eligibility: If intervention does not clearly include a CPW then EXCLUDE **Reason for exclusion: -_____ or CONTINUE**	

OUTCOME MEASURE(S): NB: Primary outcomes are those that correspond to the primary hypothesis or question as defined by the authors. Other outcomes may be incorporated if they are relevant to patient outcomes and professional practice, and meet the EPOC quality criteria.	
Main outcome measures (list): **1.** **2.** **3.** **4.** **5.** **Other**	
Was compliance or adherence to CPW measured and reported?	**Yes (specify)** **_____** **No**
What was the length of post–intervention follow-up?	
Was there a possible ceiling effect? (i.e. little room for improved outcomes)	
Ceiling effect identified by investigator:	**Yes (specify)** **_____** **No** **Not relevant**

Ceiling effect identified by reviewer:	**Yes (specify) _____ No Not relevant**
Were outcomes measured in a <u>clinical</u> (i.e. not test) situation?	**Done Not clear Not done**
Are the results relevant and interpretable?	**Done Not clear Not done**
Eligibility: If outcomes are not relevant to our stated review aims then EXCLUDE Reason for exclusion: _____ or CONTINUE	

Did both reviewers agree on inclusion / exclusion and study quality?	**Yes / No**
If no, what was the source(s) of disagreement?	

3 Working definition for a clinical pathway

MINIMUM CRITERIA FOR A CLINICAL PATHWAY	
1. Is it a structured multidisciplinary care plan?	**YES NO Can't tell**
2. Is it used to channel the translation of guidelines or evidence into local structures?	**YES NO Can't tell**
3. Does it detail the steps in a course of treatment or care in a plan, pathway, algorithm, guideline, protocol or other "inventory of actions" (i.e. the intervention had time frames or criteria based progression)?	**YES NO Can't tell**
4. Does it aim to standardise care for a specific clinical problem, procedure or episode of care in a specific population?	**YES NO Can't tell**
Source of information for minimum criteria for a clinical pathway (CPW) (page numbers):	
Eligibility: All 4 Criteria – must be "yes" Eligibility: EXCLUDE / CONTINUE	

APPENDIX E

Medline Search Strategy.
Search strategy conducted for on-going update of systematic review on the effects of clinical pathways in hospitals.

Medline (OVID)		
Medline discs used:	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
30-8-2016	Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	Scroll down for search terms
8-2-2017	Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>	Scroll down for search terms
	Date searched (if different to summary sheet):	
No.	Search terms	Results
1	Critical Pathways/	5140
2	((clinical or critical) adj2 (pathway? or path)).ti,ab.	7456
3	((care adj2 algorithm?) or clinical algorithm?).ti,ab.	1176
4	(care adj2 pathway?).ti,ab.	2616
5	(treatment adj3 algorithm?).ti,ab.	5539
6	(structured care or intensive management).ti,ab.	862
7	(standardi$ adj3 (treatment? or care or patient care or plan$)).ti,ab.	5862
8	(care adj2 (plan? or map or maps or protocol? or algorithm?)).ti,ab.	10333
9	(protocol? adj4 (nursing or treatment or management or directed or guided)).ti,ab.	25010
10	((local or locally) adj2 adapt$ adj5 guideline?).ti,ab.	79
11	(treatment model? adj10 standardi$).ti,ab.	9
12	(standardi$ adj3 (template or templates)).ti,ab.	257
13	or/1-12 [Pathways]	59310
14	Clinical protocols/	21974
15	Algorithm/ and (di.fs. or (treatment or care or patient?).ti. or diagnos$.ti,ab.)	44551
16	Practice Guidelines as Topic/ or Guideline Adherence/ or Guidelines as topic/	136358
17	((guideline or guidelines) adj2 (adher$ or implement$)).ti,ab.	5602
18	(guideline? adj4 (compliance or complying)).ti,ab.	2931
19	or/16-18 [PGL or GL Adherence]	139909
20	(adherence or care or compliance or comply$ or implement$ or impact or plan? or standardi?ed or pathway or (treatment adj3 (protocol? or algorithm?))).ti,ab.	2800181
21	19 and 20 [GL]	53817
22	*Guidelines as topic/ or *Practice Guidelines as topic/	39468
23	*Guideline Adherence/	11167
24	or/22-23 [Focussed MeSH Guideline]	47530
25	Primary health care/ or Primary Care Nursing/	59553
26	Family practice/ or General Practice/	66773
27	General Practitioners/ or Physicians, Family/ or Physicians, Primary Care/	19441

28	((general or family) adj2 (practice? or practitioner? or physician? or doctor?)).ti,ab.	97661
29	(primary adj2 (care or health care or healthcare or medical care or patient care)).ti,ab.	98355
30	(primary care or family medic$ or general practice or family practi$).jn.	8571
31	GP.ti.	3489
32	or/25-31 [Primary Care]	232583
33	Ambulatory Care/ or Community medicine/ or community health nursing/ or community health services/ or home care services/ or Community mental health services/ or Community Pharmacy Services/	127407
34	Ambulatory Care Facilities/ or Community Health Centers/	19109
35	(community or communities).ti,ab,hw.	441147
36	(((ambulatory or walk-in or neighbo?rhood or community) adj2 (clinic? or care centre or care centres or care center? or health$ centre or health$ centres or health$ center?)) or public clinic?).ti,ab.	10485
37	((urban or rural) adj3 health).ti,ab.	11119
38	or/33-37 [Community Care]	515822
39	13 and 32 [Pathway terms & PC]	3083
40	(and/13,38) not 39 [Pathways & Community-Ambulatory Care]	3399
41	(and/24,32) not (or/39-40) [Focussed GL & PC]	3395
42	(and/24,38) not (or/39-41) [Focussed GL & Community-Ambulatory Care]	2247
43	(21 and (or/32,38)) not (or/39-42) [GL & PC/Amb Care]	6871
44	((or/14-15) and ((or/26-31,38) or *Primary health care/ or *Primary Care Nursing/)) not (or/39-43) [Clinical Protocols/Algorithms Mesh & PC/Community Care-combine with RCT filter only]	3511
45	(randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.	1013198
46	exp animals/ not humans.sh.	4152952
47	45 not 46 [Cochrane RCT Filter 6.4.d Sens/Precision Maximizing]	934229
48	intervention?.ti. or (intervention? adj6 (clinician? or collaborat$ or community or complex or DESIGN$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv$ or individuali?e? or individuali?ing or interdisciplin$ or multicomponent or multi-component or multidisciplin$ or multi-disciplin$ or multifacet$ or multi-facet$ or multimodal$ or multi-modal$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib$ or prescription? or primary care or professional$ or provider? or regulatory or regulatory or tailor$ or target$ or team$ or usual care)).ab.	194948
49	(pre-intervention? or preintervention? or "pre intervention?" or post-intervention? or postintervention? or "post intervention?").ti,ab. [added 2.4]	13033
50	(hospital$ or patient?).hw. and (study or studies or care or health$ or practitioner? or provider? or physician? or nurse? or nursing or doctor?).ti,hw.	781323
51	demonstration project?.ti,ab.	2122
52	(pre-post or "pre test$" or pretest$ or posttest$ or "post test$" or (pre adj5 post)).ti,ab.	77801
53	(pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).ti,ab.	726
54	trial.ti. or ((study adj3 aim?) or "our study").ab.	760357
55	(before adj10 (after or during)).ti,ab.	394692

56	("quasi-experiment$" or quasiexperiment$ or "quasi random$" or quasirandom$ or "quasi control$" or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab,hw.	114170
57	("time series" adj2 interrupt$).ti,ab,hw.	1399
58	(time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month$ or hour? or day? or "more than")).ab.	11310
59	pilot.ti.	46690
60	Pilot projects/	92166
61	(clinical trial or controlled clinical trial or multicenter study).pt.	674918
62	(multicentre or multicenter or multi-centre or multi-center).ti.	34245
63	random$.ti,ab. or controlled.ti.	866032
64	(control adj3 (area or cohort? or compare? or condition or design or group? or intervention? or participant? or study)).ab. not (controlled clinical trial or randomized controlled trial).pt.	470246
65	evaluation studies as topic/ or prospective studies/ or retrospective studies/ [Added Jan 2013]	1079015
66	(utili?ation or programme or programmes).ti. [Added Jan 2013]	60368
67	(during adj5 period).ti,ab. [Added Jan 2013]	328905
68	((strategy or strategies) adj2 (improv$ or education$)).ti,ab. [Added Jan 2013]	22433
69	"comment on".cm. or review.pt. or (review not "peer review$").ti. or randomized controlled trial.pt. [Changed Jan 2013]	3269864
70	(rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti.	1420258
71	exp animals/ not humans.sh.	4152952
72	(or/48-68) not (or/69-71) [EPOC Methods Filter 2.5-added Evaluation Studies line forward--Jan 20130 Medline]	3177316
73	(or/39-44) and 47 [RCT Results]	3063
74	(39 and 72) not 73 [EPOC Filter Results Set 1 : Pathways & PC]	1293
75	(40 and 72) not (or/73-74) [EPOC Filter Set 2: Pathways & Community-Ambulatory Care]	1565
76	(41 and 72) not (or/73-75) [EPOC Filter Set 3: Focussed GL & PC]	1099
77	(42 and 72) not (or/73-76) [EPOC Filter Set 4: Focussed GL & Ambultory]	847
78	(43 and 72) not (or/73-77) [EPOC Filter Set 5: GL & PC/Amb care]	2586
79	or/74-78 [EPOC Filter Results]	7390
80	73 or 79	10453
81	limit 80 to yr="2015 -Current"	1257
2016 update: 30/08/2016		
No.	Search terms	Results
1	Critical Pathways/	5420
2	((clinical or critical) adj2 (pathway? or path)).ti,ab.	8083
3	((care adj2 algorithm?) or clinical algorithm?).ti,ab.	1275
4	(care adj2 pathway?).ti,ab.	3099
5	(treatment adj3 algorithm?).ti,ab.	6141
6	(structured care or intensive management).ti,ab.	927
7	(standardi$ adj3 (treatment? or care or patient care or plan$)).ti,ab.	6438
8	(care adj2 (plan? or map or maps or protocol? or algorithm?)).ti,ab.	11126

9	(protocol? adj4 (nursing or treatment or management or directed or guided)).ti,ab.	26862
10	((local or locally) adj2 adapt$ adj5 guideline?).ti,ab.	81
11	(treatment model? adj10 standardi$).ti,ab.	11
12	(standardi$ adj3 (template or templates)).ti,ab.	292
13	or/1-12 [Pathways]	64309
14	Clinical protocols/	23218
15	Algorithm/ and (di.fs. or (treatment or care or patient?).ti. or diagnos$.ti,ab.)	46262
16	Practice Guidelines as Topic/ or Guideline Adherence/ or Guidelines as topic/	142398
17	((guideline or guidelines) adj2 (adher$ or implement$)).ti,ab.	6225
18	(guideline? adj4 (compliance or complying)).ti,ab.	3159
19	or/16-18 [PGL or GL Adherence]	146461
20	(adherence or care or compliance or comply$ or implement$ or impact or plan? or standardi?ed or pathway or (treatment adj3 (protocol? or algorithm?))).ti,ab.	3037238
21	19 and 20 [GL]	56974
22	*Guidelines as topic/ or *Practice Guidelines as topic/	41843
23	*Guideline Adherence/	11918
24	or/22-23 [Focussed MeSH Guideline]	50500
25	Primary health care/ or Primary Care Nursing/	62173
26	Family practice/ or General Practice/	69506
27	General Practitioners/ or Physicians, Family/ or Physicians, Primary Care/	22382
28	((general or family) adj2 (practice? or practitioner? or physician? or doctor?)).ti,ab.	101817
29	(primary adj2 (care or health care or healthcare or medical care or patient care)).ti,ab.	106166
30	(primary care or family medic$ or general practice or family practi$).jn.	8827
31	GP.ti.	3764
32	or/25-31 [Primary Care]	244482
33	Ambulatory Care/ or Community medicine/ or community health nursing/ or community health services/ or home care services/ or Community mental health services/ or Community Pharmacy Services/	130322
34	Ambulatory Care Facilities/ or Community Health Centers/	22206
35	(community or communities).ti,ab,hw.	476877
36	(((ambulatory or walk-in or neighbo?rhood or community) adj2 (clinic? or care centre or care centres or care center? or health$ centre or health$ centres or health$ center?)) or public clinic?).ti,ab.	11292
37	((urban or rural) adj3 health).ti,ab.	12016
38	or/33-37 [Community Care]	556500
39	13 and 32 [Pathway terms & PC]	3382
40	(and/13,38) not 39 [Pathways & Community-Ambulatory Care]	3691
41	(and/24,32) not (or/39-40) [Focussed GL & PC]	3562
42	(and/24,38) not (or/39-41) [Focussed GL & Community-Ambulatory Care]	2399
43	(21 and (or/32,38)) not (or/39-42) [GL & PC/Amb Care]	7218
44	((or/14-15) and ((or/26-31,38) or *Primary health care/ or *Primary Care Nursing/)) not (or/39-43) [Clinical Protocols/Algorithms Mesh & PC/Community Care-combine with RCT filter only]	3722
45	(randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.	1063538

46	exp animals/ not humans.sh.	4304227
47	45 not 46 [Cochrane RCT Filter 6.4.d Sens/Precision Maximizing]	980712
48	intervention?.ti. or (intervention? adj6 (clinician? or collaborat$ or community or complex or DESIGN$ or doctor? or educational or family doctor? or family physician? or family practitioner? or financial or GP or general practice? or hospital? or impact? or improv$ or individuali?e? or individuali?ing or interdisciplin$ or multicomponent or multi-component or multidisciplin$ or multi-disciplin$ or multifacet$ or multi-facet$ or multimodal$ or multi-modal$ or personali?e? or personali?ing or pharmacies or pharmacist? or pharmacy or physician? or practitioner? or prescrib$ or prescription? or primary care or professional$ or provider? or regulatory or regulatory or tailor$ or target$ or team$ or usual care)).ab.	218683
49	(pre-intervention? or preintervention? or "pre intervention?" or post-intervention? or postintervention? or "post intervention?").ti,ab. [added 2.4]	15304
50	(hospital$ or patient?).hw. and (study or studies or care or health$ or practitioner? or provider? or physician? or nurse? or nursing or doctor?).ti,hw.	810807
51	demonstration project?.ti,ab.	2216
52	(pre-post or "pre test$" or pretest$ or posttest$ or "post test$" or (pre adj5 post)).ti,ab.	86771
53	(pre-workshop or post-workshop or (before adj3 workshop) or (after adj3 workshop)).ti,ab.	820
54	trial.ti. or ((study adj3 aim?) or "our study").ab.	842176
55	(before adj10 (after or during)).ti,ab.	416033
56	("quasi-experiment$" or quasiexperiment$ or "quasi random$" or quasirandom$ or "quasi control$" or quasicontrol$ or ((quasi$ or experimental) adj3 (method$ or study or trial or design$))).ti,ab,hw.	124033
57	("time series" adj2 interrupt$).ti,ab,hw.	1728
58	(time points adj3 (over or multiple or three or four or five or six or seven or eight or nine or ten or eleven or twelve or month$ or hour? or day? or "more than")).ab.	12735
59	pilot.ti.	51666
60	Pilot projects/	96615
61	(clinical trial or controlled clinical trial or multicenter study).pt.	682423
62	(multicentre or multicenter or multi-centre or multi-center).ti.	37580
63	random$.ti,ab. or controlled.ti.	934497
64	(control adj3 (area or cohort? or compare? or condition or design or group? or intervention? or participant? or study)).ab. not (controlled clinical trial or randomized controlled trial).pt.	507163
65	evaluation studies as topic/ or prospective studies/ or retrospective studies/ [Added Jan 2013]	1127398
66	(utili?ation or programme or programmes).ti. [Added Jan 2013]	64495
67	(during adj5 period).ti,ab. [Added Jan 2013]	345785
68	((strategy or strategies) adj2 (improv$ or education$)).ti,ab. [Added Jan 2013]	25129
69	"comment on".cm. or review.pt. or (review not "peer review$").ti. or randomized controlled trial.pt. [Changed Jan 2013]	3408192
70	(rat or rats or cow or cows or chicken? or horse or horses or mice or mouse or bovine or animal?).ti.	1476130
71	exp animals/ not humans.sh.	4304227
72	(or/48-68) not (or/69-71) [EPOC Methods Filter 2.5-added Evaluation Studies line forward--Jan 20130 Medline]	3387408
73	(or/39-44) and 47 [RCT Results]	3303

74	(39 and 72) not 73 [EPOC Filter Results Set 1 : Pathways & PC]	1418
75	(40 and 72) not (or/73-74) [EPOC Filter Set 2: Pathways & Community-Ambulatory Care]	1681
76	(41 and 72) not (or/73-75) [EPOC Filter Set 3: Focussed GL & PC]	1167
77	(42 and 72) not (or/73-76) [EPOC Filter Set 4: Focussed GL & Ambultory]	902
78	(43 and 72) not (or/73-77) [EPOC Filter Set 5: GL & PC/Amb care]	2716
79	or/74-78 [EPOC Filter Results]	7884
80	73 or 79	11187
81	limit 80 to yr="2015 -Current"	1138
2017 update: 08/02/2017		
No.	Search terms	Results
1	(clinical adj2 pathway?).ti.	1285
2	critical pathways/	5562
3	((clinical or critical) adj1 (pathway? or path?)).ti,ab.	5259
4	((care adj2 algorithm?) or clinical algorithm?).ti,ab.	1315
5	(care adj1 pathway?).ti,ab.	2703
6	(treatment adj3 algorithm?).ti,ab.	6455
7	(management protocol? or treatment protocol?).ti,ab.	17810
8	(care adj1 (plan? or map?)).ti,ab.	7232
9	(protocol? adj1 (nursing or directed or guided)).ti,ab.	547
10	((local or locally) adj2 adapt* adj5 guideline?).ti,ab.	85
11	(treatment model? adj10 standardi*).ti,ab.	11
12	(standardi* adj3 protocol?).ti,ab.	9894
13	systematic detection.ti,ab.	271
14	or/2-13	53386
15	clinical protocols/	24668
16	(treat* or therap*).ti,ab.	5628132
17	15 and 16	12241
18	practice guidelines as topic/	97006
19	(implement* or pathway or protocol?).ti,ab.	1185547
20	18 and 19	12971
21	(guideline? adj1 (implement* or pathway or protocol?)).ti,ab.	2112
22	or/20-21	14130
23	14 or 17 or 22	76751
24	(hospital or hospitals or hospitalis* or hospitaliz*).ti,ab.	1022715
25	exp hospital units/	90944
26	exp hospitals/	241004
27	exp hospital departments/	161398
28	hospitalization/	85875
29	or/24-28	1287170
30	1 or (23 and 29)	18164
31	randomized controlled trial.pt.	447592
32	controlled clinical trial.pt.	91833
33	multicenter study.pt.	218061
34	pragmatic clinical trial.pt.	521
35	(randomis* or randomiz* or randomly).ti,ab.	723337

36	groups.ab.	1672872
37	(trial or multicenter or multi center or multicentre or multi centre).ti.	204098
38	(intervention? or effect? or impact? or controlled or control group? or (before adj5 after) or (pre adj5 post) or ((pretest or pre test) and (posttest or post test)) or quasiexperiment* or quasi experiment* or pseudo experiment* or pseudoexperiment* or evaluat* or time series or time point? or repeated measur*).ti,ab.	7883302
39	non-randomized controlled trials as topic/	122
40	interrupted time series analysis/	239
41	controlled before-after studies/	214
42	or/31-41	8810908
43	exp animals/	20711674
44	humans/	16396415
45	43 not (43 and 44)	4315259
46	review.pt.	2223092
47	meta analysis.pt.	73858
48	news.pt.	180989
49	comment.pt.	678358
50	editorial.pt.	425203
51	cochrane database of systematic reviews.jn.	12923
52	comment on.cm.	678357
53	(systematic review or literature review).ti.	90278
54	or/45-53	7523264
55	42 not 54	6145029
56	30 and 55	10214
57	limit 56 to yr="2008 -Current"	6218

Draft data extraction sheet for realist review

Data extraction sheet		
Date	Reviewer's Initial	
Author and year		
Country		
Participants		
Implementation strategy(s)		
For what aspect(s) of program theory does this study provide evidence (i.e. evidence 'to support, refute or refine elements of theory)? *(Include a summary of the nature of the evidence and quotes/ page numbers if possible).*		
CMO Table (Or elements of CMOs) (Add extra lines if required). Include quotes or page no's		
Context	Mechanism	Outcome
What amendments to program theory might you propose based on this study?		
Comments or questions on rigour/methodology		
Priority for in-depth review: Please rank as High / Medium / Low. Why?		
Other notes/comments		