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[Category: Research/ Systematic Review Protocol]

Implementation strategies for interventions to improve the management of Chronic Kidney Disease (CKD) by primary care clinicians: Protocol for a systematic review.

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Author Statement: CCK & BT are the guarantors of the review. CCK conceptualized, designed and coordinated the study and created the initial draft and final manuscript. BT contributed to conceptualization and design of the study, helped revise the manuscript and provided final approval. CCD & MAL helped in the design of the study, helped revise the manuscript and provided final approval. NDS and HMM provided guidance in conceptualizing and designing the study, revised the final draft and provided final approval. PJE was instrumental in the literature search strategy, helped with design of the study and provided final approval. JM, ME, RGM, MA, AP & AV helped in various stages of conceptualizing and designing the study, contributed toward revision of the manuscript and provided final approval.

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Abstract

Introduction: There is a considerable implementation gap in managing early stage Chronic Kidney Disease (CKD) in primary care, despite the high prevalence and risk for increased morbidity and mortality associated with CKD. This systematic review aims to synthesize evidence of efficacy of implementation interventions aimed at primary care practitioners (PCPs) to improve CKD identification and management. We further aim to describe the interventions' behavioral change components.

Methods and Analysis: We will conduct a systematic review of studies that evaluate implementation interventions targeting PCPs and which include at least one clinically meaningful CKD outcome. We will search several electronic data bases & also conduct reference mining of related systematic reviews and publications. A team with clinical and implementation science background will independently and in duplicate screen publications, extract data and assess the risk of bias. Clinical outcomes will include all clinically meaningful medical management markers relevant to CKD management in primary care such as blood pressure, chronic heart disease and diabetes target achievements. Quantitative evidence synthesis will be performed, where possible. Planned subgroup analyses include by 1) study design (RCT or cohort design), 2) length of follow-up (12 months, 12-24 months, over 24 months), 3) type of intervention (guideline based alerts, shared care, pharmacist-facing, tailored implementation), 4) type of implementation strategy and 5) whether a behavioral or implementation theory was used to guide the study.

Ethics and dissemination: Approval by research ethics board is not required since the review will only include published and publicly accessible data. Review findings will inform a future trial of an intervention to promote uptake of CKD diagnosis and treatment guidelines in our primary care setting and the development of

complementary tools to support its successful adoption and implementation. We will publish our findings in a peer-reviewed journal and develop accessible summaries of the results.

PROSPERO registration number: CRD42018102441;

Keywords:

Chronic Kidney Disease, Primary Care Practitioner interventions, Systematic Review Protocol, Guideline Implementation, Implementation strategies

Article Summary:

Strengths and limitations of this study:

- This protocol conforms to the Preferred Reporting for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement guidelines.
- The planned evidence synthesis will shed light on what works to influence PCPs to adopt guidelines for early detection and management of CKD in primary care.
- The focus on use and reporting of implementation strategies will highlight the behavioral change strategies likely to enhance effectiveness of interventions.
- The evidence synthesis of impact on a range of clinically meaningful medical markers or outcomes in CKD includes the important dimensions of quality of care in CKD.
- The anticipated heterogeneity in reporting and measures of clinical outcomes and interventions may hinder meta-analysis.

Background

Chronic Kidney Disease (CKD) with a worldwide prevalence rate of 8-16% (1), is considered a considerable public health issue and a risk factor for increased morbidity and mortality. The estimated prevalence of CKD in individuals 60 years and older increases to 25%. CKD often remains undiagnosed or poorly managed in these individuals (1-4), in spite of existing guidelines for diagnosing and managing the disease (5-8). Given the magnitude of the problem and the potential to modify the course of the disease if diagnosed early, the importance of CKD recognition and proactive early management cannot be overstated. Since patients with CKD are often not referred to nephrologist until late in the course it is important to optimize management of the disease in primary care. This need is augmented by the relative shortage of nephrologists (9). CKD awareness, quality of care and implementation of guidelines have been found to be inadequate among primary care practitioners (PCPs), including underuse of recommended nephro-protective medications in CKD such as angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), inadequate blood pressure control and late nephrology referrals (10-12). This review aims to evaluate the evidence for interventions to improve management of CKD in primary care, targeting PCs.

The evidence to practice divide has been the focus of enquiry, recognizing that successful implementation of any practice guidelines is a multifaceted process, involving health care professionals' beliefs, knowledge, confidence and commitment, organization of care processes and other system level factors(9, 13). Qualitative research has identified specific challenges surrounding management of CKD in primary care (14). These

include issues regarding whether deterioration of renal function represents normal aging or a genuine disease in elderly people, problems and skepticism in achieving blood pressure targets and difficulty explaining the disease to patients without causing anxiety. (14). Several interventions have been developed to improve the quality of primary care management of CKD. These include reminders, some embedded in electronic medical records, creation of registries, chronic disease management, educational, and other continuous quality improvement (CQI) methods, with a small percentage of these accompanied by behavioral change interventions.

Systematic reviews on interventions targeted at clinicians managing patients with CKD have identified a number of interventions including Chronic Disease Management (CDMs) strategies(15), continuous improvement interventions (16), e-alerts (19, 20), pharmacy-facing interventions (17) and nurse led disease management programs or models of care interventions for chronic disease (18, 19). Other reviews assessed multifaceted care approaches (20) and clinical pathways for primary care (21). These reviews either are, however, are either not confined to primary care settings or do not include clinically meaningful outcomes. The three reviews that do (15, 22), do not separate interventions aimed at clinicians from those that are aimed at patients. Thus, there is a need to review interventions that aim to influence clinician behavior in managing CKD in primary care using clinically relevant medical management markers. We are also interested in the range of interventions, quality of reporting on intervention details, their underlying behavioral rationale and other relevant information that could guide the development of implementation interventions that target the right behaviors to advance the systematic

adoption and sustaining of evidence based CKD management strategies into routine practice.

The objectives of this systematic review are:

1. Synthesize the evidence of the effect of interventions, aimed at PCPs, to improve the detection and management of CKD on clinically relevant medical management markers.
2. Map the type of interventions and implementation methods used to detect and manage CKD in primary care.
3. Identify the most successful implementation approach to effect practice change around CKD management in primary care.

Methods:

This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P)(23) (see "Supplemental File 1 PRISMA-P 2015 checklist"). Considering that the studied interventions are complex (multi-component), we will follow frameworks suggested for evidence synthesis of complex interventions.(24, 25) Therefore, we will focus on determining the characteristics and circumstances in which the interventions prove to be effective; rather than focusing on a simple question of efficacy.

Patient and Public Involvement:

No patients or the public were involved since this is a systematic review of interventions targeting clinicians.

Study Registration:

This systematic review is registered with PROSPERO (registration number: CRD42018102441; http://www.crd.york.ac.uk/PROSPERO).

Criteria for considering studies for the review:

Type of Studies:

We will include randomized trials (including cluster randomized trials), non-randomized trials, before and after studies with a comparator group, and cohort studies.

Types of participants:

Studies that evaluated interventions aimed at any health care professional practicing in the primary care environment, managing care for patients with CKD or at risk of developing CKD will be included.

Types of interventions and comparators

Any intervention where implementation science methods were an integral part or a component of an intervention directed at the primary care practioners or conducted within the primary care system, organization or setting to enable managing care for patients with CKD or risk of developing CKD will be included. Comparators will include usual care or any other intervention intended to manage care of CKD patients in a primary care setting, including historical control.

Types of Outcomes:

We required at least one clinically meaningful medical marker or outcome to be assessed in each study. Those could be either process of care measures (e.g., proportion of patient taking renin-angiotensin-aldosterone system inhibitors), a relevant surrogate (e.g., blood pressure, (BP) or diabetes control) or a hard clinical outcome (e.g., mortality, dialysis).

Search methods for identification of studies:

We will search several electronic data bases including PubMed, EBSCO, CINAHL, Scopus, Ovid Medline, Ovid Cochrane Library, Ovid EMBASE, Ovid PsycINFO, Ovid EMBASE and Web of Science. We will use the Institute of Medicine (26) recommendation to guide our search strategy. (See Supplemental File 2 for sample search strategy). Due to the relatively young field of implementation science, we will focus our attention to published reports from 2000 to late 2017. Controlled vocabulary supplemented with keywords will be used to search the literature. As implementation interventions that promote the adoption and integration of evidence-based practices, interventions and policies are closely related to the fields of quality improvement, improvement science and similar mechanisms of improvement, we will include search terms associated with these fields. Reference mining of relevant publications will be conducted. We will also hand search all systematic reviews on implementation interventions to improve CKD management in primary care. In addition, we will include study protocols of potentially eligible trials at this stage, and follow up to see if these trials had been published by the time of our analysis. The searches described above will be done with the help of an experienced librarian with several years' experience in systematic review searches.

Selection:

We will upload search results into an EndNote (version 8) library. To prepare for selecting and abstracting data, reviewers will undergo education to ensure an understanding of the purpose of the review and a background of the field. Understanding of the inclusion and exclusion criteria will also be assessed through testing on a small number of studies. In the first round of

screening, two reviewers will consider the potential eligibility of studies identified by the search strategy based on the abstract and title. Reviewers will request the full text versions of all potentially eligible studies. Studies with reviewer disagreement about eligibility based on abstract and title will also undergo full text review. Eligibility at both the abstract and full text level will be assessed in duplicate and independently. Any disagreements will be resolved by consensus; in the absence of consensus, a third reviewer will arbitrate.

Data Extraction:

Extraction of data for this study will include characteristics of study participants, details of interventions, the control interventions, the monitoring for efficacy or adherence, outcome measures and measurement instruments used, and factors associated with study quality. Discrepancies in data will be adjudicated by consensus.

A preliminary review of the literature indicated considerable heterogeneity of the types and measurement methods of clinical outcomes in potentially eligible studies. We also observed a wide variation in intervention and implementation strategies. Given this complexity, the team conducting this evidence synthesis consisted of primary care clinicians, health services researchers with implementation science experience and a systematic review methodologist to identify the scope and abstraction methods for the above variables. The team met twice to refine the scope of the review, define the specific questions we sought to answer and develop consensus on definitions of interventions and outcomes. Informed by the panel discussions, we created a list of clinically relevant medical

management markers for CKD prevention and management to guide the prioritization of abstraction for clinical variables (see List 1 in Box 1).

We will create and pilot a standardized data abstraction sheet using Excel software with drop down menus that will enable abstractors to choose the relevant clinical outcomes and their respective measures, as reflected in the list below.

Implementation interventions will be broadly categorized using elements of the Chronic Care model (27, 28), and further detailed in terms of implementation strategies used, utilizing the Expert Recommendations for Implementing Change (ERIC) framework (29, 30). The broad categorizations of implementation strategies are included in List 2 (see List 2 in Box 2). More granular details of the intervention strategies under each category can be found in Waltz et al. (30). Clinicians will abstract clinical data, while two implementation science researchers will dissect and abstract details on the interventions. The lead author will coordinate integrations of these two separate abstraction efforts.

Authors of the primary studies will be contacted for clarification if data included in the publication is missing, unclear or in a format that is difficult to extract. Author contact will be initiated by email to the corresponding author. If the email is unavailable, we will search the internet to find a current email address. If the first author is not the corresponding author, the first author will be carbon copied on all emails to the corresponding author, if their email is available. Authors will be given a week to respond to emails at which time, a follow-up email will be sent. If no response is received for yet another two weeks we will attempt to contact

the author by telephone. If this was not possible, the authors will be classified as not contactable.

Methodological Quality and certainty in the evidence

We will use the Cochrane Collaboration's risk of bias tool (31) to evaluate the methodological quality of included studies. Reviewers will assess the adequacy of randomization sequence generation, concealment of treatment arm allocation, blinding of participants and outcome assessors, the degree and potential impact of missing data, the likelihood of incomplete reporting and the potential role of conflicting interests.

For non-randomized studies we will adapt the New Castle Ottawa instrument to assess risk of bias, focusing on cohort selection, comparability and outcome ascertainment(32)

We will also assess the quality of reporting on implementation outcomes, using an adapted TieDier checklist (33).

The certainty in evidence (confidence in the effect) will be evaluated using adaptations of GRADE (Grading of recommendations, assessment, development and evaluation) for complex interventions (34) and narrative synthesis.(35)

Meta-analysis:

When possible, we will generate meta-analytical estimates of treatment effects. We will use the random-effects model because of anticipated heterogeneity in studies' settings and populations. The clinical outcomes that have at least three or more studies with relevant data will be pooled. We will use Stata statistical software package to conduct the analyses(36). Other clinical outcomes, not amenable to meta-analysis, will be summarized narratively & tabulated in terms of significant findings.

Subgroups:

Subgroup analyses will be conducted to explore the causes of inconsistency and different effects in subgroups. We plan to conduct the following a priori defined sub-group analyses: 1) study design (RCT or cohort design), 2) length of follow-up (12 months, 12-24 months, over 24 months), 3) type of intervention (guideline based alerts, shared care, interventions aimed at pharmacists, collaborative and tailored interventions, 4) type of implementation (based on ERIC classification). 5) whether or not a behavioral or implementation theory was used to guide the study. If the intervention structure proves highly variable and we have a sufficient number of studies, we may attempt to explain variation in effects by conducting a meta-regression analysis of intervention and implementation characteristics by clinical outcome.

Missing Data and Sensitivity Analyses:

We will attempt to contact authors for missing data. In the event that the data are still unavailable, we will use a complete case analysis and conduct sensitivity analysis using methods described by Ebrahim et al (37) for continuous variables and Akl et al (38) for dichotomous variables.

Publication Bias:

If the number of studies per analysis is over 10, we will assess publication bias by using funnel plots, plotting the estimate of effect of trials by the inverse of its standard error. A significant publication bias will be suspected if, using Egger's test (39), the p value is < 0.10.

Discussion:

CKD detection and management in primary care is a challenging task, given the competing demands on clinicians and the asymptomatic nature of the disease. Yet its importance cannot be underscored enough given the upstream health and cost implications of disease progression in patients at risk for CKD. Several disparate interventions have been tried over the last couple of decades targeting PCPs as well as patients. This review focuses on interventions aimed at PCPs, evaluating what works, and deconstructing the nature of the interventions and their implementation to provide guidance as to what works under what circumstances in preparation for an intervention study in primary care.

This study may encounter several limitations including a high degree of heterogeneity in the interventions as well as the heterogeneity of clinical outcomes in this clinical area. Pooling data from heterogeneous populations and interventions carries inherent uncertainty.

We chose to exclude studies including solely interventions aimed at educating or informing patients even if they met all other inclusion criteria for this study as we are primarily interested in modifying clinician behavior towards increased quality of care. Our systematic review will identify evidence gaps and provide information on which interventions targeted at clinicians work best to improve the care of patients at risk of CKD or with an established diagnosis of CKD in primary care.

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Box1: List 1

Patient identification: (1) Patients identified/registered with CKD, (2) prevalence of CKD, (3) Referral to Nephrologist, (4) Other (State)

Disease progression: (1) Change in glomerular filtration rate (GFR), (2) change in proteinuria, (3) Other (State)

Lab monitoring (within the last year): (1) Creatinine or GFR, (2) Urine protein/albumin, (3) Hemoglobin, (4) Other (State)

Medical Management: (1) ACE/ARB use, (2) hypertensives - # of classes, (3) avoidance of nephrotoxic drugs, (4) any type of dosing inadequacy,

BP management: (1) Change in BP, (2) achievement of BP (</=140/90), (3) achievement of BP (</=130/80, (4) Other (State)

Diabetes management: (1) Hemoglobin A1c, (2) Achievement of HbA1c<7, (3) Other (State)

Cholesterol management: (1) Total cholesterol, (2) LDL, (3) HDL, (4) triglycerides, (5) Other (State)

Box 2. List 2

1) Use Evaluative and iterative strategies,
2) Provide Interactive Assistance,
3) Adapt & tailor to context,
4) Develop stakeholder interrelationships,
5) Train and educate stakeholders,
6) Support clinicians,
7) Encourage consumers,
8) Utilize financial strategies,
9) Change infrastructure.

Supplemental File 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	No
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	5,9
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1,2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	2
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	2
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	7,8
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	8-10
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	9,10
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	10,11,13

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplemental File-2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	11,13
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	11-13
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	13
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	13,23,24
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	13,23,24
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	14
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	14
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	14,15
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	14
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14,15
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplemental File 2

MEDLINE Search Strategy:

Data Base: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

……

1. ((chronic adj3 (kidney or renal)) or ckd).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

2. (esrd or eskd or (end stage adj2 (renal or kidney))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3. exp Renal Insufficiency/ or (chronic disease/ and kidney diseases/)

4. exp renal dialysis/ or hemodialys*.mp. or haemodialys*.mp. or "renal replacement".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

5. or/1-4

6. knowledge translation.mp. or Translational Medical Research/ or guideline*.mp. or improv*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

7. ((implement* or integrat* or change* or innovat*) adj4 (strateg* or plan* or practice* or research or complex* or incentiv* or process*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

8. 5 and 7

9. 5 and 6 and ((intervention* or implement*).mp. or 7) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

10. 8 or 9

11. 10 and (program* or adopt* or protocol* or evaluat* or application* or initiative* or promot* or incentiv* or chang*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

12. ((quality or qi) adj2 technique*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

13. 10 and "best practice".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

14. (sdm or (shared adj2 decision*) or (decision adj2 aid*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

15. 10 and 14

16. 10 and (framework* or challeng* or barrier* or roadblock* or facilitat* or obstacle* or confound*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

17. 10 and (attitude of health personnel/ or (chang* adj4 (behavior* or behaviour* or performance)).mp. or health knowledge attitude practice/) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

18. 10 and (educat* or detailing or audit* or feedback* or multifacet* or target* or outreach* or mareketing or consensus* or impact*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

19. 10 and ("clinical decision support" or reminder* or alert*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

20. 11 or 13 or 15 or 17 or 19

21. 10 and 12

22. 20 or 21

23. limit 22 to ("in data review" or in process or publisher or "pubmed not medline")

24. 22 not 23

25. ((chronic adj3 (kidney or renal)) or ckd or (esrd or eskd or (end stage adj2 (renal or kidney)))).ti. or (exp *Renal Insufficiency/ or (*chronic disease/ and *kidney diseases/))

26. exp *renal dialysis/ or *hemodialys*/ or *haemodialys*/ or *"renal replacement"/ or (renal dialysis or hemodialys* or haemodialys* or "renal replacement").ti.

27. 25 or 26

28. 24 and 27

29. 23 or 28

30. 29 and (study or trial* or cohort* or meta-analysis or review*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

31. limit 24 to (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or consensus development conference or controlled clinical trial or evaluation studies or meta analysis or multicenter study or observational study or pragmatic clinical trial or randomized controlled trial or systematic reviews or validation studies)

32. 23 and 30

33. 31 or 32

34. 24 and (study or meta-analysis or cohort* or trial*).tw.

35. 34 not 31

36. 35 and ((practice* or "primary care" or pcps).mp. or primary health care/ or "community health".mp. or "patient-cent*".mp. or providers.mp. or family practice.mp. or general practice.mp. or general practitioner*.mp. or physician, primary care/ or physicians, family/ or ambulatory care/ or professional practice/) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

37. 33 or 36

38. limit 37 to english language

39. remove duplicates from 38

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Implementation strategies for interventions to improve the management of Chronic Kidney Disease (CKD) by primary care clinicians: Protocol for a systematic review.

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31[Category: Research/ Systematic Review Protocol]

Implementation strategies for interventions to improve the management of Chronic Kidney Disease (CKD) by primary care clinicians: Protocol for a systematic review.

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Abstract

Introduction: There is a considerable implementation gap in managing early stage Chronic Kidney Disease (CKD) in primary care, despite the high prevalence and risk for increased morbidity and mortality associated with CKD. This systematic review aims to synthesize evidence of efficacy of implementation interventions aimed at primary care practitioners (PCPs) to improve CKD identification and management. We further aim to describe the interventions' behavioral change components.

Methods and Analysis: We will conduct a systematic review of studies from 2000 to October 2017 that evaluate implementation interventions targeting PCPs and which include at least one clinically meaningful CKD outcome. We will search several electronic data bases & also conduct reference mining of related systematic reviews and publications. A team with clinical and implementation science background will independently and in duplicate screen publications, extract data and assess the risk of bias. Clinical outcomes will include all clinically meaningful medical management outcomes relevant to CKD management in primary care such as blood pressure, chronic heart disease and diabetes target achievements. Quantitative evidence synthesis will be performed, where possible. Planned subgroup analyses include by 1) study design , 2) length of follow-up , 3) type of intervention , 4) type of implementation strategy , 5) whether a behavioral or implementation theory was used to guide study, 6) baseline CKD severity, 7) patient minority status, 8) study location and 9) academic setting or not.

Ethics and dissemination: Approval by research ethics board is not required since the review will only include published and publicly accessible data. Review findings will inform a future trial of an intervention to promote uptake of CKD diagnosis and treatment guidelines in our primary care setting and the development of complementary tools to support its successful adoption and implementation. We will

publish our findings in a peer-reviewed journal and develop accessible summaries of the results.

PROSPERO registration number: CRD42018102441;

Keywords:

Chronic Kidney Disease, Primary Care Practitioner interventions, Systematic Review Protocol, Guideline Implementation, Implementation strategies

Article Summary:

Strengths and limitations of this study:

- This protocol conforms to the Preferred Reporting for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement guidelines.
- The planned evidence synthesis will shed light on what works to influence primary care practitioners (PCPs) to adopt guidelines for early detection and management of chronic kidney disease (CKD) in primary care.
- The focus on use and reporting of implementation strategies will highlight the behavioral change strategies likely to enhance effectiveness of interventions.
- The evidence synthesis of impact on a range of clinical outcomes in CKD includes the important dimensions of quality of care in CKD.
- The anticipated heterogeneity in reporting and measures of clinical outcomes and interventions may hinder meta-analysis.

Background

Chronic Kidney Disease (CKD) with a worldwide prevalence rate of 8-16% (1), is considered a considerable public health issue and a risk factor for increased morbidity and mortality. The estimated prevalence of CKD in individuals 60 years and older increases to 25%. CKD often remains undiagnosed or poorly managed in these individuals (1-4), in spite of existing guidelines for diagnosing and managing the disease (5-8). Given the magnitude of the problem and the potential to modify the course of the disease if diagnosed early, the importance of CKD recognition and proactive early management cannot be overstated. Since patients with CKD are often not referred to a nephrologist until late in the course of the disease, it is important to optimize management of CKD in primary care. This need is augmented by the relative shortage of nephrologists (9). CKD awareness, quality of care and implementation of guidelines have been found to be inadequate among primary care practitioners (PCPs), including underuse of recommended nephro-protective medications in CKD such as angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), inadequate blood pressure control and late nephrology referrals (10-12). This review aims to evaluate the evidence for interventions to improve management of CKD in primary care, targeting PCPs.

The evidence to practice divide has been the focus of enquiry, recognizing that successful implementation of any practice guidelines is a multifaceted process, involving health care professionals' beliefs, knowledge, confidence and commitment, organization of care processes and other system level factors (9, 13). Qualitative research has identified specific challenges surrounding management of CKD in primary care (14).

These include issues regarding whether deterioration of renal function represents normal aging or a genuine disease in elderly people, challenges in achieving blood pressure targets and difficulty explaining the disease to patients without causing anxiety (14). Several interventions have been developed to improve the quality of primary care management of CKD. These include reminders, some embedded in electronic medical records, creation of registries, chronic disease management, educational, and other continuous quality improvement (CQI) methods, with a small percentage of these accompanied by behavioral change interventions.

Systematic reviews on interventions targeted at clinicians managing patients with CKD have identified a number of interventions including Chronic Disease Management (CDMs) strategies (15), continuous improvement interventions (16), e-alerts (17, 18) , pharmacy-facing interventions (19) and nurse led disease management programs or models of care interventions for chronic disease (17, 20). Other reviews assessed multifaceted care approaches (18) and clinical pathways for primary care (21). These reviews are however, either not confined to primary care settings or do not include clinically meaningful outcomes. The two reviews that do (15, 22), do not separate interventions aimed at clinicians from those that are aimed at patients. Thus, there is a need to review interventions that aim to influence clinician behavior in managing CKD in primary care using clinically relevant medical management markers. We are also interested in the range of interventions, quality of reporting on intervention details, their underlying behavioral rationale and other relevant information that could guide the development of implementation interventions that target the right

behaviors to advance the systematic adoption and sustaining of evidence based CKD management in routine practice.

The objectives of this systematic review are:

1. Synthesize the evidence of the effect of interventions, aimed at PCPs, to improve the detection and management of CKD on clinically relevant medical management outcomes.
2. Map the type of interventions and implementation methods used to detect and manage CKD in primary care.
3. Identify the most successful implementation approach to effect practice change around CKD management in primary care.

Methods:

This protocol adheres to the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P)(23) (see "Supplemental File 1 PRISMA-P 2015 checklist"). Considering that the studied interventions are complex (multi-component), we will follow frameworks suggested for evidence synthesis of complex interventions (24, 25). Therefore, we will focus on determining the characteristics and circumstances in which the interventions prove to be effective; rather than focusing on a simple question of efficacy.

Patient and Public Involvement:

No patients or the public will be involved since this is a systematic review of interventions targeting clinicians. Instead, clinicians will be actively involved in the conceptualization, literature search, data abstraction, analysis, interpretation and publishing of findings.

Study Registration:

This systematic review is registered with PROSPERO (registration number: CRD42018102441; http://www.crd.york.ac.uk/PROSPERO).

Proposed Dates of Review:

June 2018 to December 2019

Criteria for considering studies for the review:

Type of Studies:

We will include randomized trials (including cluster randomized trials), non-randomized trials, cross-over trials, quasi-randomized trials, before and after studies with a comparator group, and cohort studies.

Types of participants:

Studies that evaluated interventions aimed at any health care professional practicing in the primary care environment, managing care for adult patients aged 18 years or above with CKD or at risk of developing CKD will be included. Studies including adolescents and children as patients will be excluded.

Types of interventions and comparators

Any intervention where implementation science methods were an integral part or a component of an intervention directed at PCPs or conducted within the primary care system, organization or setting to enable managing care for patients with CKD or risk of developing CKD will be included. This broad categorization includes different modalities of intervention delivery. Comparators will include usual care or any other intervention intended to manage care of CKD patients in a primary care setting, including historical control.

Types of Outcomes:

We required at least one clinically meaningful medical marker or outcome to be assessed in each study. Those could be either process of care measures (e.g., proportion of patient taking renin-angiotensin-aldosterone system inhibitors), a relevant surrogate (e.g., blood pressure, (BP) or diabetes control) or a hard clinical outcome (e.g., mortality, dialysis).

Search methods for identification of studies:

We will search several electronic data bases including PubMed, EBSCO, CINAHL, Scopus, Ovid Medline, Ovid Cochrane Library, Ovid EMBASE, Ovid PsycINFO, Ovid EMBASE and Web of Science. Non-English language manuscripts will be excluded. We will use the Institute of Medicine (26) recommendation to guide our search strategy. (See Supplemental File 2 for sample search strategy). Due to the relatively young field of implementation science, we will focus our attention to published reports from 2000 to October 2017. Controlled vocabulary supplemented with keywords will be used to search the literature. As implementation interventions that promote the adoption and integration of evidence-based practices, interventions and policies are closely related to the fields of quality improvement, improvement science and similar mechanisms of improvement, we will include search terms associated with these fields. Reference mining of relevant publications will be conducted. We will also hand search all systematic reviews on implementation interventions to improve CKD management in primary care. In addition, we will include study protocols of potentially eligible trials at this stage, and follow up to see if these trials had been published by the time of our analysis. The searches

described above will be done with the help of an experienced librarian with several years' experience in systematic review searches.

Selection:

We will upload search results into an EndNote (version 8) library. To prepare for selecting and abstracting data, reviewers will undergo education to ensure an understanding of the purpose of the review and a background of the field. Understanding of the inclusion and exclusion criteria will also be assessed through testing on a small number of studies. In the first round of screening, two reviewers will consider the potential eligibility of studies identified by the search strategy based on the abstract and title. Reviewers will request the full text versions of all potentially eligible studies. Studies with reviewer disagreement about eligibility based on abstract and title will also undergo full text review. Eligibility at both the abstract and full text level will be assessed in duplicate and independently. Any disagreements will be resolved by consensus; in the absence of consensus, a third reviewer will arbitrate.

Data Extraction:

Extraction of data for this study will include characteristics of study participants, details of interventions, the control interventions, contextual factors, outcome measures for effectiveness (separated into primary and secondary) and harm, measurement instruments used, and factors associated with study quality. Discrepancies in data will be adjudicated by consensus. A third reviewer will arbitrate in the absence of consensus.

A preliminary review of the literature indicated considerable heterogeneity of the types and measurement methods of clinical outcomes in potentially eligible studies. We also observed a wide variation in

intervention and implementation strategies. Given this complexity, we included primary care clinicians, health services researchers with implementation science experience and a systematic review methodologist in the team conducting this evidence synthesis. The team met twice to refine the scope of the review, define the specific questions we sought to answer and develop consensus on definitions of interventions and outcomes. Informed by the panel discussions, we created a list of clinically relevant medical management markers for CKD prevention and management to guide the prioritization of abstraction for clinical variables (see List 1 in Box 1).

We will create and pilot a standardized data abstraction sheet using Excel software with options to include manual entry and drop down menus. The latter option for clinical outcomes for example, will enable abstractors to choose the relevant clinical outcomes and their respective measures with ease.

Implementation interventions will be broadly categorized using elements of the Chronic Care model (27, 28), and further detailed in terms of implementation strategies used, utilizing the Expert Recommendations for Implementing Change (ERIC) framework (29, 30). This is a checklist that details 73 different strategies for implementation. The broad categorizations of implementation strategies are included in List 2 (see List 2 in Box 2). More granular details of the intervention strategies under each category can be found in Waltz et al. (30). Clinicians will abstract clinical data, while two implementation science researchers will dissect and abstract details on the interventions, implementation strategies and delivery modalities. The lead author will coordinate integrations of these two separate abstraction efforts.

Relevant details of each study context will be abstracted, using guidance from the Consolidated Framework Implementation Research (CFIR) model (31) described and noted, and used in the narrative analysis. We will also abstract other contextual variables, such as country and academic medical setting versus non-academic settings. Authors of the primary studies will be contacted for clarification if data included in the publication is missing, unclear or in a format that is difficult to extract. Author contact will be initiated by email to the corresponding author. If the email is unavailable, we will search the internet to find a current email address. If the first author is not the corresponding author, the first author will be carbon copied on all emails to the corresponding author, if their email is available. Authors will be given a week to respond to emails at which time, a follow-up email will be sent. If no response is received for yet another two weeks we will attempt to contact the author by telephone. If this was not possible, the authors will be classified as not contactable.

Methodological Quality and certainty in the evidence

We will use the Cochrane Collaboration's risk of bias tool (32) to evaluate the methodological quality of included studies. Reviewers will assess the adequacy of randomization sequence generation, concealment of treatment arm allocation, blinding of participants and outcome assessors, the degree and potential impact of missing data, the likelihood of incomplete reporting and the potential role of conflicting interests.

For non-randomized studies we will adapt the New Castle Ottawa instrument to assess risk of bias, focusing on cohort selection, comparability and outcome ascertainment (33). Risk of bias abstraction will be elicited with drop down menus.

We will also assess the quality of reporting on implementation outcomes, using an adapted Template for Intervention Description & Replication (TIDieR) checklist (34).

The certainty in evidence (confidence in the effect) will be evaluated using adaptations of GRADE (Grading of recommendations, assessment, development and evaluation) for complex interventions (35) and narrative synthesis(36).

Meta-analysis:

When possible, we will generate meta-analytical estimates of treatment effects. We will use the random-effects model because of anticipated heterogeneity in studies' settings and populations. The clinical outcomes that have at least three or more studies with relevant data will be pooled. For clustered randomized trials, we will calculate "effective sample sizes" for each intervention group and combine with other randomized controlled trials. (37). Sensitivity analyses will be conducted to evaluate the robustness of the findings. We will use Stata statistical software package to conduct the analyses (38). Other clinical outcomes, not amenable to meta-analysis, will be summarized narratively & tabulated in terms of significant findings.

We will map interventions and contextual characteristics of the study with types of implementation strategies used, through tabulation methods, looking for patterns of association between them.

Narrative analysis will be conducted by noting the studies with intervention success. We define intervention success in terms of desired direction and magnitude of effectiveness on key clinical endpoints such as blood pressure control. We will thematically analyze features of these

studies, in terms of components of interventions, their associated implementation strategies and contextual features to identify factors associated with success.

Subgroups:

Subgroup analyses will be conducted to explore the causes of inconsistency and different effects in subgroups. We plan to conduct the following a priori defined sub-group analyses: 1) study design (RCT or cohort design), 2) length of follow-up (12 months, 12-24 months, over 24 months), 3) type of intervention (guideline based alerts, shared care, interventions aimed at pharmacists, collaborative and tailored interventions, 4) type of implementation (based on ERIC classification), 5) whether or not a behavioral or implementation theory was used to guide the study, 6) baseline CKD severity, 7) patient minority status 8) study location (UK, Other European countries, Australia, Canada, US, Other), and 9) academic setting or not. If the intervention structure proves highly variable and we have a sufficient number of studies, we may attempt to explain variation in effects by conducting a meta-regression analysis of intervention and implementation characteristics by clinical outcome.

Missing Data and Sensitivity Analyses:

We will attempt to contact authors for missing data. In the event that the data are still unavailable, we will use a complete case analysis and conduct sensitivity analysis using methods described by Ebrahim et al (39) for continuous variables and Akl et al (40) for dichotomous variables.

Publication Bias:

If the number of studies per analysis is over 10, we will assess publication bias by using funnel plots, plotting the estimate of effect of trials

by the inverse of its standard error. A significant publication bias will be suspected if, using Egger's test (41), the p value is < 0.10. If funnel plots are not possible, we will look at trial registries and unpublished data to assess potential publication bias.

Discussion:

CKD detection and management in primary care is a challenging task, given the competing demands on clinicians and the asymptomatic nature of the disease. Yet its importance cannot be emphasized enough given the upstream health and cost implications of disease progression in patients at risk for CKD. Several disparate interventions have been tried over the last couple of decades targeting PCPs as well as patients. This review focuses on interventions aimed at PCPs, evaluating what works, and deconstructing the nature of the interventions and their implementation to provide guidance as to what works under what circumstances in preparation for an intervention study in primary care.

This study may encounter several limitations including a high degree of heterogeneity in the interventions as well as the heterogeneity of clinical outcomes in this clinical area. Pooling data from heterogeneous populations and interventions carries inherent uncertainty. We acknowledge that the studies will include participants with considerable variation in baseline risk We also acknowledge the possibility that non-randomized participants in the control arm might have different base-line risks than participants in the intervention arm.We chose to exclude studies including solely interventions aimed at educating or informing patients even if they met all other inclusion criteria for this study as we are primarily interested in modifying clinician

behavior towards increased quality of care. Our systematic review will identify evidence gaps and provide information on which interventions targeted at clinicians work best to improve the care of patients at risk of CKD or with an established diagnosis of CKD in primary care.

Ethics and dissemination:

Approval by research ethics board is not required since the review will only include published and publicly accessible data. Review findings will inform a future trial of an intervention to promote uptake of CKD diagnosis and treatment guidelines in our primary care setting and the development of complementary tools to support its successful adoption and implementation. We will publish our findings in a peer-reviewed journal and develop accessible summaries of the results.

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Box1: List 1

Patient identification: (1) Patients identified/registered with CKD, (2) prevalence of CKD, (3) Referral to Nephrologist, (4) Other (State)

Disease progression: (1) Change in glomerular filtration rate (GFR), (2) change in proteinuria, (3) Other (State)

Lab monitoring (within the last year): (1) Creatinine or GFR, (2) Urine protein/albumin, (3) Hemoglobin, (4) Other (State)

Medical Management: (1) ACE/ARB use, (2) hypertensives - # of classes, (3) avoidance of nephrotoxic drugs, (4) any type of dosing inadequacy,

BP management: (1) Change in BP, (2) achievement of BP (</=140/90), (3) achievement of BP (</=130/80, (4) Other (State)

Diabetes management: (1) Hemoglobin A1c, (2) Achievement of HbA1c<7, (3) Other (State)

Cholesterol management: (1) Total cholesterol, (2) LDL, (3) HDL, (4) triglycerides, (5) Other (State)

Box 2. List 2

1) Use Evaluative and iterative strategies,
2) Provide Interactive Assistance,
3) Adapt & tailor to context,
4) Develop stakeholder interrelationships,
5) Train and educate stakeholders,
6) Support clinicians,
7) Encourage consumers,
8) Utilize financial strategies,
9) Change infrastructure.

Supplemental File 1

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	(Page No.#)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	1, 4, 5
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	No
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	5,10
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1,2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	2
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	2
Sponsor	5b	Provide name for the review funder and/or sponsor	n/a
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	n/a
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	7-9
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	9
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	10,11
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	11,14,17

Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplemental File-2
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	13
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	12
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	12,13,14
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	12-15
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	11-13, 25
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	14
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	15
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	14,15
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	15-16
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	15-16
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	16-17
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	15

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

Supplemental File 2

MEDLINE Search Strategy:

Data Base: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

……

1. ((chronic adj3 (kidney or renal)) or ckd).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

2. (esrd or eskd or (end stage adj2 (renal or kidney))).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3. exp Renal Insufficiency/ or (chronic disease/ and kidney diseases/)

4. exp renal dialysis/ or hemodialys*.mp. or haemodialys*.mp. or "renal replacement".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

5. or/1-4

6. knowledge translation.mp. or Translational Medical Research/ or guideline*.mp. or improv*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

7. ((implement* or integrat* or change* or innovat*) adj4 (strateg* or plan* or practice* or research or complex* or incentiv* or process*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

8. 5 and 7

9. 5 and 6 and ((intervention* or implement*).mp. or 7) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

10. 8 or 9

11. 10 and (program* or adopt* or protocol* or evaluat* or application* or initiative* or promot* or incentiv* or chang*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

12. ((quality or qi) adj2 technique*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

13. 10 and "best practice".mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

14. (sdm or (shared adj2 decision*) or (decision adj2 aid*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

15. 10 and 14

16. 10 and (framework* or challeng* or barrier* or roadblock* or facilitat* or obstacle* or confound*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

17. 10 and (attitude of health personnel/ or (chang* adj4 (behavior* or behaviour* or performance)).mp. or health knowledge attitude practice/) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

18. 10 and (educat* or detailing or audit* or feedback* or multifacet* or target* or outreach* or mareketing or consensus* or impact*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

19. 10 and ("clinical decision support" or reminder* or alert*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

20. 11 or 13 or 15 or 17 or 19

21. 10 and 12

22. 20 or 21

23. limit 22 to ("in data review" or in process or publisher or "pubmed not medline")

24. 22 not 23

25. ((chronic adj3 (kidney or renal)) or ckd or (esrd or eskd or (end stage adj2 (renal or kidney)))).ti. or (exp *Renal Insufficiency/ or (*chronic disease/ and *kidney diseases/))

26. exp *renal dialysis/ or *hemodialys*/ or *haemodialys*/ or *"renal replacement"/ or (renal dialysis or hemodialys* or haemodialys* or "renal replacement").ti.

27. 25 or 26

28. 24 and 27

29. 23 or 28

30. 29 and (study or trial* or cohort* or meta-analysis or review*).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

31. limit 24 to (clinical study or clinical trial, all or clinical trial, phase i or clinical trial, phase ii or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or consensus development conference or controlled clinical trial or evaluation studies or meta analysis or multicenter study or observational study or pragmatic clinical trial or randomized controlled trial or systematic reviews or validation studies)

32. 23 and 30

33. 31 or 32

34. 24 and (study or meta-analysis or cohort* or trial*).tw.

35. 34 not 31

36. 35 and ((practice* or "primary care" or pcps).mp. or primary health care/ or "community health".mp. or "patient-cent*".mp. or providers.mp. or family practice.mp. or general practice.mp. or general practitioner*.mp. or physician, primary care/ or physicians, family/ or ambulatory care/ or professional practice/) [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

37. 33 or 36

38. limit 37 to english language

39. remove duplicates from 38