APPENDIX A. SEARCH STRATEGIES

Table A-1. Search strategy for PubMed (December 12, 2012)

Set #	Terms	Results
1	"Nurse's Role"[Mesh] OR "Nursing Process"[Mesh] OR "Nursing Staff"[Mesh:noexp]) OR (nurse[tiab] OR nursing[tiab] OR nurses[tiab]	351362
2	(nurse[tiab] OR nursing[tiab] OR nurses[tiab]) AND (driven[tiab] OR intervention[tiab] OR interventions[tiab] OR managed[tiab] OR run[tiab] OR led[tiab] OR implemented[tiab] OR clinic[tiab] OR clinics[tiab])	43427
3	(nurse[tiab] OR nursing[tiab] OR nurses[tiab]) AND ("Diagnostic Tests, Routine"[Mesh] OR "Medication Therapy Management"[Mesh] OR "Referral and Consultation"[Mesh])	3585
4	(nurse[tiab] OR nursing[tiab] OR nurses[tiab]) AND (medication[tiab] OR drug[tiab] OR drugs[tiab]) AND (adjust[tiab] OR adjustment[tiab] OR manage[tiab] OR management[tiab] OR titrate[tiab] OR titration[tiab] OR prescribe[tiab] OR prescribing[tiab] OR initiate[tiab])	4080
5	(nurse[tiab] OR nursing[tiab] OR nurses[tiab]) AND ((order[tiab] OR ordered[tiab] OR ordering[tiab]) AND (diagnostic[tiab] OR test[tiab] OR tests[tiab]))	1168
6	#2 OR #3 OR #4 OR #5	48849
7	"Hypertension"[Mesh] OR "Diabetes Mellitus"[Mesh] OR "Heart Failure"[Mesh] OR Hyperlipidemia[MeSH] OR Hypertension[tiab] OR Diabetes Mellitus[tiab] OR Heart Failure[tiab] OR hyperlipidemia[tiab]	764735
8	#1 AND #6 AND #7	2884
9	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR randomised[tiab] OR randomization[tiab] OR randomisation[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] OR Clinical trial[pt] OR "clinical trial"[tw] OR "clinical trials"[tw] OR "evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tw] OR evaluation studies[tw] OR "intervention studies"[MeSH Terms] OR "intervention study"[tw] OR "intervention studies"[tw] OR "cohort studies"[MeSH Terms] OR cohort[tw] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tw] OR longitudinally[tw] OR "prospective"[tw] OR prospectively[tw] OR "follow up"[tw] OR "comparative study"[Publication Type] OR "comparative study"[tw] OR systematic[subset] OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[tw] OR "meta-analyses"[tw]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Case Reports[ptyp] OR Comment[ptyp]) NOT (animals[mh] NOT humans[mh])	4558979
10	"pre-post"[tiab] OR prepost[tiab] OR "post-test"[tiab] OR posttest[tiab] OR pretest[tiab] OR pre-test[tiab] OR quasi-experiment*[tiab] OR quasiexperiment*[tiab] OR quasirandom*[tiab] OR quasi-random*[tiab] OR quasi-control*[tiab] OR quasicontrol*[tiab] OR ("time-series"[tiab] AND interrupt[tiab]) OR ("time-points"[tiab] AND (multiple[tiab] OR one[tiab] OR two[tiab] OR three[tiab] OR four[tiab] OR five[tiab] OR six[tiab] OR seven[tiab] OR eight[tiab] OR nine[tiab] OR ten[tiab] OR month*[tiab] OR day[tiab] OR days[tiab] OR week*[tiab] OR hour*[tiab]) OR (before[tiab] AND after[tiab]) OR (*before[tiab] AND during[tiab]))	56936
11	(#8 AND (#9 OR #10) Publication date from 1980/01/01 to 2012/12/31, English	1822

APPENDIX B. ASSESSMENT OF PUBLICATION BIAS

Examination of ClinicalTrials.gov

We used our two main search term groups to search for clinical trials, type of nursing involvement, and disease of interest. For type of nursing, we investigated nurse's role (n=82), nurse-led protocols (n=13), nurse-managed protocols (n=79), nurse-led clinics (n=30) and nurse-managed clinics (n=136). "Nurse's roles" provided many off-topic entries. Appropriate entries under nurse-led protocols, nurse-managed protocols, and nurse-led clinics (all of which had significant overlap) were 100 percent contained under the key phrase "nurse managed clinics" or NMC. Therefore, we examined the entries found by the following combinations: NMC and diabetes (n=40), NMC and hypertension (n=14), NMC and congestive heart failure (n=19), and NMC and hyperlipidemia (n=3). Of the 76 entries produced by this search strategy, one entry overlapped in all categories, leaving 74 unique entries of which

- 38 were not completed
- 14 were not an intervention of interest (usually the nurse did not titrate medications)
- 7 expanded the role of a professional other than nurse although nurses were involved
- 5 had publications already identified in our database
- 4 were not from a country of interest
- 4 were not a population of interest
- 2 were not a disease of interest

Thus, we concluded there is no evidence of publication bias from our search of clinicaltrials.gov on May 30, 2013.

Funnel Plots

To detect possible publication bias, we produced funnel plots for outcomes reported by at least 10 studies. Plots and evaluation are presented here.

Figure B-1. Funnel plot for systolic blood pressure: indication of publication bias

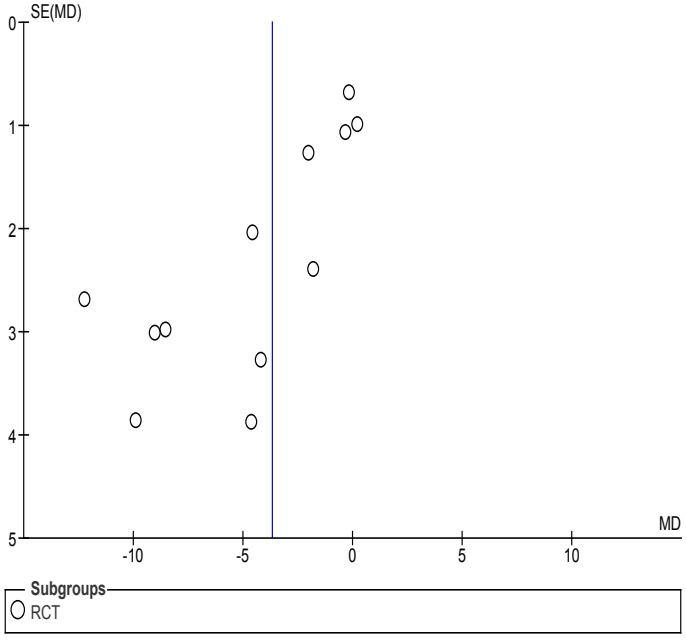


Figure B-2. Funnel plot for diastolic blood pressure: no indication of publication bias

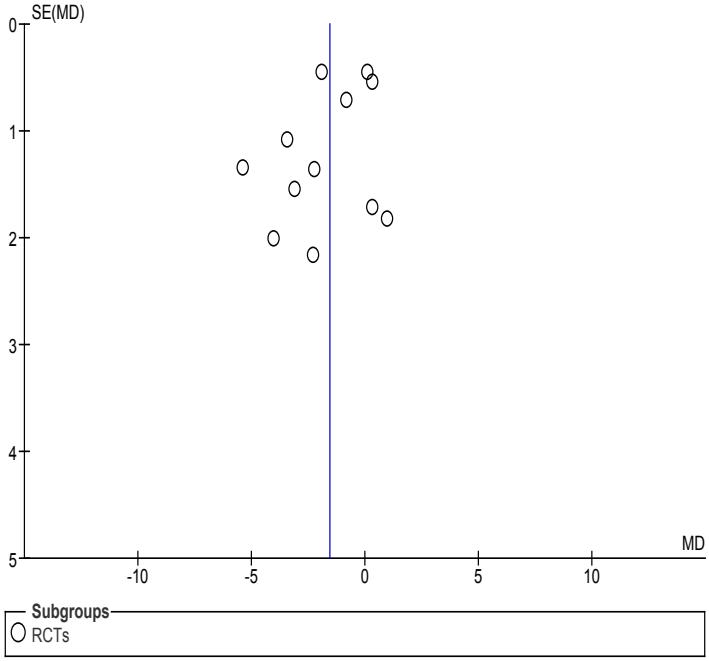


Figure B-3. Funnel plot for cholesterol at goal: no clear indication of publication bias

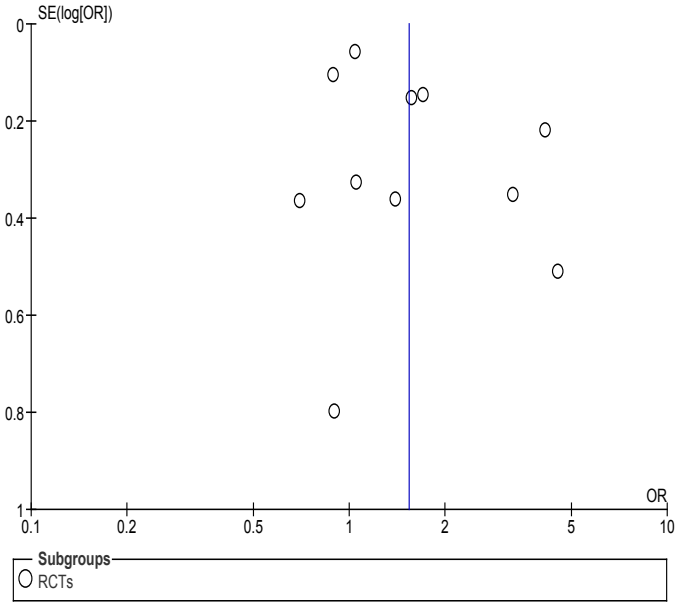


Figure B-4. Funnel plot for blood pressure at goal: some asymmetry; no clear indication of publication bias

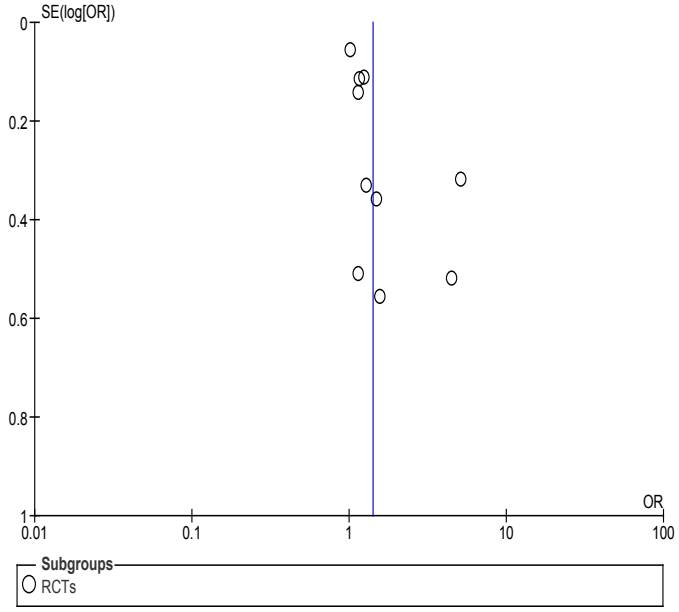
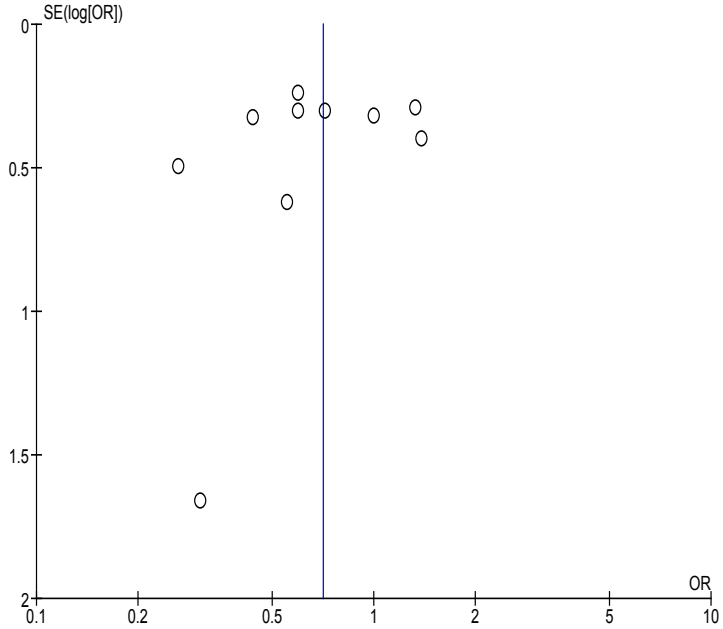


Figure B-5. Funnel plot for congestive heart failure mortality studies: no indication of publication bias



APPENDIX C. SAMPLE AUTHOR QUERY LETTER

Dear Dr. INSERT LAST NAME:

We are conducting a systematic review on **nurse-led interventions** and are writing in regards to your paper, "INSERT TITLE." To be eligible for our study, a) the intervention must utilize a nurse with similar training to a registered nurse or licensed practical nurse in the U.S.A. and b) the nurse must use a protocol to initiate or adjust one or more medications. Our preliminary review suggests your study is eligible for our review, but we require clarification about details of the intervention to make a final eligibility determination. Please answer the following:

1) Did the nurse(s) utilized in your study have similar educational training, credentials, or scope of practice to a Registered Nurse (RN) or Licensed Practical Nurse (LPN/LVN)? (see definitions below)

   a) Yes, similar to an RN or LPN

   b) Yes, similar to an RN or LPN but with the following important differences:_____

   c) No, not similar (e.g., equivalent to a U.S.A trained Advanced Practice Nurse)

2) Did the nurse use a protocol or algorithm to guide practice?

   a) Yes (We will appreciate if you share a copy of your nurse protocol. Please send by email)

   b) No

3) Did the nurse have decision making authority to initiate or adjust medications as specified in a protocol or algorithm?

   a) Yes, decision making authority

   b) No, the nurse did not initiate or adjust medications.

4) Additional clarification: (optional if other information is needed)

We sincerely appreciate your response to this query,

John W. Williams, MD, and Ryan Shaw, PhD, RN, for the Durham Evidence Synthesis Team

Description of **RN** or **LPNs** trained in U.S.A. **(ELIGIBLE** for our study**)**	Description of **Advanced Nurse Practitioners (NOT ELIGIBLE** for our study**)**
Education/training: • Diploma from a nursing school or hospital • Associate's degree in nursing (2-year degree) • Bachelor's degree in nursing (4-year degree)	**Education/training:** • Master's degree in nursing • Doctoral degree in nursing
Credentialing and Scope of Practice: • Educates patients, families, and communities on conditions and treatment plans • Assists and supports patients, families, and communities in performing lifestyle modifications • Provides emotional support to patients and their family • Monitors response to medical treatment plans • Administers medications and vaccinations • Monitors treatment adherence including medication compliance • Performs medication reconciliation • Helps perform diagnostic tests and analyzes results (i.e., blood sugar values and urine dipsticks) • Performs physical assessments including vital signs	**Credentialing and Scope of Practice includes the RN/LPN scope of practice and in addition:** • Prescribes medication and treatment • Orders and interprets diagnostic tests • Performs or assists in minor surgeries or procedures (e.g., biopsies, suturing, casting) • Can serve as a primary care provider • Includes nurse midwives, nurse anesthetists, clinical nurse specialists

APPENDIX D. CRITERIA USED IN RISK OF BIAS ASSESSMENT

I. Guidance on Assessing Risk of Bias for Randomized Controlled Trials

General instructions: (1) Rate each risk of bias item listed below as Low risk/ High risk/ Unclear risk (refer to Cochrane guidance to inform judgements). Add comments to justify ratings.
(2) After considering each quality item, give the study an overall rating of "Low risk," "Moderate risk," or "High risk" (see below).

Rating of individual items

* Indicates items contained in Cochrane Risk of Bias Tool.

1. **Selection bias:**
   a. *Randomization adequate (Adequate methods include random number table, computer-generated randomization, minimization without a random element.) **Low risk/ High risk/ Unclear risk**
   b. *Allocation concealment (Adequate methods include pharmacy-controlled randomization, numbered sealed envelopes, central allocation.) **Low risk/ High risk/ Unclear risk**
   c. Baseline characteristics (Consider whether there were systematic differences observed in baseline characteristics and prognostic factors between groups, and if important differences were observed, if the analyses controlled for these differences.) **Low risk/ High risk/ Unclear risk**

2. **Performance bias:**
   a. *Concurrent interventions or unintended exposures (Consider concurrent intervention or an unintended exposure (e.g., crossovers; contamination – some control group gets the intervention) that might bias results) **Low risk/ High risk/ Unclear risk**
   b. Protocol variation (Consider whether variation from the protocol compromised the conclusions of the study.) **Low risk/ High risk/ Unclear risk**

3. **Detection bias:**
   a. *Subjects blinded (Consider measures used to blind subjects to treatment assignment and any data presented on effectiveness of these measures.) **Low risk/ High risk/ Unclear risk**
   b. *Outcome assessors blinded, hard outcomes (Outcome assessors blind to treatment assignment for "hard outcomes" such as mortality.) **Low risk/ High risk/ Unclear risk**
   c. *Outcome assessors blinded, soft outcomes (Outcome assessors blind to treatment assignment for "soft outcomes" such as symptoms.) **Low risk/ High risk/ Unclear risk**
   d. Measurement bias (Reliability and validity of measures used.) **Low risk/ High risk/ Unclear risk**

4. **Attrition bias:**
   a. *Incomplete outcome data (Consider whether incomplete outcome data were adequately addressed, including systematic differences in attrition between groups [differential attrition]; overall loss to followup [overall attrition]; and whether an "intention-to-treat"

[ITT; all eligible patients that were randomized are included in analysis] analysis was performed.) (Note: mixed models and survival analyses are, in general, ITT.) **Low risk/ High risk/ Unclear risk**

5. **Reporting bias:**
   a. *Selective outcomes reporting (Consider whether there is any suggestion of selective outcome reporting; e.g., systematic differences between planned and reported findings.) **Low risk/ High risk/ Unclear risk**

Overall study rating

Please assign each study an overall quality rating of "Low risk," "High risk," or "Unclear risk" based on the following definitions:

A "**Low risk**" study has the least bias, and results are considered valid. A low risk study uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results. [Items 1a and 1c; 2a; 3b and 3c; and 4a are all rated low risk.]

A "**Moderate risk**" study is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems (unclear risk). As the moderate risk category is broad, studies with this rating vary in their strengths and weaknesses. [Most, but not all of the following items are rated low risk: Items 1a and 1c; 2a; 3b and 3c; and 4a.]

A "**High risk**" rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a high risk study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions. [At least one-half of the individual quality items are rated high risk or unclear risk]

Conflict of interest (recorded but not used as part of Risk of Bias Assessment)

Was there the absence of potential important conflict of interest? The focus here is financial conflict of interest. If no financial conflict of interest (e.g., if funded by government or foundation and authors do not have financial relationships with drug/device manufacturer), then answer "Yes." **Yes /No /Unclear**

II. Guidance on Assessing Risk of Bias for Nonrandomized Studies

This tool is intended to evaluate the quality of nonrandomized studies that assessed the outcomes of nurse-managed protocol interventions. Use this risk of bias tool for the following study designs: nonrandomized controlled trial, cohort studies, interrupted time series.

Instructions for use:

1. Items are organized by risk of bias domains (selection, performance, attrition, detection and reporting bias). Rate each question using the response categories listed. Focus on study design and conduct, not quality of reporting.

2. The first question, basic study design, is not used in the overall ratings but is collected for descriptive purposes.

3. After answering each item, rate the study overall as "low risk of bias," "moderate risk of bias," or "high risk of bias" based on the following definitions. This overall rating is specific to the basic study design used. For example, if the basic study design was a cohort study, then the risk of bias rating would be interpreted as "For a cohort study, the risk of bias is _____."

   A "**Low Risk of Bias**" study has the least bias, and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses recruitment and eligibility criteria that minimizes selection bias; has a low attrition rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results. These studies will meet the majority of items in each domain.

   A "**Moderate Risk of bias**" study is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid. These studies will meet the majority of items in most but not all domains.

   A "**High Risk of Bias**" rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

1. Basic Design

Is the study design prospective, retrospective, or mixed? [*Abstractor: Prospective design requires that the investigator plans a study before any data are collected. Mixed design includes case-control or cohort studies in which one group is studied prospectively and the other retrospectively.]*

- **Prospective** ☐
- **Mixed** ☐
- **Retrospective** ☐
- **Cannot determine** ☐

2. Selection Bias

2.1 Inclusion/exclusion criteria

Did the study apply inclusion/exclusion criteria uniformly to all comparison groups?

- ☐ **Yes (low risk of bias)**
- ☐ **No (high risk of bias)**
- ☐ **Cannot determine (unclear risk of bias)**
- ☐ **NA: study does not include comparison groups**

2.2. Recruitment:

Did the strategy for recruiting participants into the study differ across study groups?

- ☐ **Yes (high risk of bias)**
- ☐ **No (low risk of bias)**
- ☐ **Cannot determine (unclear risk of bias)**
- ☐ **NA (retrospective study design)**

2.3 Baseline characteristics similar or appropriate adjusted analysis

Are key characteristics of study participants similar between intervention and control groups? [Patients *Age, Race, Gender, Illness severity]* If not similar, did the analyses appropriately adjust for important differences?

- ☐ **Yes (similar or appropriate adjusted analysis; low risk of bias)**
- ☐ **Partially (only some characteristics described or some characteristics not clearly described; analysis adjust for some)**
- ☐ **No (important baseline differences, unadjusted analysis; high risk of bias)**

2.4 Comparison Group

Is the selection of the comparison group appropriate? [*Patients exposed to usual care or another quality improvement strategy is appropriate; if comparison group determined at the physician or practice level, the comparison groups should be drawn from the same system.*)

Yes (low risk of bias) ☐

No (high risk of bias) ☐

Cannot determine, no description of the derivation of the comparison cohort (unclear risk of bias) ☐

NA (study does not include a comparison cohort - case series, one-arm study) ☐

2.5 Balance prognostic variables between groups through design or analysis approaches.

Any attempt to balance the allocation between the groups? [For example, through stratification, matching, propensity scores]

Yes (low risk of bias) ☐

No (high risk of bias) ☐

Cannot determine (unclear risk of bias) ☐

3. Performance Bias

3.1 Intervention implementation

Did variation from the study protocol compromise the conclusions of the study *[Similar to a psychologist following a manualized procedure to deliver psychotherapy, the nurse-managed protocol intervention should be implemented as planned]?*

Unclear (no data reported on fidelity to protocol; unclear risk of bias) ☐

Low fidelity (few components of protocol implemented; high risk of bias) ☐

High fidelity (all key components of protocol were implemented; low risk of bias) ☐

3.2 Concurrent/concomitant interventions

Did researchers rule out any impact from a concurrent intervention, such as greater access to other specialty interventions or medications (e.g., through multivariate analysis, stratification, or subgroup analysis)?

Yes (low risk of bias) ☐

No or Partially (only some concurrent interventions eliminated; high risk of bias) ☐

Not described (unclear risk of bias) ☐

4. Attrition Bias

4.1 Equality of length of followup for participants

In cohort studies, is the length of followup different between the groups? *[Abstractor: Where followup was the same for all study patients the answer is no. If different lengths of followup were adjusted by statistical techniques, for example, survival analysis, the answer is no. Studies where differences in followup are ignored should be answered yes.]*

Yes (high risk of bias) ☐

No (low risk of bias) ☐

Cannot determine (unclear risk of bias) ☐

4.2 Completeness of followup

Was there a high rate of differential or overall attrition? *[Attrition is measured in relation to the time between baseline (allocation in some instances) and outcome measurement. Standard for overall attrition is <20 percent for <1 year f/u and <30 percent for longer term ≥ 1 year). Standard for differential attrition is ≥ 10% absolute difference.*]

Yes (high risk of bias) ☐

No (low risk of bias) ☐

Cannot determine (unclear risk of bias) ☐

4.3 Attrition affecting Participant Composition

Did attrition result in a difference in group characteristics between baseline and followup?

Yes (high risk of bias) ☐

No (low risk of bias) ☐

Cannot determine (unclear risk of bias) ☐

4.4 Intention-to-treat analysis

Is the analysis conducted on an intention-to-treat (ITT) basis, that is, the intervention allocation status rather than the actual intervention received? *[Abstractor: evaluate whether the analysis takes into account loss to followup]*

Yes (low risk of bias) ☐

No (high risk of bias) ☐

Cannot determine (unclear risk of bias) ☐

Not applicable (retrospective study) ☐

5. Detection Bias

5.1 Blind outcomes assessment

Were the outcome assessors blinded to the intervention or exposure status of participants?

Yes (low risk of bias) ☐

No or not stated and outcome could be influence by knowledge of exposure status (high risk of bias) ☐

NA (not an intervention study) ☐

5.2 Source of information re interventions/exposure

Are interventions/exposures assessed using valid and reliable measures, implemented consistently across all study participants?

Yes (low risk of bias) ☐

No (high risk of bias) ☐

Cannot determine, measurement approach not reported (unclear risk of bias) ☐

5.3 Source of information re outcomes

a. Are primary outcomes (e.g., biophysical measures, performance metrics, symptom/functional status measures) assessed using valid and reliable measures and implemented consistently across all study participants?

Yes (low risk of bias) ☐

No (high risk of bias) ☐

Cannot determine, measurement approach not reported (unclear risk of bias) ☐

b. Are confounding variables assessed using valid and reliable measures, implemented consistently across all study participants? [Major potential confounders include: age, gender, race, disease severity, overall burden of disease.]

Yes (low risk of bias) ☐

No (high risk of bias) ☐

Cannot determine, measurement approach not reported (unclear risk of bias) ☐

6. Reporting Bias

Are the potential outcomes pre-specified by the researchers? Are all pre-specified outcomes reported? [Abstractor needs to identify all pre-specified, primary outcomes that should be reported in the study.]

Yes (low risk of bias) ☐

No (at least 1 pre-specified outcome not reported; high risk of bias) ☐

Primary outcomes not pre-specified (unclear risk of bias) ☐

Tool based on: Viswanathan M, Ansari MT, Berkman ND, et al. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. AHRQ Methods for Effective Health Care [Internet]. Rockville (MD): Agency for Healthcare Research and Quality (US); 2008-. Available from: http://www.ncbi.nlm.nih.gov/books/NBK49468/.

APPENDIX E. PEER REVIEW COMMENTS

Reviewer	Comment	Response
Question 1: Are the objectives, scope, and methods for this review clearly described?		
1	Yes. I appreciated the focused and concise research questions that guided this review. The inclusion and exclusion criteria are well stated and the search was comprehensive in accordance with the design. The review process was thorough in all aspects, with sufficient narrative to support findings, data synthesis, and risk of bias and strength of evidence. As a reviewer, the careful attention to these details gave me confidence in the objectivity of the study and in the results.	Thank you.
2	Yes. No comments	Acknowledged
3	Yes. No comments	Acknowledged
4	No. No comments	Acknowledged
5	Yes. No comments	Acknowledged
6	Yes. No comments	Acknowledged
7	Yes. The overall scope of this project is to improve the care of patients with select chronic conditions (hypertension, hyperglycemia, hyperlipidemia, and congestive heart failure); the mechanism selected to achieve this goal is to expand the role of the nurse within the PACT by using nurse-managed protocols. The objectives, scope and methods are clearly described. However, it remains unclear as to how the inclusion and exclusion criteria were determined for the intervention studied. That limiting the study selection to protocols involving medication adjustment may enhance the validity and generalizability of the project is acknowledged. Nonetheless, given the complexity of chronic illness, multiple approaches are likely needed to achieve positive outcomes. Thus it would be beneficial for the reader to better understand why educational interventions and therapy evaluation studies were excluded, as these interventions can also be useful in the management of chronic illness. Finally, the rationale for using nurse satisfaction as an inclusion criterion is missing and could be a useful addition.	Thank you for the thorough comment. We agree that educational and therapy interventions are important in the management of chronic illness, and multiple systematic reviews have described this literature. Our stakeholders were interested in studies where nurses practiced beyond their typical scope of practice (e.g., medication titration). Thus, we included studies that required the nurse to have the ability to practice beyond their scope of practice and have at a minimum the autonomy to titrate/adjust medication. Studies were not excluded if they had an educational or therapy component but were required to also have this medication titration component. Nurse satisfaction was not an inclusion criteria but part of Key Question 1 to examine the effects of nurse-managed protocols. Otherwise eligible studies that reported any of the relevant outcomes (including nurse satisfaction) were included.

Reviewer	Comment	Response
8	No. Overall, this is a very well done evidence synthesis in a complicated area. There are a few areas where additional clarification is needed regarding the objectives, scope, and methods. 1) Better clarification is needed regarding how "nurse" is defined in this synthesis and the generalizability of findings to different types of nurses. Throughout the report, terms such as "non-NP nurses", "nurse-managed protocols", "RN and LPN", and "RN-based protocol interventions" are used. Each of these terms defines nurses differently. The inclusion/exclusion criteria state that the intervention had to involve an RN or LPN functioning beyond the usual scope of practice, but then later on we see that only RNs were included in the studies in the evidence base. The generalizability of the evidence base only to RNs should be made earlier on in the report. A stronger statement is also warranted in the conclusion noting that there was no evidence specifically examining the role of the LPN in nurse-managed protocols and the implications of this if considering expanding nurse-managed protocols for LPNs. 2) Additional clarification is also needed in the introduction section regarding nurse-managed protocols. A more formal definition and history/background of these protocols would be helpful to the reader in understanding the scope. While it is acknowledged that there are many variations on what this protocol entails, in its current form, it is left up to the reader to determine the definition based on the inclusion/exclusion criteria, description of the included articles, etc. Similarly, it is unclear why adjustment of medications is the only component of the nurse-managed protocol that was required as part of the inclusion criteria. Additional background on nurse-managed protocols may help clarify this. 3) Risk of Bias (Quality) and Strength of Evidence Assessment section discusses criteria for observational studies; however, key eligibility criteria include randomized controlled trial or quasi-experimental study. Clarification is needed for this discrepancy.	1) Thank you for the comment. We have made terminology for nurse more consistent throughout the manuscript. We have also specified that no studies reported using LPNs as nurse interventionists and have made a stronger statement in the discussion that there is no evidence specifically examining the role of the LPN. 2) We agree with the reviewer and have added a brief discussion of how protocols began in nursing and also provided a definition of protocol. We have further specified that these studies were limited to those that required the nurse to have the ability to practice beyond their scope of practice and have at a minimum the autonomy to titrate/adjust medication. 3) We included RCTs and quasi-experimental studies. In the section, "Risk of Bias (Quality) Assessment" we give major criteria for RCTs and quasi-experimental (observational) studies.
9	Yes. Objectives, scope and methods were described clearly, see p. 11	Thank you.
Question 2: Is there any indication of bias in our synthesis of the evidence?		
1	No. As noted above, the team was fully engaged in conducting a detailed and thorough review and used processes to mitigate bias to the extent humanly possible. The narrative supports these efforts in process and in research study review.	Acknowledged
2	No. Very clear discussion on Bias concerns of the reviewed studies	Thank you.
3	No. No comments	Acknowledged

Reviewer	Comment	Response
4	No. No comments	Acknowledged
5	No. No comments	Acknowledged
6	No. No comments	Acknowledged
7	Yes. The risk of bias was carefully addressed overall. However, one area that can potentially bias the findings and the applicability to the PACT setting lies in the lack of a consistent definition of the term, "nurse" and "nurse training" (e.g., Tables 3 & 4). The type and role of the nurse was not well defined in the studies used for this evidence synthesis. For example, many of the studies were conducted in the U.K., using "specialist" nurses. The UKCC definition of specialist nurse in the UK appears more closely resembling that of the clinical nurse specialist in the U.S. than that of the registered nurse (see Standards for Specialist Education and Practice1). Other roles included certified diabetes educator (e.g., papers authored by Philis-Tsimikas, Aubert, Houweling,), "nurse specialist" in a particular disease, such as diabetes or CHF (e.g., papers by MacMahon Tone, O'Hare, Bellary, Wallymahmed, Berger), or "case manager" (e.g., papers by DeBusk, DeBusk); a rapid review of these papers did not find thorough descriptions of these roles nor of the educational preparation needed to qualify for such roles.	Thank you for the comment. We have made terminology for nurse more consistent throughout the manuscript. We have also specified that no studies reported using LPNs as nurse interventionists and have made a stronger statement in the discussion that there is no evidence specifically examining the role of the LPN. We have also added detail in Tables 4 and 5 (formerly Tables 3 and 4) under nurse training. Furthermore, we have included an appendix and additional description about querying authors when we were unsure of the educational role of the nurse. Authors for all included studies responded that the nurse interventionists used were a U.S.-equivalent RN.
7	Caution should be emphasized when generalizing these interventions to settings using nurses without such educational preparation and experience, and warrants more careful discussion early in the review. This concern is partially addressed in the clinical implications section (page 42), but given the importance, it warrants inclusion in the section describing the interventions (Tables 3 & 4), as well as in the executive summary. Perhaps additional information related to the role of the nurse in question and relevant educational preparation was obtained during the investigators' author query; if so, further delineation of role and educational preparation/training would help the reader.	Details on the education and preparation needed for a nurse to assume a responsibility to titrate medications is a gap in the literature (Table 2), noted as a limitation, and further research is warranted. We have added a key point to the executive summary that educational preparation was not well reported.
8	No. No comments	Acknowledged
9	No. Multiple sources of bias in the STUDIES reviewed were addressed and considered in the interpretation of the findings	Acknowledged
Question 3: Are there any <u>published</u> or <u>unpublished</u> studies that we may have overlooked?		
1	No. The dominance of physician's leading all aspects of the health team through medical orders is not a surprise; it is surprising that there is so little in the research literature to support the autonomous contributions of other health professionals who spend considerably more time with patients. Given the era of evidenced-based practice, which grew out of care maps and other designs to manage patient care on a specified trajectory, it is equally distressing that the resources expended on those efforts has not been captured in the literature. My strong sense is that you have captured the state-of-research for these common health conditions.	Acknowledged

Reviewer	Comment	Response
2	No. I am aware that Portland VA Medical Center initiated some Nurse Run Protocols for initiation of insulin management and also hypertension. I do not know if there was any intent to publish as the protocols were not subject to the research disclaimers typically communicated.	Acknowledged
3	Yes. Comments: Watts, SA, Lawrence, RH, & Kern, E. (2011). Diabetes nurse care manager training program: enhanced care consistent with the chronic care and patient-centered medical home models. Clinical Diabetes, 29, 25-33. This VHA study found positive effects of nurses using diabetes protocols. This study addresses both the educational requirements for nurses as well as describing nurse satisfaction outcomes.	Thank you. We have added this study to the literature search numbers and added it to the discussion. This article by Watts, et al. (2011) will be quite useful as an exemplar for intervention descriptions, but it was not included in the report except in the Discussion as it did not meet the Cochrane EPOC Guidelines for study designs.
4	No. Not aware of any.	Acknowledged
5	No. No comments	Acknowledged
6	No. No comments	Acknowledged
7	No. A quick literature review did not reveal any substantive additional studies overlooked in this synthesis.	Acknowledged
8	No. No comments	Acknowledged
9	No. I am not aware of any that were omitted	Acknowledged
Question 4: Please write additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report.		
1	The VA – especially through the PACT model – should advance the role of nurses and other health professionals who are relevant to population health needs. The Advanced Practice Nurse who is prepared as a practice scholar (DNP) or a research scholar (PhD) is in the strongest position to develop, implement, and evaluate clinical protocols. These protocols should be evidence-driven and intersect with standard medical protocols for disease management. Nursing protocols should reflect the practice of nursing in that individual, family, and environmental/community needs should be included as part of a holistic approach. Behavioral protocols, reinforcement and motivation, and environmental adaptations should be clearly stated in interventional terms. The use of Registered Nurses to implement and evaluate approved protocols should be done once an assessment is made of the RNs clinical knowledge, decision-making confidence and adaptability, communication capacity (verbal and written) with patients, families, and health team members, and their capacity to be accountable. A well-rounded professional nurse will possess these qualities, but not all nurses possess these traits; some are most comfortable in a role where they are directed. Based on the review of the literature and the complexity of decision-science demanded to operate under protocol (regardless of how detailed), I would cautiously proceed with the use of an LPN in this role.	Thank you for this thorough comment. We agree that a well-rounded professional nurse will possess all the qualities to safely use nurse-managed protocols. However, because the studies included in this review did not use LPNs, we can only generalize the findings to that of the RN. We agree that further research is warranted as to the use of LPNs. We have added additional details regarding the need for more information on the clinical knowledge, decisionmaking confidence, and communication capacity needed for a nurse in this role.

Reviewer	Comment	Response
2	Appendix D, Page 65, took a while to find the explanations for the NLC and DMP abbreviations.	We have spelled out those terms (nurse-led clinic and disease management program) in the table cells. That table is now in Appendix F.
3	No comments	Acknowledged
4	No comments	Acknowledged
5	"All 29 studies required the nurse to have the autonomy to titrate medications; however, only 20 reported that the nurse was allowed to independently initiate a new medication." This review is excellent. Just one comment. I wonder about the use of the word "only" in the quote above. It implies that 20 is small portion but in fact it is actually 2/3rds of the sample. This is a small point but in our organization it has been extremely hard to get any action on this important health care delivery strategy. I would prefer to avoid any argument for those who find it hard to imagine using our excellent nursing colleagues in this way.	We have rewritten this section to simply describe that 20 of the 29 studies allowed the nurse to also prescribe medications in addition to titration.
6	No comments	Acknowledged
7	PACT embraces the concept of "team". The authors acknowledge the importance of the role of specific team members – physicians, nurse practitioners, physician assistants, and nurses (pg 43). The role of the LPN does not appear to fit within the body of evidence presented and warrants further description as to how the LPN role might still be utilized within the PACT model outside the scope of using nurse-managed protocols (pg 43). Clarifying what is meant by "nurses", including other nursing roles, such as the clinical nurse specialist and expanded-role registered nurse, would strengthen this comprehensive, high-quality evidence synthesis summary.	We have provided more detail that while our initial search included the use of LPNs, no studies used an LPN as the nurse interventionist. We generalize the findings to the RN and recognize that the absence of studies utilizing LPNs is a limitation of this review and warrants further research.
8	1) Page 23, first line in last paragraph under Treatment Adherence, it states "Among the studies that reported treatment adherence to medication"; however, earlier it was stated that only one study reported treatment adherence to medication. This inconsistency should be revised. 2) Not sure I agree with the conclusion that "Nurse-managed protocols may be most effective for managing illnesses where self-management and patient adherence to medications is needed," (pg. 8 and 44). Only one study directly examined patient adherence to medications; therefore, further support is needed to justify this conclusion.	Thank you noticing this. We have amended this inconsistency. We have revised this section to focus on using nurse-managed protocols where a nurse could titrate or prescribe important and frequently used medications for diseases such as diabetes where medication titration and self-management are both key.
9	No comments.	Acknowledged

Reviewer	Comment	Response
Optional Dissemination and Implementation Questions		
Question 5: Are there any clinical performance measures, programs, quality improvement measures, patient care services, or conferences that will be directly affected by this report? If so, please provide detail.		
1	I believe this report could make a major contribution related to the IOM report, The Future of Nursing: Leading Change, Advancing Health and the Robert Wood Johnson Campaign for Action that is implementing major components of the IOM report. This report is germane to several key aspects of the report findings: expanded scope of practice, leadership development, testing new models of care, lifelong learning and expanding nurse competencies to meet the emerging public demands for access to care. Further, the implications for the process of developing nurses to assume expanded responsibilities should be observed and evaluated for sharing throughout the nursing community. There are many organizations who would benefit from the PACT model (I see this as part of model development) as the VA has defined the elements of the medical home.	Thank you.
2	Performance Measures exist for Diabetes Hemoglobin A1C > 9% or not done within a year, Cholesterol control in patients with Diabetes or Ischemic Heart disease, as well as hypertension. The hope is that appropriate Nurse run protocols can show improvement in these areas.	Acknowledged
3	Yes. The Office of Nursing Services is currently conducting several nurse protocol pilot programs in order to gather information to form national guidance. This report will be utilized in the formation of the national guidance	Acknowledged
4	No comments	Acknowledged
5	Absolutely, it provides the evidence to support revolutionizing how health care is delivered in the VA and will enable us to transform how care is delivered at every level of the organization. There will be no clinical service untouched.	Acknowledged
6	This will enhance our understanding and support utilization of nurse-managed protocols in PACT as well as specialty care transformation.	Acknowledged
7	Performance measures are currently described within this report as is PACT.	Acknowledged
8	No comments	Acknowledged
9	This review should inform the efforts in PACT to encourage nursing practice at the highest level of licensure. The data reviewed here also suggest some additional studies that would be appropriate to implement across sites using PACT, including the Centers of Excellence in Primary Care Education.	Acknowledged

Reviewer	Comment	Response
Question 6: Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.		
1	The question remains as to what a nurse-managed protocol looks like: how is it different than standing orders? How is it different from a care map? Is it designed to allow autonomy, or is it algorhymic in nature to avoid risk and to "catch" potentially weaker nurses by guiding them to a desired set of activities? This work should be done prior to implementation, or it will confound point-of-care providers as just another tool. So, it should LOOK different than other existing tools, should be LIMITED in scope to clinical conditions, and it must complement the reality that no patient has JUST one "chronic" medical condition – so the judgment tied to its use must place it within the context of the WHOLE patient medical portfolio of concerns.	We agree. There are a lot of details about nurse-managed protocols that are needed for next steps and implementation. Further investigation and translational research are needed.
2	If there are any hyperlinks to the study report themselves it would simplify getting more detail on what the specific protocols initiated were.	This is a good suggestion. Currently our reports are available only in pdf format, but we will pass the comment along to the ESP coordinating office.
3	Know the components that led to a successful intervention – such as hours and content of training, use of electronic medical record decision support, the development of clinical competency for evaluation.	We have included this information as recommendations for future research.
4	I thought that the satisfaction of the nursing staff listed first did not reflect a patient centered approach	Thank you for the comment. We agree that nurse satisfaction, while an important outcome, is not a patient-centered outcome. However, we present the results in the order listed in the Key Questions. Our executive summary, key points, and strength of evidence table focus on patient-centered and important biophysical outcomes.
5	See my comment in question # 4 above. "This may be particularly useful for diseases such as diabetes that have a preclinical phase in which the risk of complication is relatively high, or where medication titration and self-management are key to adequate management but symptoms are minimal or not yet clinically serious" I think this statement is speculative. We should stick to the evidence. My worry is that the elements in the VA who have been resisting this advance will latch on to this statement and slow our progress especially for those patients who are further along their disease progression and could therefore benefit in the short run. My recommendation would be eliminate this statement all together unless there is strong evidence that this is the only group where nurse protocols are effective.	Thank you. We have reworded this statement and moved away from the speculative phrasing.
6	Effective communication of the report findings will be valuable for facilitating implementation.	Acknowledged
7	See comments above for suggestions.	Acknowledged

Reviewer	Comment	Response
8	No comments	Acknowledged
9	Implementation of some of the protocols that were assessed in the studies reviewed would be facilitated by identification of links to the protocols, themselves, as well as translational work to be conducted within the VA sites, e.g. PACT and COE PCE sites	We agree. However, studies typically cited a guideline and gave only summary information about protocols. As part of our author queries, we requested copies of the protocol but the protocol was only provided by a single author. We highlighted the study by Watts et al. (2011), which gives detailed information about the protocol.
Question 7: Please provide us with contact details of any additional individuals/stakeholders who should be made aware of this report.		
1	Susan Hassmiller, RWJ Project Director – Campaign for Action; Mary Naylor – University of Pennsylvania – whose work with the transitional care model may be of assistance. Kathy Apple and Dr. Franklin Shaffer, with the National Council of State Boards of Nursing and Council on Graduates of Foreign Schools of Nursing, respectively, to guide their work.	Acknowledged
2	Dr. David Macpherson involved with Primary Care Field Advisory Committee. David.Macpherson@va.gov	Acknowledged
3	ONS will want to distribute this widely. PCS, including PACT, Specialty care and PBM should be made aware of the report	Acknowledged
4	Tri Council members, Diane Mancino, Debra Barksdale	Acknowledged
5	I think nursing service will be very receptive to these findings. Our greatest challenge will be with the specialty community and especially the specialist from a prior generation and/or who have not worked outside the VA. I would spend some informal time with the leaders of specialty care operations to solicit their support before distributing this review widely.	Acknowledged
6	In addition to PACT/Primary Care and Nursing, would also involve Specialty Care and Geriatrics.	Acknowledged
7	Marthe Mosley, PhD, RN, CCNS, Associate Director, Clinical Practice; Christine Engstrom, PhD, CRNP, Director, Clinical Practice, Storm Morgan, BSN, RN, MBA, ONS PACT Program Manager; Office of Nursing Service, Field Advisory Committees (cardiovascular, diabetes/ metabolic)	Acknowledged
8	No comments	Acknowledged
9	This is a timely and important study that should be circulated widely within and outside of the VA. Many of the protocols that were tested would most likely be appropriate for implementation within the Federally Qualified Health Centers and Nurse Managed Clinics, both of which have organizational structures to facilitate exchanges of information and findings in this report.	Acknowledged

APPENDIX F. STUDY CHARACTERISTICS TABLE

Table F-1. Characteristics of included studies

Study[a]	Location Setting Sponsoring Organization N Participants	Age in Years Female (%) Race/Ethnicity (%)	Target Condition Baseline Severity Measure	Study Duration Outcomes Reported	Intervention and Comparator[b]	Design and Quality
Cardiovascular risk factors: Diabetes						
Aubert, 1998[1]	Florida, USA Primary care clinics Private system 138 randomized, 100 completed	Median age (IQR) Intervention group: 53.0 (47.0 to 61.0) Usual care: 54.0 (46.0 to 60.0) Female, grand mean for total: 60.2 Race/ethnicity, grand mean for total: White 76.5	Diabetes, mixed type 1 and 2 HbA1c> 7%	12 months • A1c • Blood pressure • Total and LDL cholesterol	Intervention Nurse-led clinic + team care for glucose run by RN+ST including education Comparator Usual care	RCT Moderate risk of bias, fair quality
Bellary, 2008[2]	Western Europe Primary care clinics National Health System, UK 1486 randomized, 1486 completed	<Age 45: 14% Age 45–65: 56% >Age 65: 30% Total female: 47.7 Race/ethnicity: NR	Diabetes, all type 2 Severity: NR	Every 2 months for 20 months • A1c • Blood pressure • Total cholesterol • Performance measure	Intervention Nurse-led clinic for glucose, blood pressure, and lipids run by RN+ST including education Comparator Usual care	RCT Low risk of bias, good quality
Fischer, 2012[3] (Fischer, 2008[4])	Colorado, USA Primary care clinic US Government 762 randomized, 762 completed	Age, grand mean for total (SD): 58.4 (NR) Female, grand mean for total: 61.0 Race/ethnicity, grand mean for total: Black 3.3 Hispanic 81.4 White 13.5 Other 2.0	Diabetes, type NR Creatinine <3.0 mg/dL	20 months • A1c • Total and LDL cholesterol • Performance measure	Intervention Disease management program for glucose, blood pressure, and lipids run by RN+ST including education and self-management Comparator Usual care	RCT Low risk of bias, good quality

Study[a]	Location Setting Sponsoring Organization N Participants	Age in Years Female (%) Race/Ethnicity (%)	Target Condition Baseline Severity Measure	Study Duration Outcomes Reported	Intervention and Comparator[b]	Design and Quality
Houweling, 2009[5]	Western Europe Primary care clinics Netherlands 95 randomized, 84 completed	Age, grand mean for total (SD): 61.4 (NR) Female, grand mean for total: 53.3 Race/ethnicity: NR	Diabetes, all type 2 Severity: NR	12 months • A1c • Blood pressure • Total and LDL cholesterol • HRQOL • Performance measure	Intervention Nurse-led clinic for glucose, blood pressure, lipids run by nurse Comparator Usual care	RCT Moderate risk of bias, fair quality
Houweling, 2011[6]	Western Europe Primary care clinics Netherlands 230 randomized, 206 completed	Age, grand mean for total (SD): 60.0 (NR) Female, grand mean for total: 52.4 Race/ethnicity: NR	Diabetes, all type 2 Severity: NR	14 months • A1c • Blood pressure • Total cholesterol • HRQOL • Performance measure	Intervention Nurse-led clinic for glucose, blood pressure, and lipids run by RN+ST including education Comparator Usual care	RCT Low risk of bias, good quality
Cardiovascular risk factors: Diabetes with hypertension and hyperlipidemia						
MacMahon Tone, 2009[7]	Western Europe Hospital-based diabetes care clinic Ireland 200 randomized, 188 completed	Age, grand mean for total (SD): 61.7 (NR) Female, grand mean for total: 46.0 Race/ethnicity: NR	Diabetes, type 2 (with hypertension and hyperlipidemia) Total cholesterol >4.8 mmol/L, LDL >2.6 mmol/L, or blood pressure >130/80 mm Hg	12 months • Behavioral adherence • Performance measure • A1c • Blood pressure • Total and LDL cholesterol	Intervention Nurse-led clinic for glucose, blood pressure, and lipids run by specialist nurse including education Comparator Usual care	RCT Moderate risk of bias, fair quality
Meulepas, 2008[8]	Western Europe Primary care clinics Government (not US) 993 randomized, 900 completed (non-RCT)	Age, grand mean for total (SD): 69.5 (NR) Female, grand mean for total: 53.5 Race/ethnicity: NR	Diabetes, type 2 (with hypertension and hyperlipidemia) Severity: NR	36 months • Behavioral adherence • Performance measure • A1c • Total cholesterol	Intervention Nurse-led clinic for glucose, blood pressure, and lipids run by nurse including education Comparator Concurrent usual care: Active recall of patients on central diabetes registry	Non-RCT Moderate risk of bias, fair quality

Study[a]	Location Setting Sponsoring Organization N Participants	Age in Years Female (%) Race/Ethnicity (%)	Target Condition Baseline Severity Measure	Study Duration Outcomes Reported	Intervention and Comparator[b]	Design and Quality
New, 2003[9] (Mason, 2005[10])	Western Europe Shared care clinic National Health System, UK Randomized: 1014 in hypertension group and 683 in hyperlipidemia group Completed: 835 in hypertension group and 627 in hyperlipidemia group	Median age (IQR) Hypertension group: 63.5 (55.4 to 72.1) Usual care: 63.7 (56.4 to 71.9) Hyperlipidemia group: 56.5 (45.1 to 66.9) Usual care: (56.4 to 71.9) Female, grand mean for total: hypertension group, 50.0; hyperlipidemia group, 50.0 Race/ethnicity: NR	Diabetes, type NR (with hypertension and hyperlipidemia) SBP ≥140 or DBP ≥80 mmHg or total cholesterol ≥5.0 mmol/L	Mean intervention length 2.5 months, mean followup 18 months • Blood pressure • Total cholesterol • Performance measure	Intervention Nurse-led clinic for blood pressure and lipids run by specialist nurse including education and self-management Patients seen every 4 to 6 weeks for 30- to 45-minute appointments until targets achieved Comparator Usual care	RCT Moderate risk of bias, fair quality
New, 2004[11]	Western Europe Primary care clinics General practices in Salford, UK 10,303 randomized, 9977 completed	Cluster RCT of 44 practices in UK National Health Service Patient-level demographics NR	Diabetes, type NR with hypertension and hyperlipidemia) Blood pressure >140/80 mmHg or total cholesterol >5 mmol/L	24 months • Blood pressure • Total cholesterol • Performance measure	Intervention Nurse-led clinic + education outreach for blood pressure and lipids run by specialist nurse including education and behavioral Comparator Reverse control: 2-arm study where other intervention was control and vice versa	RCT Moderate risk of bias, fair quality
Philis-Tsimikas, 2004[12]	California, USA Primary care clinics US Government 290 randomized, 229 completed (non-RCT)	Age, grand mean for total: 50.5 (NR) Female, grand mean for total: 68 Race/ethnicity: NR	Diabetes, type 2 (with hypertension and hyperlipidemia) HbA1c >9%	12 months • A1c • Blood pressure • Total cholesterol • Performance measure	Intervention Nurse-led clinic + peer for glucose, blood pressure, and lipids run by RN+ST including education and self-management Comparator Concurrent usual care	Non-RCT High risk of bias, poor quality

Study[a]	Location Setting Sponsoring Organization N Participants	Age in Years Female (%) Race/Ethnicity (%)	Target Condition Baseline Severity Measure	Study Duration Outcomes Reported	Intervention and Comparator[b]	Design and Quality
Taylor, 2003[13]	California, USA Primary care clinic Private system 169 randomized, 127 completed	Age, grand mean for total: 55.2 (NR) Female, grand mean for total: 47.5 Race/ethnicity, grand mean for total: Black 8.0 Hispanic 18 White 62.0 Other 12.0	Diabetes, type 1 and 2 (with hypertension and hyperlipidemia) HbA1c >10%	12 months • A1c • Blood pressure • Total and LDL cholesterol • Performance measure	Intervention Disease management program + group education for glucose, blood pressure, and lipids run by RN+ST including education and self-management Comparator Usual care	RCT Moderate risk of bias, fair quality
Wallymahmed, 2011[14]	Western Europe Diabetes center United Kingdom 81 randomized, 78 completed	Age, grand mean for total: 34.7 (NR) Female, grand mean for total: 44.5 Race/ethnicity: NR	Diabetes, type 1 (with hypertension and hyperlipidemia) HbA1c ≥8%	24 months • A1c • Blood pressure • Total and LDL cholesterol • Performance measure	Intervention Nurse-led clinic for glucose, blood pressure, and lipids run by RN+ST including education Comparator Usual care	RCT Moderate risk of bias, fair quality
Cardiovascular risk factors: Diabetes with hypertension						
Bebb, 2007[15]	Western Europe Primary care clinics National Health System, UK 1534 randomized, 1420 completed	Age, grand mean for total: 64.3 (NR) Female, grand mean for total: 41.0 Race/ethnicity, grand mean for total: White 90.5 Other 9.5	Diabetes, type 2 (with hypertension) None	12 months • Blood pressure • Performance measure	Intervention Nurse-led clinic + algorithm implemented for blood pressure run by RN+ST Comparator Usual care	RCT Moderate risk of bias, fair quality
Denver, 2003[16]	Western Europe Outpatient clinic Hospital-affiliated, United Kingdom 120 randomized, 120 completed	Age, grand mean for total: 61.2 (NR) Female, grand mean for total: 36.7 Race/ethnicity, grand mean for total: White 39 Other 61	Diabetes, type 2 (with hypertension) BP >140/80 mmHg	6 months • A1c • Blood pressure • Total cholesterol • Performance measure	Intervention Nurse-led clinic for blood pressure run by nurse including education Comparator Usual care	RCT High risk of bias, poor quality

Study[a]	Location Setting Sponsoring Organization N Participants	Age in Years Female (%) Race/Ethnicity (%)	Target Condition Baseline Severity Measure	Study Duration Outcomes Reported	Intervention and Comparator[b]	Design and Quality
O'Hare, 2004[17]	Western Europe Primary care clinics General practices 361 randomized, 325 completed	Total age: 58.8 (11.7) Total female: (49.0) Race/ethnicity: Other:100	Diabetes, type 2 (with hypertension) HbA1c >7%, SBP >140, DBP >80 mmHg, total cholesterol >5 mmol/L	12 months • A1c • Blood pressure • Performance measure	Intervention Nurse-led clinic for glucose, blood pressure, and lipids run by nurse including education and self-management Comparator Usual care	RCT Moderate risk of bias, fair quality
Cardiovascular risk factors: Hypertension						
Rudd, 2004[18]	California, USA Primary care clinics Private system 150 randomized, 137 completed	Age, grand mean for total (SD): 61.2 (NR) Female, grand mean for total: 36.7 Race/ethnicity, grand mean for total: White 39 Other 61	Hypertension SBP >140 mm Hg or DBP >90 mm Hg	6 months • Blood pressure	Intervention Disease management program for blood pressure run by care manager including education, behavioral, and self-management Comparator Usual care	RCT Low risk of bias, good quality
Cardiovascular risk factors: Hyperlipidemia						
Allison, 1999[19]	Minnesota, USA Cardiac rehabilitation center University-affiliated 195 randomized, 152 completed	Total age (SD): 64.0 (11.0) Total female: (18.0) Race/ethnicity: NR	Hyperlipidemia Severity: NR	17 months • Total and LDL cholesterol • Protocol adherence • Behavioral adherence • Performance measure	Intervention Nurse-led clinic for lipids run by RN+ST including education, behavioral, and self-management Comparator Usual care	RCT Moderate risk of bias, fair quality
DeBusk, 1994[20]	California, USA Single site (not reported) Private system 585 randomized, 425 completed	Age, grand mean for total (SD): 57.0 (NR) Female, grand mean for total: 21.3 Race/ethnicity, grand mean for total: White 77	Hyperlipidemia Severity: NR	12 months • Total and LDL cholesterol • Behavioral adherence	Intervention Disease management program for lipids run by RN+ST including education and self-management Comparator Usual care	RCT Moderate risk of bias, fair quality

Study[a]	Location Setting Sponsoring Organization N Participants	Age in Years Female (%) Race/Ethnicity (%)	Target Condition Baseline Severity Measure	Study Duration Outcomes Reported	Intervention and Comparator[b]	Design and Quality
Congestive heart failure						
Angermann, 2012[21]	Western Europe 9 hospital-based call and care centers German health system 715 randomized, 567 completed	Age, grand mean for total (SD): 68.6 (NR) Female, grand mean for total: 29.4 Race/ethnicity: NR	CHF LVEF ≤40%	6 months • CHF mortality • HRQOL • Performance measure	Intervention Disease management program for CHF run by specialist nurse and including self-management; delivered by telephone Comparator Usual care	RCT Low risk of bias, good quality
Berger, 2010[22]	Western Europe Hospital clinics Vienna, Austria 278 randomized, 278 completed	Age, grand mean for total (SD): 72.0 (NR) Female, grand mean for total: 32.7 Race/ethnicity: NR	CHF NYHA class III or IV, cardiothoracic ratio >0.5 or LVEF <40%	12 months • CHF mortality	Intervention Disease management program for CHF run by specialist nurse and including education; delivered by telephone Comparator Multidisciplinary care or usual care	RCT Moderate risk of bias, fair quality
DeBusk, 2004[23]	California, USA Multisite (sites not reported) Private system 462 randomized, 389 completed	Total age (SD): 72.0 (11.0) Total female: (49.0) Race/ethnicity: Black (5.8) Hispanic (3.0) White (84.0) Other (7.6)	CHF Severity: NR	12 months • CHF mortality	Intervention Disease management program for CHF run by care manager and including education, behavioral and self-management Comparator Usual care	RCT Low risk of bias, good quality
Ekman, 2003[24]	Western Europe University hospital Gothenburg, Sweden 145 randomized, 108 completed	Age, grand mean for total (SD): 57.0 (NR) Female, grand mean for total: 15.1 Race/ethnicity: NR	CHF Boston criteria score ≥8 and NYHA class III or IV	1.5 months • CHF mortality • Performance measure	Intervention Nurse-led clinic for CHF by nurse including education; delivered by visit Comparator Usual care	RCT Moderate risk of bias, fair quality
Giordano, 2007[25]	Western Europe Telemedicine Italian hospitals and primary care clinics 460 randomized, 455 completed	Age, grand mean for total (SD): 80.0 (NR) Female, grand mean for total: 38.7 Race/ethnicity: NR	CHF Severity: NR	12 months • CHF mortality • Performance measure	Intervention Disease management program for CHF run by RN+ST; delivered by telephone Comparator Usual care	RCT Low risk of bias, good quality

Study[a]	Location Setting Sponsoring Organization N Participants	Age in Years Female (%) Race/Ethnicity (%)	Target Condition Baseline Severity Measure	Study Duration Outcomes Reported	Intervention and Comparator[b]	Design and Quality
Krantz, 2008[26]	Colorado, USA Cardiology and diabetes clinic US public health care for vulnerable and indigent 64 randomized, NR completed	Age, grand mean for total (SD): 53 (NR) Female, grand mean for total: 31.2 Race/ethnicity, grand mean for total: Black 28.1 Hispanic 42.5 White 28.1 Other 1.6	CHF LVEF ≤40%	1 to 6 months of intervention; followup measurements at 2.5 and 6 months • CHF mortality • Performance measure	Intervention Nurse-led clinic for CHF run by nurse specialist and including education; delivered by visit Comparator Usual care	RCT Moderate risk of bias, fair quality
Mejhert, 2004[27]	Western Europe Hospital referral center University-affiliated 208 randomized, 208 completed	Total age (SD): 75.8 (7.1) Total female: (42.3) Race/ethnicity: NR	CHF LVEF ≤45% or atrioventricular plane displacement ≤10 mm	Intervention timeframe NR; 18 months of followup • CHF mortality • HRQOL	Intervention Nurse-led clinic for CHF run by nurse including education and self-management; delivered by visit Comparator Usual care	RCT Moderate risk of bias, fair quality
Sisk, 2006[28]	New York, USA 4 hospitals in Harlem Not-for-profit institutions 406 randomized, 406 completed	Total age (SD): 59.4 (13.7) Total female: (46.3) Race/ethnicity; Black (45.8) Hispanic (32.5) White (15.3) Other (6.4)	CHF LVEF <40%	6 months of intervention; followup every 3 months for 1 year and at 18 months • CHF mortality • HRQOL • Performance measure	Intervention Disease management program for CHF run by RN+ST including education and self-management; delivered mainly by telephone after initial assessment Comparator Usual care	RCT Low risk of bias, good quality
Stromberg, 2003[29]	Western Europe Outpatient programs posthospitalization 3 hospitals and associated clinics, Sweden 106 randomized, 63 completed	Age, grand mean for total (SD): 77.5 (NR) Female, grand mean for total: 38.8 Race/ethnicity: NR	CHF NYHA class II to IV	12 months • CHF mortality • Behavioral adherence	Intervention Nurse-led clinic for CHF run by specialist nurse and including self-management including education and behavioral Comparator Usual care	RCT Low risk of bias, good quality

Study[a]	Location Setting Sponsoring Organization N Participants	Age in Years Female (%) Race/Ethnicity (%)	Target Condition Baseline Severity Measure	Study Duration Outcomes Reported	Intervention and Comparator[b]	Design and Quality
Thompson, 2005[30]	Western Europe Nurse-led outpatient heart failure clinics National Health System, UK 106 randomized, 106 completed	Age, grand mean for total (SD): 72.5 (NR) Female, grand mean for total: 27.6 Race/ethnicity: NR	CHF LVEF <45%	6 months • CHF mortality • HRQOL • Performance measure • Medication adherence	Intervention Nurse-led clinic for CHF run by nurse including education and self-management; delivered by home visit Comparator Usual care	RCT Low risk of bias, good quality
Other eligible diagnosis						
Dorr, 2008[31]	Utah, USA Primary care clinics Private system 3732 randomized, 3732 completed (non-RCT)	Age, grand mean for total (SD): 76.2 (NR) Female, grand mean for total: 65.0 Race/ethnicity, grand mean for total: White 96	Age >65 years and complex medical presentation None	Mean 27 months • CHF mortality • Medication adherence • Hospitalizations • Emergency department visits	Intervention Disease management program for older adults run by RN+ST including education and behavioral Comparator Concurrent usual care	Non-RCT Low risk of bias, good quality

[a] Companion article is cited in parentheses where applicable.
[b] All interventions included nurse-titrated medication (by eligibility criteria) and patient education.
Abbreviations: CHF=congestive heart failure; DBP=diastolic blood pressure; HbA1c=glycosylated hemoglobin; HRQOL=health-related quality of life; IQR=interquartile range; LDL=low-density lipoprotein; LVEF=left ventricular ejection fraction; NR=not reported; NYHA=New York Heart Association; RCT=randomized controlled trial; RN+ST=nurse with study-specific training; SBP=systolic blood pressure; SD=standard deviation; UK=United Kingdom

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APPENDIX G. SUBGROUP ANALYSES

Table G-1. Subgroup analyses[a,b]

Outcome	Non-US vs. US	Telephone vs. in-person	Single vs. multiple intervention target	Education with self-management or behavioral vs. not
Cardiovascular risk studies				
A1c (MD)	**-0.2 (I^2=34%) vs. -0.92 (I^2=0%) p=0.0003**	No studies in telephone group	**-1.1 (1 study) vs. -0.31 (I^2=55%) p=0.005**	-0.46 (I^2=84%) vs. 0.35 (I^2=16%) p=0.64
Systolic blood pressure (MD)	-3.24 (I^2=76%) vs. -6.55 (I^2=0%) p=0.17	-8.50 (1 study) vs. -3.27 (I^2=74%) p=0.10	-5.47 (I^2=85%) vs. -3.51 (I^2=74%) p=0.62	-2.12 (I^2=61%) vs. -5.86 (I^2=83%) p=0.15
Diastolic blood pressure (MD)	-1.58 (I^2=75%) vs. -1.49 (I^2=54%) p=0.96	-3.10 (1 study) vs. -1.46 (I^2=74%) p=0.31	-1.27 (I^2=63%) vs. -1.71 (I^2=73%) p=0.75	-1.36 (I^2=71%) vs. -1.99 (I^2=76%) p=0.62
Blood pressure performance measure (OR)	1.41 (I^2=77%) vs. 1.50 (1 study) p=0.87	No studies in telephone group	2.06 (I^2=84%) vs. 1.39 (I^2=75%) p=0.56	1.10 (I^2=22%) vs. 1.94 (I^2=80%) p=0.07
Total cholesterol (MD)	-7.61 (I^2=89%) vs. -12.71 (I^2=85%) p=0.55	**-24.33 (1 study) vs. -7.17 (I^2=91%) p=0.0008**	-14.17 (I^2=90%) vs. -7.79 (I^2=87%) p=0.58	-10.62 (I^2=95%) vs. -8.17 (I^2=85%) p=0.80
LDL cholesterol (MD)	-11.94 (I^2=91%) vs. -12.21 (I^2=91%) p=0.98	**-24.7 (1 study) vs. -9.22 (I^2=85%) p=0.03**	-11.67 (I^2=95%) vs. -12.18 (I^2=86%) p=0.97	-19.72 (I^2=73%) vs. -8.32 (I^2=89%) p=0.28
Cholesterol performance measure (OR)	1.31 (I^2=79%) vs. 1.85 (I^2=82%) p=0.29	2.6 (I^2=91%) vs. 1.28 (I^2=73%) p=0.12	2.12 (I^2=92%) vs. 1.37 (I^2=79%) p=0.53	1.51 (I^2=91%) vs. 1.60 (I^2=74%) p=0.89
Congestive heart failure studies				
Death (OR)	0.67 (I^2=59%) vs. 0.83 (I^2=0%) p=0.48	**0.64 (I^2=0%) vs. 1.18 (I^2=0%) p=0.02**	NA	0.72 (I^2=51%) vs. 0.67 (I^2=44%) p=0.82
Hospitalizations (OR)	0.77 (I^2=74%) vs. 0.91 (I^2=13%) p=0.55	0.87 (I^2=63%) vs. 0.66 (I^2=75%) p=0.61	NA	0.91 (I^2=47%) vs. 0.58 (1 study) p=0.07
CHF Hospitalizations (OR)	0.56 (I^2=38%) vs. 0.74 (I^2=0%) p=0.27	No studies in in-person group	NA	**0.75 (I^2=0%) vs. 0.47 (I^2=0%) p=0.04**
ACE/ARB performance measure (OR)	1.10 (I^2=0%) vs. 1.35 (1 study) p=0.51	1.2 (I^2=0%) vs. 1.03 (I^2=25%) p=0.61	NA	1.12 (I^2=0%) vs. 1.26 (I^2=0%) p=0.71

[a] If statistically significant main differences were found, the results are presented in bold type.
[b] If statistically significant subgroup differences were found, the group showing the larger effect is identified.
Abbreviations: ACE/ARB=angiotensin-converting enzyme inhibitor/angiotensin receptor blocking; CHF=congestive heart failure; LDL=low-density lipoprotein; MD=mean difference; OR=odds ratio

APPENDIX H. GLOSSARY

Abstract screening

The stage in a systematic review during which titles and abstracts of articles identified in the literature search are screened for inclusion or exclusion based on established criteria. Articles that pass the abstract screening stage are promoted to the full-text review stage.

ClinicalTrials.gov

A registry and results database of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov provides information about a trial's purpose, location, and participant characteristics among other details.

Cochrane Database of Systematic Reviews

A bibliographic database of peer-reviewed systematic reviews and protocols prepared by the Cochrane Review Groups in The Cochrane Collaboration.

Companion article

A publication from a trial that is not the article containing the main results of that trial. It may be a methods paper, a report of subgroup analyses, a report of combined analyses, or other auxiliary topic that adds information to the interpretation of the main publication.

Confidence interval (CI)

The range in which a particular result (such as a laboratory test) is likely to occur for everyone who has a disease. "Likely" usually means 95 percent of the time. Clinical research studies are conducted on only a certain number of people with a disease rather than all the people who have the disease. The study's results are true for the people who were in the study but not necessarily for everyone who has the disease. The CI is a statistical estimate of how much the study findings would vary if other different people participated in the study. A CI is defined by two numbers, one lower than the result found in the study and the other higher than the study's result. The size of the CI is the difference between these two numbers.

Data abstraction

The stage of a systematic review that involves a pair of trained researchers extracting reported findings specific to the research questions from the full-text articles that met the established inclusion criteria. These data form the basis of the evidence synthesis.

DistillerSR

An online application designed specifically for the screening and data extraction phases of a systematic review.

Embase

The Excerpta Medica database (EMBASE) produced by Elsevier, a major biomedical and pharmaceutical database indexing over 3500 international journals in the following fields: drug research, pharmacology, pharmaceutics, toxicology, clinical and experimental human medicine, health policy and management, public health, occupational health, environmental health, drug dependence and abuse, psychiatry, forensic medicine, and biomedical engineering or instrumentation. There is selective coverage for nursing, dentistry, veterinary medicine, psychology, and alternative medicine.

Exclusion criteria
The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions.

Full-text review
The stage of a systematic review in which a pair of trained researchers evaluates the full-text of study articles for potential inclusion in the review.

GRADE
Grading of Recommendations Assessment, Development, and Evaluation (GRADE), a system of assessing the quality of medical evidence and evaluating the strength of recommendations based on the evidence.

Inclusion criteria
The criteria, or standards, set out before the systematic review. Inclusion criteria are used to determine whether an individual study can be included in a systematic review. Inclusion criteria may include population, study design, sex, age, type of disease being treated, previous treatments, and other medical conditions.

Optimal information size
The number of patients that need to be included in a pooled analysis (meta-analysis) to provide sufficient power to detect the smallest clinically important difference in treatment effect.

PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses, an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses.

Publication bias
The tendency of researchers to publish experimental findings that have a positive result, while not publishing the findings when the results are negative or inconclusive. The effect of publication bias is that published studies may be misleading. When information that differs from that of the published study is not known, people are able to draw conclusions using only information from the published studies.

PubMed®
A database of citations for biomedical literature from MEDLINE®, life science journals, and online books in the fields of medicine, nursing, dentistry, veterinary medicine, the health care system, and preclinical sciences.

Randomized controlled trial (RCT)
A prospective, analytical, experimental study using primary data generated in the clinical environment. Individuals similar at the beginning of the trial are randomly allocated to two or more treatment groups and the outcomes the groups are compared after sufficient followup time. Properly executed, the RCT is the strongest evidence of the clinical efficacy of preventive and therapeutic procedures in the clinical setting.

Risk

A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Statistical significance

A mathematical technique to measure whether the results of a study are likely to be true. Statistical significance is calculated as the probability that an effect observed in a research study is occurring because of chance. Statistical significance is usually expressed as a P-value. The smaller the P-value, the less likely it is that the results are due to chance (and more likely that the results are true). Researchers generally believe the results are probably true if the statistical significance is a P-value less than 0.05 ($p<.05$).

Strength of evidence (SOE)

A measure of how confident reviewers are about decisions that may be made based on a body of evidence. SOE is evaluated using one of four grades: (1) *High* confidence that the evidence reflects the true effect; further research is very unlikely to change reviewer confidence in the estimate of effect; (2) *moderate* confidence that the evidence reflects the true effect; further research may change the confidence in the estimate of effect and may change the estimate; (3) *low* confidence that the evidence reflects the true effect; further research is likely to change the confidence in the estimate of effect and is likely to change the estimate; and (4) *insufficient*; the evidence either is unavailable or does not permit a conclusion.

Systematic review

A summary of the clinical literature. A systematic review is a critical assessment and evaluation of all research studies that address a particular clinical issue. The researchers use an organized method of locating, assembling, and evaluating a body of literature on a particular topic using a set of specific criteria. A systematic review typically includes a description of the findings of the collection of research studies. The systematic review may also include a quantitative pooling of data, called a meta-analysis.