Evidence-based Practice Center Systematic Review Protocol

Project Title: Transitional Care Interventions To Prevent Heart Failure Readmissions

I. Background and Objectives for the Systematic Review

Heart failure (HF) is a major clinical and public health problem and a leading cause of hospitalization and health costs in the United States. It is the most common principal discharge diagnosis among Medicare beneficiaries and the third highest for hospital reimbursements, according to 2005 data from the Centers for Medicare and Medicaid Services (CMS).[1] Up to 20 percent of patients hospitalized with HF are readmitted within 30 days.[2-5] These numbers vary by geographic area and insurance coverage.[6] Interventions aimed specifically at preventing readmission among patients with HF have emerged; these are often referred to as "transitional care interventions."[7, 8] The CMS recently began using readmission rates as a publicly reported metric and has lowered reimbursements to hospitals with excessive risk-standardized readmission rates. An assessment of the effectiveness and harms of transitional care interventions is needed to support policy and clinical decisionmaking about strategies to reduce readmission rates among adults with HF.

Epidemiology of Heart Failure in the United States

Nearly 7 million Americans 18 years of age and older were diagnosed with HF in 2010; an additional 3 million Americans will have the condition by 2030.[9,10] Data from the Framingham Heart Study sponsored by the National Heart, Lung, and Blood Institute indicate that the incidence of HF increases with age; it reaches 1 per every 100 people after 65 years of age.[11] Coronary disease and uncontrolled hypertension are the highest population-attributable risks for HF.[12] Three-quarters of HF cases have antecedent hypertension. Survival after HF diagnosis has improved over time, as shown by data from the Framingham Heart Study[13] and the Olmsted County Study.[14] However, the death rate remains high: 50 percent of people diagnosed with HF die within 5 years after diagnosis.[13,14] Among Medicare beneficiaries, more than 30 percent of patients with HF die within 1 year after hospitalization.[15]

Black Americans have the highest risk of developing HF, followed by Hispanic, white, and Chinese Americans.[16-19] This higher risk among black Americans reflects differences in the prevalence of hypertension and diabetes mellitus and in socioeconomic status.[17,18] Black Americans have the highest proportion of incident HF not preceded by clinical myocardial infarction (75 percent).[17] They also have greater 30-day, 1-year, and 5-year case fatality rates than white Americans.[19] Men are usually more likely to develop HF than women,[16-19] although some data indicate otherwise.[20]

In many cases, unplanned readmissions to the hospital indicate poor health outcomes for patients. Readmissions can reflect suboptimal quality of care during the index hospitalization and lack of support or coordination in the transition to home and postdischarge care. An analysis of 2007 to 2009 Medicare claims data showed that 24.8 percent of beneficiaries admitted with HF

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were readmitted within 30 days; 35.2 percent of those readmissions were for HF, and the remainder of readmissions were for diverse indications (e.g., renal disorders, pneumonia, arrhythmias, and septicemia/shock).[5] The broad range of acute conditions responsible for readmissions may reflect a "posthospitalization syndrome"—a generalized vulnerability to illness among recently discharged patients.[5,21]

Heart Failure Readmission: Relevance to Clinical Decisionmaking and Policy

Although a crude measure, hospital readmission within 30 days of discharge has long been used as a quality metric. However, there is uncertainty about the extent to which readmissions are preventable. Rates of preventable readmissions vary significantly based on the methodology used to judge whether readmissions are avoidable.[22] In 2007, the Medicare Payment Advisory Commission called for hospital-specific public reporting of readmission rates, identifying HF as a priority condition. The Commission stated that readmissions for HF were common, costly, and often preventable.[23] The rate of potentially preventable readmissions for HF was estimated to be 12.5 percent; this rate is based on claims data that identifies "red flags" in readmission diagnoses that are likely to represent conditions associated with a prior admission (and therefore likely preventable).[24] As a result, in 2009 the CMS began public reporting of all-cause readmission rates after HF hospitalization, and in 2010 the Patient Protection and Affordable Care Act[25] authorized financial penalties for hospitals with the highest risk-adjusted readmission rates during the first 30 days after discharge.

A review of the effectiveness of transitional care interventions grouped by setting and temporal relationship to the index hospitalization may help identify those areas most important for quality improvement. Transitional care interventions aim to address patient level (i.e., education, self-care) and system factors (i.e., coordination of care across settings) to support the transition from hospital to home and avoid preventable readmissions. The optimal components of these interventions are unclear, and there is uncertainty regarding the effect of these interventions on other health-care utilization rates (beyond readmission rates). So far, efforts to reduce readmissions after HF hospitalizations have been largely unsuccessful. National data show no evidence that readmission rates for HF patients have fallen during the past 2 decades, despite the observation that HF hospitalizations in the United States have declined by almost 30 percent during the past decade.[26]

Existing Guidelines Regarding the Prevention of Heart Failure Readmissions

The 2009-focused update of the 2005 American Heart Association/American College of Cardiology (AHA/ACC) guidelines addressed postdischarge HF disease-management interventions.[27] These guidelines focus on the importance of discharge planning, emphasizing written discharge instructions or educational material targeted to the patient or caregiver at discharge. The recommendations stated that discharge instructions should address the following: activity level, diet, discharge medications, a followup appointment, weight monitoring, and what to do if symptoms worsen.[27] The AHA/ACC guidelines also recommend that "postdischarge systems of care, if available, should be used to facilitate the transition to effective outpatient care for patients hospitalized with heart failure."[27] The 2010 Heart Failure Society of America (HFSA) guidelines are similar; their guidance emphasizes specific components of discharge

planning.[28] The HFSA guidelines recommend that "consideration of referral for formal disease management" should be a part of the discharge planning assessment.[28]

In addition to guideline recommendations, several national performance measures pertain to the standard of care for hospital discharge of people with HF. The Joint Commission performance measures mandate that all patients with HF should receive comprehensive written discharge instructions or other educational materials that address activity level, diet, discharge medications, followup appointment, weight monitoring, and plans of what to do should symptoms worsen.[29] These measures are publicly reported by hospitals. In 2011, the ACC/AHA/AMA (American Medical Association) Performance Consortium added a documented postdischarge appointment to the list of recommended HF performance measures.[30] Required documentation includes location, date, and time for a followup office visit or home health care visit.

Readmission for Heart Failure: Usual Care

Despite the availability of national guidelines and performance measures, current clinical practice in the care of adults with HF after hospitalization varies greatly. A recent telephone survey of 100 U.S. hospitals found wide variation in inpatient care processes, education, discharge processes, care transition, and quality-improvement methods for patients hospitalized with HF.[26] Individualized processes of care and 30-day HF readmission rates were not significantly related. However, hospitals with the lowest rates of readmissions had modestly higher discharge and transitional care domain scores. The discharge and transitional care domain included a variety of mechanisms to help coordinate care across settings, such as communication with the patient's primary care provider and timely scheduling of outpatient followup before the patient is discharged.

Heart Failure Disease-Management Interventions and Transition of Care

One difficulty in categorizing interventions that aim to reduce readmission rates for adults with HF lies in the variability of taxonomy used to describe the components of these interventions.[31] The AHA provides a taxonomy of disease management that specifies eight domains: patient population, intervention recipient, intervention content, delivery personnel, method of communication, intensity and complexity, environment, and clinical outcomes.[31] Previous systematic reviews of disease management and clinical service interventions for adults with HF have grouped these interventions according to content, setting, and method of delivery. In general, the specific types of interventions have been the following: patient education and self-care instruction (both inpatient and outpatient), case management, multidisciplinary outpatient care, telephone support, telemedicine, and increased clinic visits.

The phrase *transitional care interventions* has been used more recently to describe disease-management interventions targeted toward populations transitioning from one care setting to another. Naylor and colleagues[7] defined transitional care as "a broad range of time-limited services designed to ensure health care continuity, avoid preventable poor outcomes among at-risk populations, and promote the safe and timely transfer of patients from one level of care to another or from one type of setting to another." These interventions overlap with disease-management, case-management, and discharge-planning interventions. However, transitional

care emphasizes the "sending and the receiving aspects of the transfer" between settings; it aims specifically to avoid poor clinical outcomes arising from uncoordinated care.[32]

This taxonomy fits well with the goal of reviewing interventions aimed at preventing 30-day readmissions among adults with HF. Categorizing interventions by "health care exchange points" (predischarge, postdischarge, and interventions bridging the transition) may help guide implementation of effective interventions. This classification is consistent with another recent taxonomy used to evaluate disease-management interventions aimed at reducing 30-day readmission rates in a general population (excluding disease-specific interventions).[33] No clear consensus exists about when the transition period ends; although evaluating 30-day readmissions is important for certain stakeholders (hospitals, payers, quality improvement organizations), outcomes beyond this period are clinically important and may benefit from overall improvements in care coordination related to transitional care interventions. However, outcomes far away from the index hospitalization also may reflect the natural history of HF or other processes and not necessarily factors related to transitions in care.

Rationale for Evidence Review

Despite an overall reduction in admissions among patients with HF, rates of readmission have been stable. Uncertainty remains regarding effective strategies to reduce readmission rates among adults with HF. A Health Technology Assessment prepared for the Agency for Healthcare Research and Quality (AHRQ) in 2007 addressed nonpharmacological interventions for postdischarge care of patients with HF.[34] Since the publication of that report, the literature evaluating transitional care interventions for patients with HF has expanded. Previous systematic reviews have addressed HF disease-management programs. According to one meta-review,[35] however, the overall quality of the reviews are mixed, and reviews often do not take into account program complexity and heterogeneity. Potential harms or unintended consequences of interventions do not appear to have been widely considered in previous reviews. Patients with HF who are typically older and sicker and have multiple chronic conditions often receive assistance from informal caregivers to help them manage their illness. Previous literature documents that burden is high among caregivers of patients with HF[36-38] and that burden is associated with worse mental and physical health outcomes in caregivers.[36-41] In addition, there may be unintended consequences of reducing readmissions rates—an increase in emergency room or acute care visits, for example. Given recent developments in the CMS policy for reimbursement to hospitals with excess risk-adjusted 30-day readmission rates, a review is needed that focuses specifically on the efficacy and unintended consequences of transitional care interventions for adults with HF.

II. The Key Questions

Question 1

Among adults who have been admitted for HF, do transitional care interventions increase or decrease the following health care utilization rates?

a. Readmission rates

b. Emergency room visits
c. Acute care visits
d. Hospital days (of subsequent readmissions)

Question 2

Among adults who have been admitted for HF, do transitional care interventions increase or decrease the following health and social outcomes?

a. Mortality rate
b. Functional status
c. Quality of life
d. Caregiver burden
e. Self-care burden

Question 3

This question has three parts:

a. What are the components of effective interventions?
b. Among effective interventions, are particular components necessary?
c. Among multicomponent interventions, do particular components add benefit?

Question 4

This question has three parts:

a. Does the effectiveness of interventions differ based on intensity (e.g., duration, frequency/periodicity) of the interventions?
b. Does the effectiveness of interventions differ based on delivery personnel (e.g., nurse, pharmacist)?
c. Does the effectiveness of interventions differ based on method of communication (e.g., face-to-face, telephone, Internet)?

Question 5

Do transitional care interventions differ in effectiveness or harms for subgroups of patients based on age, sex, race, ethnicity, socioeconomic status, disease severity (left ventricular ejection fraction or New York Heart Association classification), or coexisting conditions?

Summary of Revisions to the Key Questions

These questions were available for public comment from February 22 through March 21, 2013. Based on the public comments, we have added additional health care utilization outcomes to Key Question (KQ) 1 (emergency room and acute care visits). We have included all health outcomes in KQ 2, also adding functional status as an outcome of interest. Because of the

difficulty in defining "complexity," we removed this term and revised KQ 2 (now KQ 3) to address the effectiveness of interventions based on the number and type of components included. Feedback from members of the Technical Expert Panel (TEP) was important in helping to frame potential "harms" or unintended consequences of transitional care interventions. It became clear that the potential harms are the same as the effectiveness outcomes (although the direction of benefit would be in the opposite direction). For this reason, we have revised KQs 1 and 2, asking whether transitional care interventions increase or decrease health care utilization (KQ 1) and health outcomes (KQ 2), rather than asking about the same outcomes in a separate question devoted to harms.

For all of the above KQs, the following PICOTS (**p**opulation, **i**ntervention, **c**omparator, **o**utcomes, **t**iming, and **s**etting) criteria apply:

- **Population(s)**
  - Adults with HF requiring inpatient admission
  - Recruited during the index hospitalization or within 1 week of the index hospitalization
- **Interventions**
  - Transitional care interventions
    - Predischarge interventions, such as:
      - HF-specific discharge planning
      - Medication reconciliation
      - Appointment scheduling before discharge
      - Patient or caregiver education before discharge
    - Postdischarge interventions, such as:
      - Increased planned or scheduled clinic visits
      - Home visits
      - Multidisciplinary outpatient HF management
      - Heart failure specialty clinic management
      - Telemedicine
      - Telephone support or patient hotline
    - Interventions bridging predischarge and postdischarge care, such as:
      - Transition coach
      - HF-specific case management spanning inpatient and outpatient care
      - Interventions to increase provider continuity (same provider continuity between inpatient and outpatient care)
- **Comparators**
  - Usual care, routine care, or standard care

- Comparison of one intervention with another type of intervention

- **Outcomes**

  - Health and Social Outcomes
    - Mortality
    - Quality of life, using a validated measure
    - Functional status, using a validated measure
    - Caregiver burden
    - Self-care burden

  - Health Care Utilization Outcomes
    - Readmissions (all causes and HF-related readmissions)
    - Emergency room visits
    - Acute-care visits
    - Hospital days (of subsequent readmissions)

- **Timing**

  - Followup for at least 30 days from the start of the intervention
  - Excludes outcomes measured more than 6 months after the index hospitalization

- **Setting**

  - Intervention occurring during the index hospitalization, before discharge
  - Intervention initiated as an outpatient following the index hospitalization
  - Interventions bridging the transition from inpatient to outpatient care

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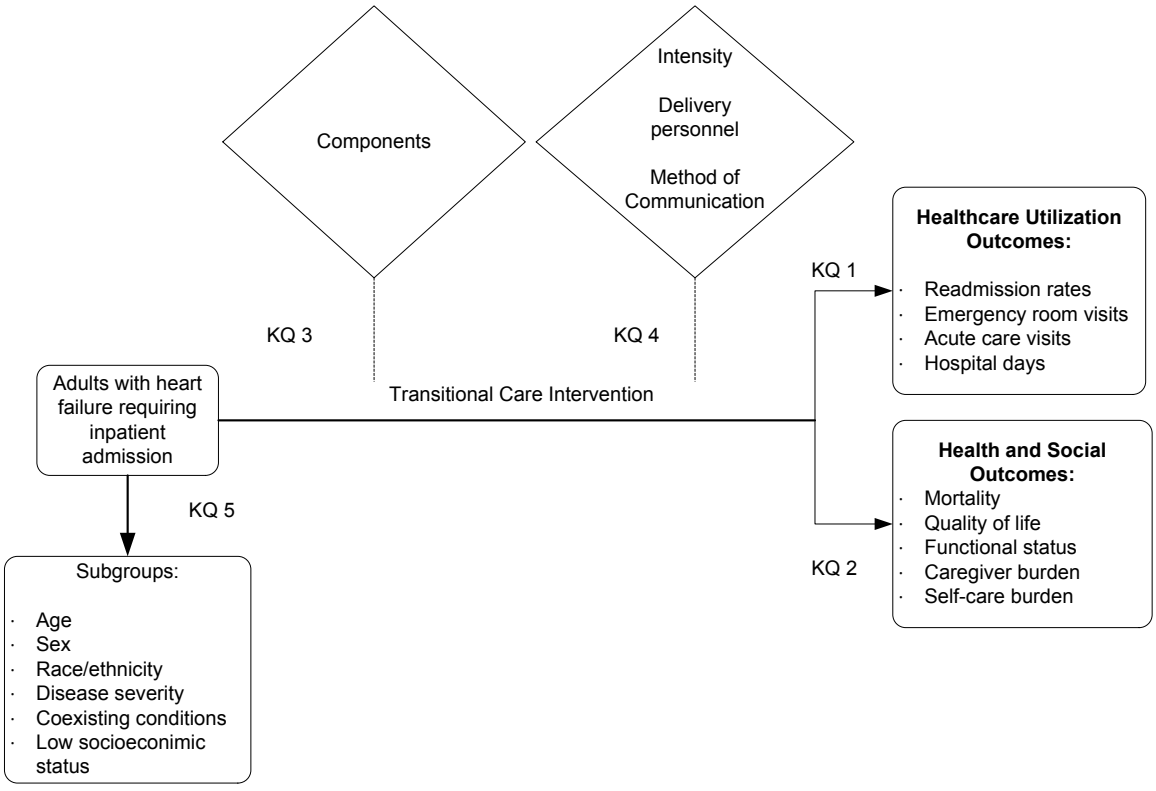
III. Analytic Framework

Figure 1. Draft analytic framework for transitional care interventions to prevent heart failure readmissions



Abbreviations: KQ = key question

IV. Methods

A. Criteria for Inclusion/Exclusion of Studies in the Review

Table 1 presents the inclusion/exclusion criteria for our review.

Table 1. Inclusion/exclusion criteria

Category	Criteria	
	Inclusion	Exclusion
Population	• Adults (age 18 years or older) with HF requiring inpatient admission • Recruited during hospitalization or within 1 week of the index hospitalization	Children and adolescents under 18
Geography	No limits	
Time period	• 1990 to the present • Searches to be updated after the draft report goes out for peer review	

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Category	Criteria	
	Inclusion	**Exclusion**
Length of followup	At least 30 days	Less than 30 days
Settings	• Intervention occurring during the index hospitalization, before discharge • Intervention initiated as an outpatient following the index hospitalization • Interventions bridging the transition from inpatient to outpatient care	All other settings (e.g., discharge to a skilled nursing facility or rehabilitation center)
Interventions	As defined above in the PICOTS	• proBNP guided therapy • Pharmacotherapy • Physician training (e.g., CME on evidence-based treatment for HF patient management) • Surgical interventions or invasive procedures (e.g., left ventricular assist device, ultrafiltration, dialysis) • Technology aimed at guiding evaluation of patient volume status (e.g., pulmonary artery pressure sensor, segmental multifrequency bioelectrical impedance analysis)
Comparators	As defined above in the PICOTS	
Outcomes	As defined above in the PICOTS	
Publication language	English	All other languages†
Admissible evidence (study design and other criteria)	• Original research • Eligible study designs include the following: ○ For all KQs, randomized controlled trials ○ For two outcomes (caregiver burden and self-care burden), we will also include nonrandomized controlled trials or prospective cohort studies with an eligible comparison group.	• Case series • Case reports • Nonsystematic reviews • Systematic reviews • Editorials • Letters to the editor • Articles rated as having high risk of bias¶ • Case-control studies • Retrospective cohort studies • Studies with historical, rather than concurrent, control groups

† Because of limited time and resources, we will include only studies published in English.
¶ We plan to conduct sensitivity analyses based on risk of bias, when appropriate.
Abbreviations: CME = continuing medical education; KQ = Key Question; proBNP = probrain natriuretic peptide; PICOTS = populations, interventions, comparators, outcomes, timing, and setting.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

To identify articles relevant to each KQ, we will begin with a focused MEDLINE® search on heart failure, readmission, and transitional care by using a variety of terms, medical subject headings (MeSH®), and major headings and limiting our search to English-language and human-only studies; relevant terms are listed in Table 2. We will also search the Cochrane Library and the Cumulative Index to Nursing and Allied Health Literature (CINAHL®) by using analogous search terms. We will conduct quality checks to ensure that the known studies (i.e., studies

identified in the 2007 AHRQ Health Technology Assessment and during topic nomination and refinement) are identified by the search. If they are not, we will revise and rerun our searches.

We will limit our database search to articles published from 1990 through the present. This timepoint was used as the start date for the 2007 AHRQ Technology Assessment[34] and is associated with advances in the medical management of HF, including the increased use of beta-blockers.

For all KQs, we will use the literature search results from the 2007 AHRQ Technology Assessment for the period from 1990 to 2007. We will reapply our current inclusion and exclusion criteria to the trials included in that review; our criteria are similar but narrower in scope (e.g., limited to outcome timings no longer than 6 months from the index hospitalization). As stated above, we will then search for randomized controlled trials published from 2007 through the present using the literature search terms outlined in Table 2. We will also search for prospective cohort studies relevant to the effect of transitional care interventions for HF on caregiver burden and self-care burden from 1990 to the present. These particular outcomes may be less likely to be reported in randomized controlled trials. The 2007 AHRQ Technology Assessment was limited to randomized controlled trials and did not report on these outcomes. Systematic reviews will be used for background information or to ensure completeness of the literature search.

We will search the "gray literature" for unpublished studies relevant to this review and will include studies that meet all the inclusion criteria and contain enough methodological information for assessment of internal validity/quality. Gray literature sources will include ClinicalTrials.gov and the World Health Organization's International Clinical Trials Registry Platform.

Our search strategy was reviewed by the TEP. In addition, to attempt to avoid retrieval bias, we will manually search the reference lists of landmark studies and background articles on this topic to look for any relevant citations that might have been missed by our electronic searches.

We will also conduct an updated literature search (of the same databases searched initially) concurrent with the peer-review process. Any literature suggested by Peer Reviewers or public comment respondents will be investigated and, if found appropriate, incorporated into the final review. Appropriateness will be determined by the same methods listed above.

Table 2. Literature search terms

Populations	"congestive heart failure" OR "heart failure, congestive" OR "heart failure"[MeSH Term]
Readmission	Readmission OR rehospitalization OR recurrence [MeSH] OR "patient readmission"[MeSH]

Transitional Care	"case management"[MeSH] OR "rehabilitation"[MeSH] OR "continuity of patient care"[MeSH] OR "patient discharge"[MeSH] OR "patient transfer"[MeSH] OR transition* OR postdischarge OR post-discharge OR coordination OR coordinate OR transfer OR post-acute care OR postacute care OR post-hospital* OR posthospital* OR subacute care OR sub-acute care OR discharge OR referral OR continuity OR "critical pathways"[MeSH Terms] OR "critical pathways"[Text Word] OR "critical pathway"[All Fields] OR "critical path"[all fields] OR "critical paths"[all fields] OR "clinical path" [all fields] OR "clinical paths" [all fields] OR "clinical pathway" [all fields] OR "clinical pathways"[all fields] OR "telemedicine"[MeSH Terms] OR telemedicine[Text Word] OR telehealth[all fields] OR eHealth[all fields] OR "Mobile Health"[all fields] OR "Home Care Services, Hospital-Based"[MeSH] OR "Hospital Based Home Cares"[All Fields] OR "Hospital Home Care Services"[All Fields] OR "Hospital-Based Home Care"[All Fields] OR "Hospital Based Home Care"[All Fields] OR "Hospital-Based Home Cares"[All Fields] OR "home nursing"[MeSh] OR "Nonprofessional Home Care"[All Fields] OR "home nursing"[all fields] OR "Non-Professional Home Care"[All Fields] OR "Physical Therapy Modalities"[MeSH] OR "physical therapy"[All Fields] OR "physical therapies"[all fields] OR "Exercise Therapy"[MeSH] OR "exercise therapy"[All Fields])
Study Designs for all KQs	randomized[title/abstract] AND controlled[title/abstract] AND trial[title/abstract]) OR (controlled[title/abstract] AND trial[title/abstract]) OR "controlled clinical trial"[publication type] OR "Randomized Controlled Trial"[Publication Type] OR "Single-Blind Method"[MeSH] OR "Double-Blind Method"[MeSH] OR "Random Allocation"[MeSH] ("review"[Publication Type] AND "systematic"[tiab]) OR "systematic review"[All Fields] OR ("review literature as topic"[MeSH AND "systematic"[tiab]) OR "meta-analysis"[Publication Type] OR "meta-analysis as topic"[MeSH Terms] OR "meta-analysis"[All Fields]
Additional Study Designs for Caregiver burden and Self-care burden Outcomes	"prospective cohort" OR "prospective studies"[MeSH] OR (prospective*[All Fields] AND cohort[All Fields] AND (study[All Fields] OR studies[All Fields])) OR (controlled[title/abstract] AND trial[title/abstract]) OR "controlled clinical trial"[publication type]
Limits	Humans English language **NOT the following:** Autobiography, Bibliography, Biography, Case Reports, Classical Article, comment, Congresses, Consensus Development Conference, Dictionary, Directory, Editorial, Electronic supplementary materials, Festschrift, In Vitro, Interactive Tutorial, Interview, Lectures, Legal Cases, Legislation, Letter, News, Newspaper article, Patient Education Handout, Personal Narratives, Periodical Index, Pictorial works, Popular works, Portraits, Scientific Integrity Review, Video Audio Media, Webcasts

C. Data Abstraction and Data Management

All titles and abstracts identified through our searches will be independently reviewed for eligibility against our inclusion/exclusion criteria by two trained members of the research team. Studies marked for possible inclusion by either reviewer will undergo a full-text review. For studies without adequate information to determine inclusion or exclusion, we will retrieve the full text and then make the determination. All results will be tracked in an EndNote® database (Thomson Reuters, New York, NY).

We will retrieve and review the full text of all articles identified for possible inclusion during the title/abstract review phase. Each full-text article will be independently reviewed by two trained members of the research team for inclusion or exclusion based on the eligibility criteria described above. If both reviewers agree that a study does not meet the eligibility criteria, the study will be excluded. If the reviewers disagree, conflicts will be resolved by discussion and

consensus or by consulting a third member of the review team. As described above, all results will be tracked in an EndNote database. We will record the reason that each excluded full-text publication did not satisfy the eligibility criteria so that we can later compile a comprehensive list of such studies.

For studies that meet the inclusion criteria, we will abstract important information into evidence tables. We will design data abstraction forms to gather pertinent information from each article, including characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. Trained reviewers will abstract the relevant data from each included article into the evidence tables. All data abstractions will be reviewed for completeness and accuracy by a second member of the team.

D. Assessment of Methodological Risk of Bias of Individual Studies

To assess the risk of bias (i.e., internal validity) of studies, we will use predefined criteria based on the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*,[42] including questions to assess selection bias, confounding, performance bias, detection bias, and attrition bias (i.e., those about adequacy of randomization, allocation concealment, similarity of groups at baseline, masking, attrition, whether intention-to-treat analysis was used, method of handling dropouts and missing data, validity and reliability of outcome measures, and treatment fidelity).

In general terms, results from a study assessed as having low risk of bias are considered to be valid. A study with moderate risk of bias is susceptible to some risk of bias but probably not enough to invalidate its results. A study assessed as having high risk of bias has significant risk of bias (e.g., stemming from serious issues in design, conduct, or analysis) that may invalidate its results. We plan to omit studies deemed to have high risk of bias from our main data synthesis and main analyses; we will include them only in sensitivity analyses.

Two independent reviewers will assess risk of bias for each study. Disagreements between the two reviewers will be resolved by discussion and consensus or by consulting a third member of the team.

E. Data Synthesis

If we find multiple similar studies for a comparison of interest, we will consider quantitative analysis (i.e., meta-analysis) of the data from those studies. To determine whether quantitative analyses are appropriate, we will assess the clinical and methodological heterogeneity of the studies under consideration following established guidance.[43] We will do this by qualitatively assessing the PICOTS of the included studies, looking for similarities and differences.

When appropriate, studies will be combined by using a random-effects model while accounting for variation among studies.[44] We will assess the presence of statistical heterogeneity among studies by using standard X^2 tests and the magnitude of heterogeneity by using the I^2 statistic.[45,46] Statistical heterogeneity will be explored by using subgroup analysis or meta-regression. We plan to stratify analyses and/or perform subgroup analyses when possible and appropriate. Planned stratifications or categories for subgroup analyses include those listed in KQs 3, 4, and 5.

When quantitative syntheses are not appropriate (e.g., because of clinical heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we will synthesize the data qualitatively.

We will present findings in the report as they relate to the transitional care setting (predischarge, postdischarge, and interventions bridging predischarge and postdischarge care).

F. Grading the Strength of Evidence for Individual Comparisons and Outcomes

We will grade the strength of evidence based on the guidance established for the Evidence-based Practice Center (EPC) Program.[47] Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: risk of bias (including study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers other optional domains that may be relevant for some scenarios, such as dose-response association, plausible confounding that would decrease the observed effect, strength of association (i.e., magnitude of effect), and publication bias.

Table 3 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer the KQs on the comparative effectiveness, efficacy, and harms of the interventions in this review. Two reviewers will assess each domain for each key outcome, and differences will be resolved by consensus.

Table 3. Definitions of the grades of overall strength of evidence

Grade	Definition
High	High confidence that the evidence reflects the true effect: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect: Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect: Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Source: Owens et al., 2010[47]

We will grade the strength of evidence for all outcomes related to health care utilization and health outcomes. We will not grade the evidence for KQ 3; this question is a descriptive question.

G. Assessing Applicability

We will assess the applicability of individual studies as well as the applicability of a body of evidence following guidance from the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[48] For individual studies, we will examine conditions that may limit applicability based on the PICOTS structure. Such conditions may be associated with heterogeneity of treatment effect, measurement of absolute (rather than relative) benefits and harms, and the ability to generalize the effectiveness of an intervention to use in everyday practice. Some factors identified a priori that may limit the applicability of evidence include the

following: age of enrolled populations; sex of enrolled populations (e.g., few women may be enrolled in the studies); race/ethnicity of enrolled populations; socioeconomic status of enrolled populations; co-occurring disorders of enrolled populations; setting; and medication adherence.

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VI. Definition of Terms

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Transitional care has been defined as "a broad range of time-limited services designed to ensure health care continuity, avoid preventable poor outcomes among at-risk populations, and promote the safe and timely transfer of patients from one level of care to another or from one type of setting to another."[7] The concept can overlap disease management, case management, and discharge-planning interventions. Transitional care emphasizes both sending and receiving aspects of the transfer of patients between settings, and it aims specifically to avoid poor clinical outcomes arising from uncoordinated care.[32]

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale. Changes made to the protocol should not be incorporated throughout various sections of the protocol. Instead, protocol amendments should only be noted in Section VII of the protocol, preferably in a tabular format (please see the example table below) and the date of the amendment noted at the top of the protocol.

Date	Section	Original Protocol	Revised Protocol	Rationale
This should be the effective date of the change in protocol.	Specify where the change would be found in the protocol.	Describe the language of the original protocol.	Describe the change in the protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use a justification such as "because the AE/TOO/TEP/Peer reviewer told us to" but explain what the change hopes to accomplish.

VIII. Review of Key Questions

For all EPC reviews, the EPC reviewed and refined KQs as needed with input from Key Informants and the Technical Expert Panel (TEP) to ensure that the questions are specific and explicit about what information is being reviewed. In addition, the KQs were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

The end-users of research, Key Informants include patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informant role is to provide input into identifying the KQs for research that will inform health care decisions. The EPC solicits input from Key Informants when developing questions for systematic review or when identifying high-priority research gaps and needed new research. Key Informants are not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer- or public-review mechanism.

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Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals are invited to serve as Key Informants, and those who present with potential conflicts may be retained. The Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes, as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design, and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not perform analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the peer- or public-review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts, and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer Reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. The EPC considers peer-review comments on the preliminary draft of the report in preparing the final draft of the report. Peer Reviewers do not participate in writing or editing the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer-review comments are documented and will, for Comparative Effectiveness Reviews and Technical Briefs, be published 3 months after the publication of the Evidence Report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer Reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

XII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. The EPC core team has no

conflicts to disclose. Related financial conflicts of interest that cumulatively total more than $1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract Nos. HHSA 290-2012-00008-I and HHSA 290-32003-T from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.