



Evidence-based Practice Center Systematic Review Protocol

Project Title: *Management of High-Need, High-Cost Patients: A Realist and Systematic Review*

I. Background and Objectives for the Review

Background

Payers in the U.S. health care system, particularly Medicare and Medicaid, are increasingly requiring health care systems, coordinated care organizations, and health care professionals to progress from payment through fee-for-service arrangements toward alternative payment models that include financial risk.¹⁻⁴ For this reason, the challenge of addressing high-need, high-cost (HNHC) patients is increasingly pressing. Health care systems participating in alternative payment models, particularly those that include financial risk, acknowledge that their success in these models depends, in large part, on their effectiveness in addressing the care and costs for HNHC patients.^{5, 6}

Although HNHC patients represent a small proportion of the patient population, they account for a substantial proportion of health care costs.⁷⁻¹¹ Health care systems would like to accomplish two goals in relation to HNHC patients: (1) reduce their health care use that is potentially preventable or modifiable, which is often acute care in the emergency department (ED) or hospital inpatient setting,¹²⁻¹⁶ and (2) increase their quality of care.¹⁴⁻¹⁶ Despite strong motivation to address the burden of HNHC patients, multiple challenges and controversies complicate approaches to identifying HNHC patients and determining the causal mechanisms of complex interventions that affect health care utilization, cost, and quality of care.

Purpose of the Review and Approach

This review has three main objectives, all with the shared purpose of identifying actionable evidence to support informed decisions for clinicians, health care systems, and payers. The first is to describe approaches to identifying HNHC populations. The second is to develop and refine theory explaining why particular interventions, in various circumstances, are more likely to be successful in changing potentially preventable or modifiable health care use and improving quality of care for HNHC patients. The third is to review the evidence supporting the overall effectiveness of these interventions. We will use qualitative and quantitative synthesis methods in conducting the review.

Defining High-Need, High-Cost Patients

Researchers and practitioners have not decided on a single definition of HNHC patients, those high-need patients for whom high costs are potentially preventable or modifiable. One direct approach is to identify the patients with the highest costs during a historical time period, but no consensus has been reached on the appropriate duration of the time period and the number and types of utilization.^{12, 13} Also, focusing on cost alone can

obscure detecting high-need patients. A large percentage of high-cost patients use this level of care for a relatively short period of time, and it is the appropriate choice for treating their condition (e.g., certain types of cancer or orthopedic surgery patients).¹⁷ A second approach is to identify HNHC patients based on diagnoses, such as individuals with multiple co-occurring chronic conditions (one or more of which may be a behavioral health condition).^{18, 19} Relying chiefly on a diagnostic definition, however, ignores that not all high-need patients are HNHC. A large percentage of high-need patients use care appropriately, even if it may be costly (i.e., needed health care is received through ongoing relationships with primary care and specialist providers). Further refinement in defining and predicting whether individuals with high-need chronic conditions are at risk of being high users of potentially preventable or modifiable health care may be related to identifying additional risk factors.²⁰ Overall, HNHC patients include those patients for whom reducing use of high-cost health care services in favor of other types of care is theorized to result in better care and better outcomes.

To facilitate our synthesis of the evidence on approaches to identifying and describing HNHC patients and to explore the relationships among the approaches, we will conduct a “best fit” framework synthesis.²¹ Consistent with this approach, we begin from an a priori identified framework that we will use to sort evidence into themes across included studies (i.e., the distinguishing characteristics and reasons why some patients are HNHC). During our review of the evidence, we will use an iterative process to consider new themes that are not captured in the initial framework. In the end, we will present a summary of the data and syntheses of the evidence and our conclusions within a framework corresponding to our final conceptual model.

We propose to begin the synthesis using the taxonomy developed by the National Academy of Medicine in their report *Effective Care for High-Need Patients: Opportunities for Improving Outcomes, Value, and Health* as our a priori framework.²⁰ This taxonomy groups HNHC patients first based on their clinical and functional characteristics. Among the six patient groups presented in the taxonomy, four meet the inclusion criteria for this review: nonelderly disabled, multiple chronic conditions, major complex chronic condition, and frail elderly. (the additional two categories, children with complex needs and advancing illness/end-of-life care are outside the scope of the review.) Within these assigned groups, the taxonomy proposes additional, cross-patient group assessment based on behavioral health factors and social risk factors that are believed to influence how individuals use health care and increase the risk of receiving fragmented care. Behavioral health factors include persistent and serious mental illness, substance abuse, cognitive decline, and chronic toxic stress. Social risk factors include low socioeconomic status, low health literacy, social isolation, community deprivation, and housing insecurity.

Understanding Interventions for High-Need, High-Cost Patients

To gain a greater understanding of the complex alternative payment and delivery models, social interventions, and health programs that are used to address health care utilization among HNHC patients, we will use a realist review approach. Consistent with this approach, our goal is to explain what works (or fails), for whom, under what circumstances, and why.²² We will seek to identify, elucidate, and refine the various

underlying theories that could explain the approach of different complex interventions, explore implementation chains, assess intermediate outcomes, and examine modifications or adaptations applied in various circumstances.²²

Using the terminology of the realist approach, reviewers seek to determine how particular contexts have “triggered” mechanisms to generate outcomes.²³ The relationships are summarized as context + mechanism = outcome (CMO). Context is the “backdrop,” the variety of features that can affect the implementation of a program, including participant characteristics, program setting, resources, and history that trigger or modify the processes through which an intervention produces an outcome.²⁴ Mechanisms are the underlying processes that work in specific contexts to generate the outcomes of interest. The intervention is thought of as manipulating or changing the context so that specific mechanisms can be triggered.²⁴ Finally, the outcome is the impact or behaviors that arise from the inter-relationship between mechanisms and contexts.

Using a systematic review approach, one would describe a group of studies of interventions as community health workers whose task is to increase the percentage of patients who regularly go to primary care physician office visits. Using a realist approach, one would seek to describe why the community health worker intervention might work. For example, when isolated patients living in a large city, who must be self-reliant in getting to their doctors’ appointments are provided with one-on-one assistance from a community health worker on how to use the bus system (C), the patients are more likely to get to their office visits (O) because they are more confident and have greater agency that they will be successful (M). A second CMO configuration in the causal pathway might be that regular visits with a clinician (C) result in greater medication adherence and fewer visits to the ER (O) because patients trust that their clinicians know them and care about their welfare (M).

In addition, to further support the goal of producing actionable information, we will also use traditional Evidence-based Practice Center systematic review methods to synthesize the evidence of the overall effectiveness of the interventions that are included as the final focus of the realist portion of the review.

Initial Rough Theory: Controversies and Challenges Regarding Interventions

A realist review begins with an “initial rough theory,” a beginning theory of what interventions are expected to do. Using this approach, the scope, focus, and refinement of the review evolve as the review proceeds; the process includes regular input from stakeholders.²⁴ For this review, we begin broadly, presenting the controversies and challenges in determining the reasons why various interventions or particular features of interventions may be effective in changing HNHC patient health care use.

Describing and Understanding Effective Interventions

In developing the protocol, we conferred with a Key Informant (KI) stakeholder panel to help ensure that the focus of the review would be relevant to potential end users. The KI panel consisted of two clinician health researchers, one representative of a nongovernmental health policy organization and one representative from a health system research organization; one health system quality officer; and one statistician/survey scientist. (Section IX describes the role of KIs.) KIs differed in their views about the

nature of effective interventions for HNHC patients. Some thought that effective interventions could have broad applicability and be relevant across multiple causes of high utilization. Others thought that effective interventions need to be targeted to subpopulations of patients; what is effective for one subpopulation may not be effective for another or only effective in certain circumstances and settings. The following are models of organizing the delivery of health care that are theorized as the context for influencing and improving both care delivery and costs for HNHC patients.

Payer-Level Interventions

Accountable Care Organizations (ACOs). ACOs align financial incentives for care coordination and joint financial and health outcome accountability among a large group of health care providers across the health care continuum (ambulatory outpatient, acute care, post-acute care, and home health settings). An assumption underlying success in an ACO model is that providers, whether consciously or unconsciously, act to maximize the health of the patient while also maximizing their own financial incentive in caring for the patient. ACOs use a variety of strategies to accomplish such goals, including the following:

1. Increasing physicians' access to a uniform source of complete information about patients' health utilization and health status to support care coordination;
2. Using techniques such as population segmentation and risk stratification to focus resources on HNHC populations; and
3. Using various approaches to increasing coordination among health care settings, particularly during transitions between settings in episodes of care:
 - a. outpatient→ED→outpatient
 - b. outpatient→inpatient→post-acute care→home health→outpatient.

Also, increasingly, ACOs include strategies to address social determinants of health. These strategies support the notion that addressing barriers to accessing appropriate health care services is as important as coordinating care and ensuring equal access to care.

Patient-Centered Medical Homes (PCMH). The PCMH model encompasses five core attributes: comprehensive care, patient-centered care, coordinated care, accessible services, and quality/safety. Although this model is intended to promote changes in cost, access, and quality for all patients, it may have the greatest impact on HNHC patients because HNHC patients can yield the greatest reduction in expenditures and improvement in health outcomes. Care coordination is a central component, particularly during health care setting transitions (as described above in relation to ACOs), based on the assumption that PCMHs can reduce unnecessary duplication of services and lower preventable utilization of health care in costly settings (predominately ED and inpatient care).

The implementation of PCMH models is broadly variable, but most PCMHs encompass the five core attributes. The interaction of these five attributes may trigger the mechanisms that produce beneficial impact on health care expenditures and health outcomes of the HNHC population.

Home-Based Primary Care. Home-based primary care moves the delivery of the majority of primary care from an ambulatory office-based setting to a patient's place of residence.²⁵ Intended to be a comprehensive care delivery model, this model typically involves a team-based approach and combines home-based care for medical needs with intensive management and care coordination. Home-based programs typically serve a population that has a high probability of being HNHC because participants commonly have complex chronic conditions and functional limitations. Home-based primary care may benefit HNHC patients if such approaches can better address patients' specific needs, values, and preferences. If HNHC patients have difficulty accessing traditional office-based care, home-based primary care may be especially beneficial.

Clinicians are believed to be able to obtain greater insight into patient needs with home visits, often finding environmental and nonmedical factors related to patients' problems. HNHC patients may require frequent monitoring, intense management, or rapid follow-up that cannot be easily accommodated by an office-based provider. Home-based primary care may also be able to help HNHC patients avoid complications from hospital care (e.g., certain infections, delirium) when hospitalizations themselves can be averted or shortened. Several additional assumptions underlying the success of this approach is that the HNHC patients can be identified, that intervening at home is cost-effective, and that the teams work well together.

Health System and Provider-Level Interventions

At the health system and clinician levels, data can be used to report health care service use that may indicate that a patient is HNHC and needs additional services. ED alerts inform clinicians that a patient has received care in the ED, which can help them identify patients whose patterns of care might be considered HNHC and in need of additional support services. Hotspotting uses data to identify patients whose costs are outliers, such as the HNHC population; understand the problem; dedicate resources; and design effective interventions.²⁶ Hotspotting typically includes multidisciplinary, coordinated care that treats the whole patient and attends to the nonmedical and social determinants that affect health, including housing, mental health, substance abuse, and emotional support. The underlying premise is that intensive and highly individualized care, addressing the unique needs of an HNHC patient, including social determinants of health, will improve health outcomes and reduce health expenditures beyond the cost of the high intensity, highly individualized hotspotting intervention.

Health-Related Interventions

At the patient level, supportive services and social determinants of health-related interventions can affect the success or failure of complex social interventions. They are intended to bridge the gap between health care professionals who deliver direct care and an individual patient. Persons in a variety of roles may provide supportive services, such as social workers, community health workers, patient navigators, and peer-to-peer networks.

Patient support services are intended to address common barriers related to resource limitations, education, and treatment adherence, thereby improving patient outcomes. Relatedly, the environment and social determinants of health, such as low income, poor

education and nutrition, homelessness, and lack of transportation, have been identified as predisposing factors limiting access to care. For example, stable housing could improve patients' ability to interact consistently with their health care providers and social support systems, which, in turn, could increase adherence to their treatment plan.²⁷

Applying a Clear Classification Taxonomy

A challenge in conducting a review on management of HNHC patients is the absence of a consensus in the field of a unifying classification schema or taxonomy of interventions. This gap complicates organizing key dimensions of these interventions into meaningful distinctions for grouping and separating their components.²⁸

Intervention classification in recent systematic reviews regarding HNHC patients differs significantly. One systematic review stratified interventions as home-based, clinic-based, and primary care augmentation.¹⁵ Another categorized interventions into case management, individual care plans, and information sharing.¹³ Baker and colleagues stratified interventions by population type: adults (i) with two or more chronic diseases, (ii) with one chronic disease and depression, and (iii) identified as at risk for high health care utilization.¹⁴

We propose to organize our findings starting with a taxonomy of interventions that maps to mechanisms that the review team theorizes are related to the success of interventions for HNHC patients. We will attempt to separately address context, outcomes, and mechanisms at the payer, health care system, provider, and patient levels and those that cut across interventions.

II. The Key Questions

Key Questions

Initially proposed Key Questions (KQs) were posted for public comment February 7, 2019, through March 7, 2019. We received comments from two individuals. The first individual wrote, "As important as identifying high utilization/high cost patients is understanding patterns of persistence from year to year. That is critical for prioritization of interventions and the most effective interventions for patients with one or two years of high cost versus multiple ongoing years." We agree with the comment. In describing HNHC patients (KQ 1), we will limit the population to individuals with at least 1 year of high-cost care. Within that population, we will present the patterns of persistent health care use and costs described in the studies. The second individual commented that being breastfed is a "potent health indicator" and would like the review to include the relationship between having been breastfed as a child and being HNHC as an adult. While this may be a salient characteristic of the HNHC population, for this analysis, we need to be able to observe past or predicted high utilization. We did not find any studies that examine the relationship between breastfeeding in infancy with high utilization in adulthood.

Table 1 outlines the substantive changes between the preliminary KQs and those included in this protocol. The "final" KQs appear below the table.

Table 1. Changes to KQs and PICOTS

Original Element	Source	Comment	Decision and Changes	Rationale (Implications for Evidence Report)
Population name	KI	KIs thought the term “high utilizer” should be changed to “high-need, high-cost (HNHC),” which has become a more commonly used term.	Change made	No implications for the workload of the review
KQ 1	EPC	The EPC modified KQ 1. KQ 1a-KQ 1e have not been modified.	Original question: What are the characteristics of patients who are “high utilizers”? Protocol revised question: (see below)	The EPC modified KQ 1 for clarity.
KQ 2	EPC	The EPC modified KQ 2 to follow the format of a realist review.	Original question: What are the effective interventions for adults identified as high utilizers of health care? Protocol revised questions: (see below)	The EPC modified KQ 2 to answer this question using a realist review approach. The edits are intended to support the goal of understanding the mechanisms that explain successful outcomes in complex interventions serving HNHC patients.
KQ 3	EPC	The EPC intends to answer KQ 3, using systematic review methods to support the findings concerning the interventions included in answering KQ 2, using realist review methods.	Original question: Overall, what is the evidence about which interventions targeting which patient groups lead to the highest overall improvement in health outcomes and cost savings for patients, clinicians, providers, and payers? Protocol revised question: (see below)	The original question was a comparative effectiveness question. Based on our conversations with KIs and our initial review of the literature, we believe that it will be valuable to the field to focus on the more fundamental question of why and how particular interventions work (KQ 2) and the evidence of effectiveness and harms of these interventions (KQ 3).

EPC = Evidence-based Practice Center; HNHC = high-need, high-cost; KI = Key Informant; KQ = Key Question.

KQ 1 (“best fit” framework synthesis): What criteria identify or can be used to predict that patients will be HNHC and why?

KQ 1a. How do criteria incorporate patient clinical characteristics?

KQ 1b. How do criteria incorporate patient health behaviors and sociodemographic characteristics (e.g., age, social determinants of health, insurance status and source of coverage, and access to the health care system)?

KQ 1c. How do criteria incorporate types, amount, duration, and patterns of persistent use of potentially preventable or modifiable health care use?

KQ 1d. Do criteria differ at the payer, health care system, or provider levels?

KQ 1e. How can observed or predicted potentially preventable or modifiable high use of health care be differentiated from necessary and appropriate use?

KQ 2 (realist review): What are the mechanisms that lead to reductions in potentially preventable or modifiable health care use and result in improved health outcomes and cost savings in interventions serving HNHC patients?

KQ 2a. What are the important contexts, such as the characteristics of the HNHC patients, the broader health care delivery system, and the community, that impact whether mechanisms facilitate the desired outcomes?

KQ 3 (systematic review): Overall, what is the effectiveness and harms of interventions, included in answering KQ 2, in reducing potentially preventable or modifiable health care use and costs and improving health outcomes among HNHC patients?

PICOTS and Classification Taxonomy

We made no substantive changes to the population, interventions, comparators, outcomes, timing, settings, and study design (PICOTS). As we proceed with the review, we anticipate that we will further focus our analysis and want to discuss decisions with our Technical Expert Panel (TEP) on multiple occasions. These occasions can include any or all of the following:

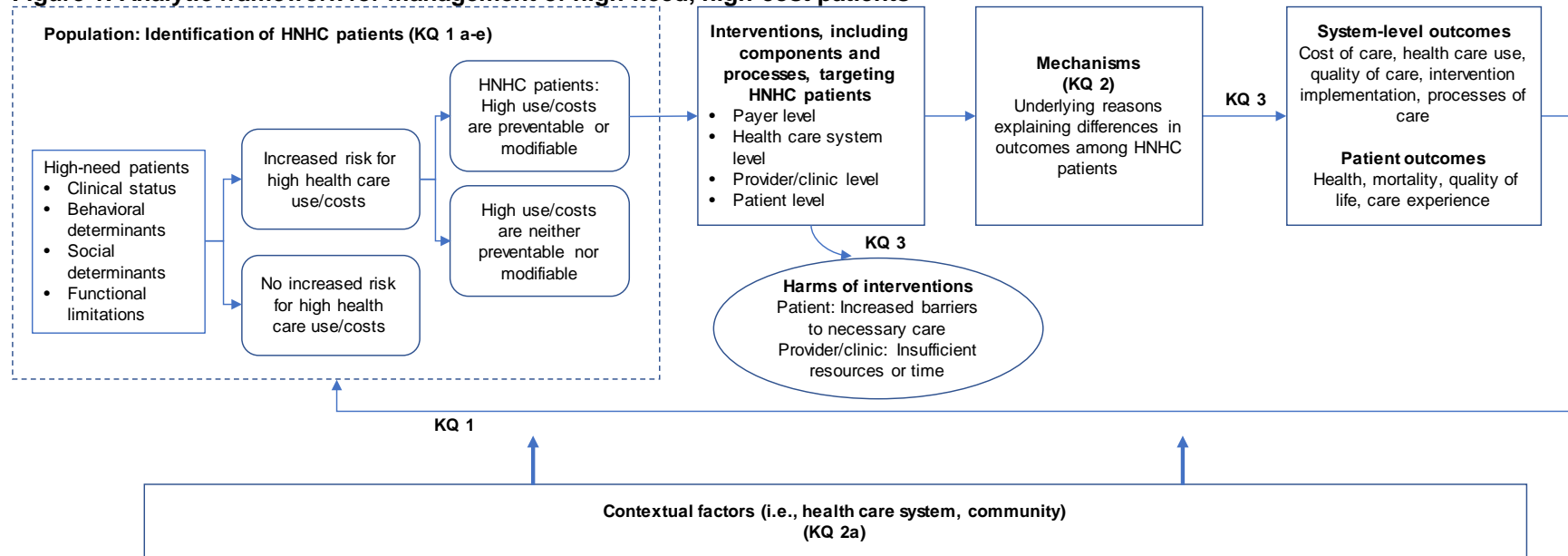
1. Receiving input on whether we have identified the relevant studies or programs and, if we have not, where to find additional information;
2. Refining the HNHC population for the purposes of the review, including whether to combine subpopulations or keep them separate; and
3. Discussing the theories of why and when various mechanisms are activated by effective complex interventions within particular contexts to produce outcomes.

Our final goal is to present our findings within the context of a unifying classification schema or taxonomy. We may seek feedback from our TEP and members of our KI stakeholder panel on whether what we develop will be useful to individuals and organizations that are seeking actionable information.

III. Analytic Framework

Figure 1 presents the analytic framework for the review and depicts the KQs in relation to the PICOTS. The figure illustrates how HNHC patients may be identified, how interventions that target HNHC patients together with contextual factors trigger different mechanisms of action that may result in systems-level outcomes (i.e., cost, utilization, and quality of care) and patient outcomes (i.e., health, mortality, and patient experience), and harms that may occur because of the interventions.

Figure 1. Analytic framework for management of high-need, high-cost patients



Abbreviations: HNHC = high-need, high-cost; KQ: Key Question

IV. Methods

Criteria for Inclusion/Exclusion of Studies in the Review

Table 2 presents the initial inclusion and exclusion criteria for the PICOTS of the review. In keeping with realist review methods, we will refine the scope of the review as we uncover evidence and focus the depth and breadth of the review.²⁹ We will address KQ 1 using a “best fit” framework synthesis methodology and KQ 2 using a realist review methodology; with these approaches, all study designs, if relevant, are admissible for inclusion. We will answer KQ 3 using a systematic review methodology, resulting in admissible study designs being more limited.

Table 2. Inclusion/exclusion table

PICOTS	Inclusion	Exclusion
Population	KQs 1, 2, and 3: Noninstitutionalized adults, 18 years of age or older KQ 1: One or more years of potentially preventable or modifiable high health care cost and/or use KQs 2 and 3, two groups: a) HNHC patients with one or more years of potentially preventable or modifiable high health care cost and/or use; b) HNHC patients with one or more years of potentially preventable or modifiable high health care cost and/use AND either 2 or more chronic physical health conditions, or a combination of 1 or more chronic physical health conditions and 1 or more behavioral health conditions	Patients receiving a high level of health care services that are considered appropriate for their condition OR high level of health care services are measured for less than 1 year OR end-of-life care
Intervention	KQ 1: Not relevant, interventions not necessary for inclusion KQs 2 and 3: Alternative delivery models (e.g., ACOs, coordinated care organizations, health homes, home-based primary care, behavioral health integration) System- or practice-level interventions (e.g., emergency department alerts, hotspotting) Patient supportive services (e.g., community health workers, social workers, patient navigators, care coordinators, case and care managers, intensive primary care support, medication management, health reliance specialists, self-management instruction, and peer-to-peer support) Social determinants of health-related interventions (e.g., transportation, health literacy, housing support, caregiver support)	KQs 2 and 3: Interventions for which the relevance for and impact on HNHC patients cannot be determined
Comparator	KQ 1: Comparison population or no comparator KQ 2: Any intervention, treatment as usual, or no comparator intervention KQ 3: Any intervention or treatment as usual	KQ 3: No comparator

Table 2. Inclusion/exclusion table (continued)

PICOTS	Inclusion	Exclusion
Outcomes	<p>KQ 1: Population characteristics described or predicted</p> <p>KQs 1, 2, and 3: Health care use: decreases in ED visits, EMS use, and hospitalizations; changes in primary care or specialist visits or other necessary and appropriate types of care (e.g., care manager visits, telephone followup) and use of support services</p> <p>Patient health behavior (e.g., treatment adherence, empowerment, knowledge, self-care)</p> <p>Patient health outcomes: all-cause mortality, disease and condition-specific outcomes, health indicators, quality of life</p> <p>Patient satisfaction with care</p> <p>Physicians' and health professionals' satisfaction with clinical practice</p> <p>Costs</p> <p>Patient and health professional harms such as increased barriers to necessary care, clinician time, and/or resource trade-offs of other duties</p>	All other outcomes, including behavioral health outcomes
Time frame	<p>Potentially preventable or modifiable high cost health care use measured for 1 year or more</p> <p>KQ 3: Measurement of outcomes at 1 year or more after implementation of the intervention.</p>	Shorter time periods
Settings	<p>Health care and support services delivery settings, including outpatient, ED, the broader health care delivery environment, community characteristics related to social determinants of health</p> <p>KQ 1: United States</p> <p>KQs 2 and 3: patient-level interventions: very high human development index countries; Health system or payer-level interventions: United States</p>	Institutional care settings, such as hospitals, skilled nursing, long-term care facilities, and prisons or jails
Study design	<p>KQs 1 and 2: All study designs except reviews summarizing across original studies or interventions</p> <p>KQ 3: Randomized controlled trials, cluster randomized trials, cohort studies, case-control studies, quasi-experimental designs with a comparison group</p>	KQ 3: All other designs
Language	Studies published in English	Studies published in languages other than English
Publication type	All publications that allow abstraction and interpretation of findings	KQ 3 only: Abstract-only publications

ACO = Accountable Care Organization; ED = emergency department; EMS = emergency management services; HNHC = high-need high-cost; KQ = Key Question; PICOTS = population, intervention, comparator, outcomes, time frame, settings

Searching for the Evidence: Literature Search Strategies to Identify Relevant Studies to Answer the Key Questions

Areas of Focus for Searches

We will conduct this review following the methodology of a “best fit” framework synthesis (for KQ 1), realist review (for KQ 2), and a systematic review (for KQ 3).²² In conducting the realist

review, we anticipate that starting from our rough theory, our searches will be iterative in a way that will enable us to uncover the underlying mechanisms in complex interventions that are related to approaches or components that may be effective with HNHC patients in different contexts and why.

To answer KQ 1, our goal is to review the evidence to develop an actionable description of HNHC patients that captures the distinguishing characteristics of populations whose high utilization is potentially modifiable. Based on input from our KI stakeholders during development of the protocol, HNHC populations will be identified in our searches through different approaches, including the following:

1. Multiple health conditions (i.e., multiple co-occurring chronic conditions, including behavioral health conditions),
2. Multiple health conditions coupled with additional risk factors (i.e., functional limitations, behavioral factors, financial factors, or social risk factors), and
3. Health services use (e.g., overuse of ED, inpatient, or other high-cost services).

To answer KQs 2 and 3, our attention will focus on the following kinds of interventions:

1. Complex structural changes and alternative financial arrangements (e.g., ACOs, PCMHs, and health homes),
2. Novel approaches to delivering services and providing information to clinicians (e.g., interdisciplinary teams, hotspotting), and
3. Adding any patient-centered component to an existing health care delivery system (e.g., patient navigator, peer support, and caregiver supports).

We also expect relevant interventions to be a source for further defining populations of interest.

Sources of Literature

To begin to identify articles relevant to the review, we initially conducted a focused search of MEDLINE via PubMed search (Appendix A). Our broader search will include both databases and gray literature sites, including Cochrane Clinical Trials Central Register, PsycINFO, Cumulative Index of Nursing and Allied Health Literature, EMBASE, Web of Science, Clinicaltrials.gov, and Academic Search Premier.

Our overall search results fall into three “buckets” because we will need to use more than one approach to finding the literature that identifies HNHC patient populations and, relatedly, relevant interventions. The buckets are as follows:

1. Studies identifying the population by using the text terms “high utilizer/medically complex/high needs” and similar terms. Medical Subject Heading (MeSH) terms are not available to identify the population using these types of terms.
2. Studies identifying the population by using the MeSH term “multiple chronic conditions” or similar terms, limited to individuals with functional limitations, behavioral factors (e.g., health risk behaviors or serious mental illness), or social risk factors.
3. Studies identifying populations by limiting them to specific conditions or combinations of conditions (e.g., cardiovascular disease, diabetes, or both), when such populations also had functional limitations or behavioral or social risk factors.

We will also search for evaluation reports or other gray literature on government websites. These will include the following: the Centers for Medicare & Medicaid Services, particularly its Center for Medicare and Medicaid Innovation, which supports development of Medicaid demonstrations and other alternative payment models; the National Institute on Drug Abuse; the Centers for Disease Control and Prevention; the National Institute on Aging; the Human Resources Services Administration; the Veterans Administration; the National Library of Medicine (for HSRProj), and Social Work Abstracts. Nongovernment-sponsored studies will be searched on websites of such organizations as the Camden Coalition, the Center for Health Care Strategies, the Commonwealth Fund, the Kaiser Family Foundation, the Milbank Memorial Fund, the National Academy of Medicine, Patient-Centered Outcomes Research Institute, the Robert Wood Johnson Foundation, and the Social Interventions Research & Evaluation Network Evidence Library.

Following our preliminary searches as recommended for a realist review, we will conduct snowball searches, including reviewing reference lists of included studies, identifying whether included studies are cited in newer articles, and looking for related studies, such as those suggested by PubMed.³⁰ In addition, we know that we will need to relax our population restrictions to examine whether some studies of interventions, such as those related to ACOs, health homes, community health workers, patient navigators, care managers, and others, focus on patients who are *at risk* of being HNHC and thus may not be identified through one of our three population buckets.

Quality Assurance for Searches

We will conduct quality checks to ensure our search identifies known studies. If not, we will revise and rerun our searches. An experienced librarian familiar with systematic reviews will design and conduct all searches in consultation with the review team. We will also conduct an updated literature search (of the same databases searched initially) concurrent with the process for peer and public review of the draft report. We will investigate any literature that peer reviewers or the public suggest and, if appropriate, will incorporate them into the final review. We will identify all eligible studies using the same criteria described above.

Data Abstraction and Data Management

As with systematic reviews, a wide range of documents can be relevant in a realist synthesis. Two trained research team members will independently review all titles and abstracts identified through searches for eligibility against our inclusion/exclusion criteria using Abstrackr.³¹ 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[®] bibliographic database (Thomson Reuters, New York, NY).

We will retrieve and review the full text of all titles included during the title/abstract review phase and through hand searches. Two trained team members will independently review each full-text article for inclusion or exclusion based on the eligibility criteria described above (Table 3). 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.

For the realist review, we will evaluate articles for their relevance and robustness in answering the review questions and their contribution to theory building and testing. For all KQs, we will also evaluate articles as to whether the methods that authors used to generate data are credible and trustworthy.²⁹ We will record the reason that we concluded that any excluded full text did not satisfy the eligibility criteria so that we can later compile a comprehensive list of such studies.

For studies that meet our inclusion criteria, we will abstract relevant information into tables. To answer the realist review question (KQ 2), we will abstract data relevant for our analyses and synthesis, including context, intervention, mechanisms, outcomes, and theories. We expect to refine the data extraction process continually as the review progresses; we anticipate data selection and appraisal will be ongoing and conducted in parallel with the analysis.²⁹

To answer the systematic review question (KQ 3), we will design evidence tables to gather pertinent information from each article; these data will include characteristics of study populations, settings, interventions, comparators, study designs, methods, and results. Trained reviewers will extract the relevant data from each included article into the evidence tables. A second member of the team will review all data abstractions for completeness and accuracy.

Realist Review: Quality Appraisal

Quality appraisal in realistic reviews is not focused on assessing the risk of bias of individual studies but rather on assessing the rigor used to develop one or more program theories. In realist reviews, assessing study rigor occurs throughout the process of synthesis and includes all of the key aspects of the review process: the quality of the theory development, the data identified as relevant and analyzed, and the inferences made from the data.³²

We will, therefore, appraise data based on relevance (whether included articles can contribute to theory building and testing), trustworthiness (whether the data in a study have been obtained empirically, using methods that are clearly stated and whether the information could be found in more than one source), plausibility of the argument underlying the theory (the coherence of the argument, including its breadth in explaining the data, its simplicity and fit with existing theory), and rigor (whether included articles are methodologically credible with regard to outcomes reported and methods used for testing propositions). Our appraisal approach will consider how our findings (theory and observation of relationships) have evolved at each evidential step. As such, we will use RAMESES project standards to guide our judgments in quality appraisal tasks.^{29, 32-34}

Previous realist reviews have applied qualitative methods to appraisal. Standards tools include the UK Cabinet Office quality framework and a Critical Appraisal Skills Programme tool.³⁴ However, according to a study comparing appraisal methods in realist reviews, Dixon-Woods et al.³⁵ found tool-based approaches to be similar in the level of agreement to those using unprompted judgment.^{35, 36, 37}

Assessment of Methodological Quality or Risk of Bias of Individual Studies

For KQs 1 and 2, we will appraise each included qualitative research study in terms of rigor and validity using the Critical Appraisal Skills Programme checklist for qualitative research.³⁸ Our goal is to have a consistent approach for evaluating the strengths and limitations in individual studies. However, as recommended by the authors of the checklist, the results will not be used to

create a scoring system. Descriptive studies that count or seek to identify characteristics of HNHC patients will be assessed in relation to the threat of selection bias and confounding, as relevant. Other studies, such as theory and opinion used to answer KQ 2, will be solely appraised using the realist review quality appraisal approach discussed above.

For KQ 3, we will use the criteria set forth by the Agency for Healthcare Quality and Research's (AHRQ's) *Methods Guide for Comparative Effectiveness Reviews*. To assess the risk of bias (i.e., internal validity), we will use the ROBINS-1³⁹ tool for observational studies and the Cochrane randomized controlled trial (RCT) tool⁴⁰ for RCTs. For both RCTs and observational studies, risk of bias assessment will include questions to assess all the following:

1. Various types of bias, including selection bias, confounding, performance bias, detection bias, and attrition bias;
2. Concepts about adequacy of randomization (for RCTs only), such as similarity of groups at baseline, and masking; and
3. Method of handling dropouts and missing data, whether intention-to-treat analysis was used, reliability and validity of outcome measures, and treatment fidelity.⁴¹

Two independent reviewers will assign risk of bias ratings for outcomes from each study; they will also specify when the risk of bias for an individual outcome may be lower than the rating for the study overall. Disagreements between the two reviewers will be resolved by discussion and consensus or by consulting a third member of the team.

We will give a low risk of bias rating for outcomes that meet all criteria. Studies that do not report their methods sufficiently may be rated as unclear risk of bias. We will give a high risk of bias rating to outcomes from studies that have a methodological shortcoming in one or more categories and will exclude them from our main analyses.

Data Synthesis

Realist Review: Three Main Targets of Analysis

In a realist review, the goal of the synthesis is to develop and then “test” (confirm, refute, or refine), against the data from included documents, realist causal explanations for outcomes. Analysis of the data should also be directed to understanding the relationships of the CMO configurations that have been developed within the program theory or theories. The realist causal explanation for outcomes takes the form of CMO configurations. Specifically, a CMO configuration describes and explains the relationship between particular features that have been interpreted as functioning as context, particular mechanisms, and particular outcomes. In a sentence, such a CMO presentation will take the form of “In ‘X’ context, ‘Y’ mechanism is activated or triggered, and it causes ‘Z’ outcome.” The synthesis presents evidence to support two main conclusions: (1) that the specific features of context exist and affect the activation of a mechanism of action (entities, processes, or structures) and (2) that the hypothesized mechanisms exist and cause outcomes.²⁴

Systematic Review: Procedures for Analysis and Synthesis

For KQ 3, we will follow standard EPC (AHRQ) procedures to summarize all included studies in narrative form and in summary tables that tabulate the important features of the study

populations, design, intervention, outcomes, setting (including geographic location), and results. Apart from documenting basic study characteristics, we will include findings only from studies of low, medium, or unclear risk of bias in our main report, which we will synthesize either qualitatively or quantitatively (insofar as possible).

Findings from studies determined to be of high risk of bias will appear in the evidence tables in the appendix. If feasible, we may do qualitative or quantitative sensitivity analyses to gauge the difference in conclusions stemming from including and excluding studies considered high risk of bias.

If we find three or more studies for a comparison of an outcome of interest, we will consider pooling our findings by using quantitative analysis (i.e., meta-analysis) of the data from those studies. We will also consider conducting network meta-analysis using Bayesian methods to compare the interventions with each other if we identify at least three studies that tested the same intervention with a common comparator. For all analyses, we will use random effects models to estimate pooled or comparative effects; unlike a fixed-effects model, this approach allows for the likelihood that the true population effect may vary from study to study. To determine whether quantitative analyses are appropriate, we will assess the clinical and methodological heterogeneity of the studies under consideration following established guidance.

Systematic Review: Grading the Strength of Evidence

For KQ 3, we will grade the strength of evidence (SOE) based on the guidance established for the EPC Program.⁴² Developed to grade the overall strength of a body of evidence, this approach incorporates five key domains: risk of bias (includes study design and aggregate quality), consistency, directness, precision of the evidence, and reporting bias. It also considers other optional domains that may be relevant for some scenarios, such as a dose-response association, plausible confounding that would decrease the observed effect, and strength of association (magnitude of effect).

Table 3 describes the grades of evidence that can be assigned. Grades reflect the strength of the body of evidence to answer KQs on the effectiveness and harms of the interventions included in this review. Two reviewers will assess each domain for each key outcome; they will resolve any differences by consensus discussion. If the volume of evidence is large, we may focus the SOE grading on outcomes of substantial importance to decisionmakers and those commonly reported in the literature.

Table 3. Definitions of the grades of overall strength of evidence⁴²

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.

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*.⁴³ We expect to be able to do this for all three KQs.

For individual studies, we will examine conditions that may limit applicability based on the PICOTS structure. The assessment of applicability is integral to a realist review through its consideration of context within CMO configurations. We will present when patterns across studies either were not tested or do not appear to operate similarly in particular settings.

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VI. Definition of Terms

This section is not applicable.

VII. Summary of Protocol Amendments

If we need to amend this protocol, we will give the date of each amendment, describe the change and give the rationale in this section. Changes will not be incorporated into the protocol. Table 4 below illustrates the approach.

Table 4. Table of changes to 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 protocol.	Justify why the change will improve the report. If necessary, describe why the change does not introduce bias. Do not use justification as “because the AE/TOO/TEP/Peer reviewer told us to” but explain what the change hopes to accomplish.

AE = associate editor; TEP = Technical Expert Panel; TOO = task order officer

VIII. Review of Key Questions

AHRQ posted the KQs on the AHRQ Effective Health Care Website for public comment. The EPC refined and finalized the KQs after reviewing public comments and obtaining input from KIs and the TEP. This input is intended to ensure that the KQs are specific and relevant.

IX. Key Informants

KIs are the end users of research. They can include patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, health care systems, payers, and others with experience in making health care decisions. Within the EPC program, the KI role is to provide advice about identifying the KQs for research that will inform health care decisions. The EPC solicits input from KIs when developing questions for systematic review or when identifying high-priority research gaps and needed new research.

KIs are not involved in analyzing the evidence or writing the report; they also have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism.

KIs must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Because of their role as end users, individuals are invited to serve as KIs and those who present with potential conflicts may be retained. The AHRQ Task Order Officer (TOO) and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts constitute a multidisciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes and identify studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, study questions, design, and 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 suggest approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor do they contribute to the writing of the report. They 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 \$5,000 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 AHRQ 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 all peer review comments on the draft report in preparing the final report. Peer Reviewers do not participate in writing or editing the final report or other products. The final report does not necessarily represent the views of individual reviewers. The EPC will complete a disposition of all peer review comments. The disposition of comments for systematic reviews and technical briefs will be published 3 months after the publication of the evidence report.

Potential Peer Reviewers must disclose any financial conflicts of interest greater than \$5,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than \$5,000. 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. Related financial conflicts of interest that cumulatively total greater than \$1,000 will usually disqualify EPC core team investigators.

XIII. Role of the Funder

This project was funded under Contract No. HHS290201500011I from AHRQ, U.S. Department of Health and Human Services. The AHRQ TOO 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 AHRQ or the U.S. Department of Health and Human Services.

XIV. Registration

This protocol will be registered in the international prospective register of systematic reviews (PROSPERO).

Appendix A

Search	Query	Items Found
#1	Search (((("high utilizer" OR "high utilizers of health care" OR "high utilizing" OR "super utilizers" OR "super utilizing" OR "frequent utilization" OR "frequent utilisation" OR "frequent utilizers" OR "heavy utilization" OR "heavy utilizers" OR "high attenders" OR "repeat users" OR "hyperusers" OR "revolving door patients" OR "hyperutilization" OR "overutilization" OR "recidivism")) OR "frequent users") OR "frequent user" OR "medically complex" OR "high need" Sort by: Best Match	3460
#2	Search (((("Multiple Chronic Conditions"[Mesh]) OR "Comorbidity"[Mesh]) OR "multimorbidity" [MeSH] Sort by: Best Match	100740
#3	Search (((((((((((("Diabetes Mellitus"[Mesh]) OR "Heart Failure"[Mesh]) OR "Cardiovascular Diseases"[Mesh]) OR "Hypertension"[Mesh]) OR "Pulmonary Disease, Chronic Obstructive"[Mesh]) OR "Asthma"[Mesh]) OR "Chronic Pain"[Mesh]) OR "Headache"[Mesh]) OR "Anterior Wall Myocardial Infarction"[Mesh]) OR "Kidney Failure, Chronic"[Mesh]) OR "Dementia"[Mesh]) OR "Alzheimer Disease"[Mesh]) OR "Lung Diseases, Obstructive"[Mesh]) OR "Stroke"[Mesh]) OR "Arrhythmias, Cardiac"[Mesh]))) OR "chronic gastrointestinal disorder") OR "Coronary Disease"[Mesh] Sort by: Best Match	3003277
#4	Search (("Disabled Persons"[Mesh]) OR "Frail Elderly"[Mesh]) OR "Mobility Limitation"[Mesh] Sort by: Best Match	75328
#5	Search (("health risk behaviors") OR ("Behavioral Symptoms"[Mesh]) OR "Substance-Related Disorders"[Mesh]) OR "Depression"[Mesh]) OR "Anxiety"[Mesh]) OR "Cognitive Dysfunction"[Mesh])) OR (("serious mental illness") OR "chronic toxic stress") Sort by: Best Match	654519
#8	Search ("Homeless Persons"[Mesh]) OR (((((((("Social Determinants of Health"[Mesh]) OR "Social Isolation"[Mesh]) OR "Poverty"[Mesh]) OR "Educational Status"[Mesh]) OR "Literacy"[Mesh]) OR "Intimate Partner Violence"[Mesh]) OR "Medically Uninsured"[Mesh])) OR (((("food insecurity") OR "housing instability") OR "unemployed") OR "physical safety") OR "community deprivation") OR "adverse childhood experiences")) Sort by: Best Match	138695
#9	Search (#2 OR #4 OR #5 OR #8) Sort by: Best Match	918962
#10	Search (#3 AND #9) Sort by: Best Match	105820
#11	Search (#3 AND #9) Sort by: Best Match Filters: Humans	103615
#12	Search (#3 AND #9) Sort by: Best Match Filters: Humans; Adult: 19+ years	75716
#13	Search (#3 AND #9) Sort by: Best Match Filters: Humans; English; Adult: 19+ years	67531
#14	Search (#3 AND #9) Sort by: Best Match Filters: Publication date from 2000/01/01; Humans; English; Adult: 19+ years	55068
#16	Search (((((((((((("Patient-Centered Care"[Mesh]) OR "Disease Management"[Mesh])) OR (((("health home") OR "Accountable Care Organizations"[Mesh]) OR "Managed Care Programs"[Mesh])) OR ("Community Health Workers"[Mesh]) OR "Case Management"[Mesh]) OR "care coordination") OR "patient care management")))) OR (((((((("hotspotting") OR "patient navigation"[MeSH Terms]) OR "care management") OR "multidisciplinary team care") OR "integrated behavioral health") OR "diversion strategies") OR "self management support") OR "health coaching") OR "transition care") OR "enhanced primary care") OR "interdisciplinary care")) OR "patient navigation")) OR (((((((("House Calls"[Mesh]) OR "Text Messaging"[Mesh] OR "home visit") OR "pharmacy care management") OR "caregiver support")) OR "medicaid management") OR "care management") OR "medication assistance") OR "home care") OR "transitional care")) OR "warm handoff") OR "diversion team") Sort by: Best Match	207066
#17	Search (#14 AND #16) Sort by: Best Match	1686
#18	Search (#17 OR #1) Sort by: Best Match	5143
#19	Search (#17 OR #1) Sort by: Best Match Filters: English	4987

Search	Query	Items Found
<u>#20</u>	Search (#17 OR #1) Sort by: Best Match Filters: English; Adult: 19+ years	<u>3229</u>
<u>#21</u>	Search (#17 OR #1) Sort by: Best Match Filters: Humans; English; Adult: 19+ years	<u>3229</u>
<u>#22</u>	Search (#17 OR #1) Sort by: Best Match Filters: Publication date from 2000/01/01; Humans; English; Adult: 19+ years	<u>3009</u>