I. Background and Objectives for the Systematic Review

Definition of Nephrolithiasis

Nephrolithiasis, or kidney stone disease, is a condition in which individuals form calculi (stones) within the renal pelvis and tubular lumens. Stones form from crystals that precipitate (separate) out of the urine. Stone formation may occur when the urinary concentration of crystal-forming substances (calcium, oxalate, uric acid) is high and/or that of substances that inhibit stone formation (citrate) is low.

Epidemiology of Nephrolithiasis

Although nephrolithiasis may occur at any age, onset is more common in young and middle-aged adults. Lifetime prevalence is estimated at 13 percent for men and 7 percent for women. Following an initial stone event, the spontaneous 5-year recurrence rate is 35 to 50 percent. Medical conditions that increase the risk of nephrolithiasis include primary hyperparathyroidism, obesity, diabetes, and gout. In large observational studies, dietary factors associated with increased risk of nephrolithiasis include low fluid intake and low dietary calcium. However, evidence is mixed for diets with increased animal protein, low dietary magnesium, low dietary potassium, and increased sodium. With respect to fluid intake, different beverage types appear to have different impacts on the risk of nephrolithiasis.

Approximately 80 percent of adults with nephrolithiasis have stones comprised predominately of calcium oxalate and/or calcium phosphate. By comparison, struvite stones and uric acid stones each account for 5 to 10 percent of stones, and cystine stones are rare. The most common biochemical abnormality identified in patients with nephrolithiasis is hypercalciuria; other abnormalities may include hypercalcemia, hyperuricemia, hyperuricosuria, hyperoxaluria, hypernatriuria, and hypocitraturia.

Clinical Presentation of Nephrolithiasis

Nephrolithiasis often is incidentally identified in asymptomatic patients who undergo plain radiographs or computed tomographic imaging for another indication. Small stones generally pass through the urinary tract without symptoms. While larger stones may cause symptoms, more than 90 percent of stones ≤5 mm in diameter still pass through the urinary tract without intervention, as compared to spontaneous passage of approximately 50 percent of stones 5 to 10 mm in diameter. Potential symptoms of nephrolithiasis include: urinary symptoms such as dysuria, hematuria, and urgency; renal colic with severe abdominal and flank pain; nausea and vomiting; urinary tract obstruction; infection; and acute, though generally transient, impairment in renal function. Large struvite stones remain in the renal pelvis and may not cause pain. Some
studies have suggested that nephrolithiasis also may increase the risk of chronic kidney disease.\textsuperscript{17,18} Nephrolithiasis also may lead to hospitalizations and procedure-related morbidity. Direct medical expenditures for nephrolithiasis in the United States have been estimated at $2.1 billion annually.\textsuperscript{1}

**Laboratory Evaluation of Nephrolithiasis**

Clinical guidelines recommend laboratory evaluation of patients who experience a kidney stone. Testing may include an analysis of stone composition and biochemical evaluations of blood (e.g., calcium, albumin, creatinine, uric acid, potassium, bicarbonate) and urine (e.g., pH, volume, calcium, creatinine, uric acid, oxalate, citrate, sodium).\textsuperscript{19} Clinicians may use these results initially to guide treatment selection or later as a marker of treatment adherence or effectiveness. However, the value of baseline and followup laboratory evaluations in patients with nephrolithiasis are unclear. Controversies include whether pretreatment laboratory test results predict effectiveness of treatment on final health outcomes; whether treatment tailored to pretreatment laboratory results is associated with better final health outcomes than empiric therapy; and whether followup biochemical test results are valid surrogates for predicting the effectiveness of treatment on final health outcomes. Current practice varies in the use of both initial and followup biochemical testing, particularly in patients who present with a stone for the first time.

**Prevention of Recurrent Stone Disease**

Many randomized controlled trials (RCTs) have studied dietary or pharmacological interventions to reduce risk of recurrent nephrolithiasis. And, although recommendations to modify different dietary components and to consider selected pharmacological therapy have been included as part of large clinical guidelines on the management of nephrolithiasis,\textsuperscript{19,20} these guidelines have referenced few of these RCTs.

**Dietary therapy for prevention of recurrent stone disease**

Dietary interventions are designed primarily to alter the concentration of one or more crystal-forming and/or crystal-inhibiting substances in the urine. Increasing water intake should increase urine volume and lower the urinary concentration of all crystal-forming substances. More narrowly targeted dietary interventions include: reducing dietary oxalate to lower urinary oxalate and the risk of calcium oxalate stones; reducing dietary animal protein and other purines to lower urinary uric acid and the risk of uric acid stones; and increasing dietary calcium to bind intestinal oxalate and thereby lower urinary oxalate and the risk of calcium oxalate stones. Though some patient demographic characteristics and comorbidities predict recurrent stone outcomes, little is understood about the impact these factors have on the relative effectiveness of treatments. And, while patient metabolic and stone characteristics sometimes are used to justify tailored dietary interventions, their impact on treatment outcomes also is not well understood.

**Pharmacological therapy for prevention of recurrent stone disease**
Previous systematic reviews of RCTs of pharmacological therapies have reported that although thiazide diuretics\textsuperscript{22-24} and citrate therapy\textsuperscript{24,25} reduce stone recurrence, evidence was insufficient for the efficacy of other pharmacological treatments.\textsuperscript{22,24,26,27} However, these reviews did not include numerous, more recent RCTs. In addition, these reviews did not evaluate evidence that compared different pharmacological treatments with each other or that compared combinations of pharmacological treatments versus monotherapy, and did not account for baseline fluid and diet intake or fluid and dietary cointerventions. Previous reviews also left unresolved the potential impact of patient demographics, comorbidities, biochemical measures, and stone characteristics on pharmacological treatment outcomes.

**Purpose of Proposed Comparative Effectiveness Review**

There is significant variation in current medical practice regarding management to prevent recurrent nephrolithiasis. Clinical uncertainty exists regarding the effectiveness, comparative effectiveness, and adverse effects of different dietary and pharmacological preventive treatments; the value of urine and blood biochemical measures for initiating and/or modifying treatment; and the potential impact of patient and stone characteristics on important treatment outcomes. Where data allow, the proposed systematic review and meta-analysis will comprehensively address all these questions. Our findings should inform providers and patients making treatment decisions, organizations developing clinical guidelines, and policymakers making coverage decisions. Results also should effectively define the limitations of existing evidence and the parameters of any future RCTs or other research studies needed to address remaining evidence gaps.

**II. The Key Questions**

The draft Key Questions (KQs) were posted for public comment on the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program Web site. The public input affirmed the relevance of this topic, though it did not result in changes in the topic scope or the proposed KQs. Based on internal discussions and input from the Technical Expert Panel (TEP), additional therapeutic interventions were added. In addition, questions were added to address whether the efficacy of therapies differs according to baseline biochemical measures and whether the efficacy of therapies as measured by stone outcomes correlates with followup biochemical measures.

**Question 1**

In adults with a history of nephrolithiasis, do results of baseline stone composition and blood and urine chemistries predict the effectiveness of diet and/or pharmacological treatment on final health outcomes and intermediate stone outcomes, and reduce treatment adverse effects?

a. Do effectiveness and adverse effects of treatment differ according to patient baseline stone composition and blood and urine biochemical measures?

b. Does treatment tailored to the results of baseline stone composition and blood and urine chemistries improve final health outcomes and intermediate stone outcomes and reduce adverse effects when compared to empiric treatment?
Question 2

In adults with a history of nephrolithiasis, what is the effectiveness and comparative effectiveness of different dietary therapies on final health outcomes and intermediate stone outcomes?

   a. Does effectiveness of diet therapy differ according to patient baseline demographic and comorbid characteristics?
   b. Does effectiveness of diet therapy differ according to patient baseline diet and fluid intake?
   c. Does effectiveness of diet therapy differ according to characteristics of stone history?

Question 3

In adults with a history of nephrolithiasis, what is the evidence that dietary therapies used to reduce the risk of recurrent stone episodes are associated with adverse effects?

   a. Does the risk of adverse effects differ according to patient baseline demographic and comorbid characteristics?
   b. Does the risk of adverse effects differ according to patient baseline diet and fluid intake?
   c. Does the risk of adverse effects differ according to characteristics of stone history?

Question 4

In adults with a history of nephrolithiasis, what is the effectiveness and comparative effectiveness of different pharmacological therapies on final health outcomes and intermediate stone outcomes?

   a. Does effectiveness differ according to patient baseline demographic and comorbid characteristics?
   b. Does effectiveness differ according to patient baseline diet and fluid intake?
   c. Does effectiveness differ according to characteristics of stone history?

Question 5

In adults with a history of nephrolithiasis, what is the evidence that pharmacological therapies to reduce the risk of recurrent stone episodes are associated with adverse effects?

   a. Does the risk of adverse effects differ according to patient demographic and comorbid characteristics?
   b. Does the risk of adverse effects differ according to patient baseline diet and fluid intake?
   c. Does the risk of adverse effects differ according to characteristics of stone history?
Question 6

In adults with a history of nephrolithiasis being treated to prevent stone recurrence, do results of followup blood and urine biochemistry measures predict final health outcomes and intermediate stone outcomes?

a. Does prediction of final health outcomes and intermediate stone outcomes differ according to the frequency or duration of followup biochemistry measurements?

PICOTS Criteria

- **Population(s):**
  - Inclusion: Adults (age 18 years and older) with a history of nephrolithiasis.
  - Exclusion: 1) Patients with ongoing acute renal colic, 2) patients undergoing treatment to assist in stone passage, or 3) patients who underwent lithotripsy less than 90 days earlier and have not been documented to be stone free by high-resolution imaging (e.g., a computerized tomography scan).

- **Interventions:**
  - KQ 1:
    - For the subquestion about whether treatment effectiveness differs according to patient baseline laboratory results: Dietary or pharmacological therapy (see KQs 2 and 3 for dietary therapies and KQs 4 and 5 for pharmacological therapies).
    - For the subquestion about comparing tailored and empiric treatment: Baseline evaluation of stone composition and blood and urine biochemistry followed by tailored dietary or pharmacological therapy (see KQs 2 and 3 for dietary therapies and KQs 4 and 5 for pharmacological therapies).

  - KQs 2 and 3: Dietary therapy
    - Specific individual or combined diet changes (e.g., intake of fluids, calcium, animal protein, sodium, fruit and fiber, purine, oxalate, potassium, soft drinks, citrus, multicomponent diets, others).
    - Empiric dietary instructions.
    - Dietary instructions directed by patient demographics, comorbid conditions, baseline diet, baseline urine or blood biochemical testing, and/or by stone type.

  - KQs 4 and 5: Pharmacological therapy (see Table 1)
    - Trials of individual pharmacological agents will be included in the review if they currently are available in the United States for prescription as monotherapy or combination therapy. In addition, trials of over-the-counter medications and
supplements will be included. Both trials with and without a dietary cointervention will be eligible.

- KQ 6: Not applicable.

<table>
<thead>
<tr>
<th>Table 1. Pharmacological therapy*</th>
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<tr>
<td><strong>Class</strong></td>
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<td>Thiazide diuretic</td>
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<td>Heavy metal chelator</td>
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<td>Dietary supplements</td>
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<tr>
<td>Combination pharmacologic therapy, others (e.g., Oxalobacter formigenes)</td>
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*Treatments not approved or available in the United States will be considered beyond the scope of this review (e.g., thiazide diuretics: bendroflumethazide, trichlorothiazide, polythiazide; magnesium supplements: magnesium aspartate hydrochloride; phosphate supplements: orthophosphate, potassium acid phosphate, sodium cellulose phosphate).*

Abbreviations: ACE = angiotensin-converting enzyme; FDA = U.S. Food and Drug Administration; NA = not applicable.

- **Comparators:**
  - **KQ 1:**
    - For the subquestion about whether treatment effectiveness differs according to patient baseline laboratory results: No treatment, usual care, placebo, dietary therapy, pharmacological therapy, combination pharmacological therapy, or a combination diet plus pharmacological therapy.
    - For the subquestion about comparing tailored and empiric treatment: Empiric dietary, pharmacological, or combination therapy.
  - **KQs 2 and 3:**
– No treatment, usual care, placebo, other dietary therapy, pharmacological therapy, or combination pharmacological therapy.

  o KQs 4 and 5:

   – No treatment, usual care, placebo, dietary therapy, other pharmacological therapy, other combination pharmacological therapy, or other combination diet plus pharmacological therapy.

  o KQ 6:

   – Not applicable.

**Outcomes:**

  o KQs 1, 2, 4 and 6:

   – Final health outcomes

   ▪ Symptomatic stone recurrence
   ▪ Pain
   ▪ Urinary tract obstruction with acute renal failure
   ▪ Infection
   ▪ Procedure-related morbidity
   ▪ Emergency room visits, hospitalizations (e.g., for renal colic, acute renal failure)
   ▪ Quality of life (general, urologic)
   ▪ End-stage renal disease

   – Intermediate stone outcomes

   ▪ Radiographically detected stone recurrence
   ▪ Change in stone size

  o KQs 3 and 5:

   – Adverse effects (e.g., nausea, diarrhea, hypokalemia, weight change, hyperlipidemia, hyperglycemia)
   – Treatment adherence (e.g., self-report questionnaire, pill count)

**Timing**

  o Final health outcomes and intermediate outcomes: Minimum of 12 months for followup
  o Adverse effects: Minimum of 3 months for followup
III. Analytical Framework

Figure 1. Analytic Framework: Recurrent Nephrolithiasis in Adults: A Comparative Effectiveness Review of Preventive Medical Strategies

Abbreviations: KQ = key question.

IV. Methods

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

Individual studies meeting the PICOTS criteria described above will be included. The rationale for the minimum of 1-year followup for treatment efficacy is that we believe a shorter duration is unlikely to be sufficient time for treatments to impact recurrent stone outcomes, and shorter trials are more likely to focus on treatments to assist in stone expulsion. The rationale for excluding participants who underwent lithotripsy less than 90 days earlier and are not documented to be stone free is that stone passage could reflect passage of residual stone.
fragments related to the procedure rather than the effect of secondary preventive therapy. For the KQs related to effectiveness, we will limit eligibility to RCTs meeting the PICOTS criteria and published in full text and in English language. RCTs as short as 3 months in duration may be considered to address the KQs related to the adverse effects of the various treatments (but not for efficacy outcomes). The rationale for the shorter required duration for studies reporting adverse effects is that many adverse treatment effects may manifest in less than 1 year. If evidence from these trials is still considered insufficient to evaluate adverse effects, we may consider for adverse effects data (but not for efficacy outcomes) the inclusion of RCTs that did not report final health outcomes or intermediate stone outcomes but only reported blood or urine biochemical outcome measures. Limiting included trials to those published in English is not ideal. However, previous research has documented little bias in systematic reviews limiting trials of medical treatments to those published in English.28

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

We will identify evidence for this review by searching relevant bibliographic databases, as well as several sources commonly used to identify grey literature. Bibliographic database searching will utilize MEDLINE and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify RCTs published in 1948 to the present (see below). Initially, the search strategy will identify studies indexed with the MeSH term urolithiasis and related keywords. Results from this initial search will be limited to relevant publication types or keywords to identify controlled trials, RCTs, systematic reviews, and meta-analyses. Bibliographic database searches will be supplemented with hand searching of the reference lists of included studies, previous systematic reviews, and relevant clinical guidelines. Additional search strategies may include forward citation searching of included RCTs and systematic reviews by using the Web of Science and Google Scholar. The literature search will be updated while the draft report is under public and peer review.

Grey literature searching may include searches of regulatory data, trial registries, and abstracts and conference proceedings.29 We will also review industry scientific information packets for products relevant to the prevention of recurrent nephrolithiasis. These materials may include regulatory documents and reports of conducted trials. Additionally, we will search ClinicalTrials.gov and the International Controlled Trials Registry Platform to identify relevant registered and completed trials. These sources will be used to identify trials not previously identified. Published and registered trials will be compared to assess potential outcomes-reporting bias. Trials registered but not published will be evaluated qualitatively to comment on the potential publication bias relevant to this topic.

The search strategies we will use are outlined below:

- Ovid MEDLINE Search Strategy

1. urolith*.mp. or exp Urolithiasis/
2. (urinary calcul* or kidney calcul* or ureteral calcul* or renal calcul* or kidney stone*).mp.
3. renal colic.mp. or exp Renal Colic/
4. hypercalciuria.mp. or exp Hypercalciuria/

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5 exp Hyperoxaluria, Primary/ or exp Hyperoxaluria/ or hyperoxaluria.mp.
6 hyperuricemia.mp. or exp Hyperuricemia/
7 cystinuria.mp. or exp Cystinuria/
8 (hyperuricosuria or hypercitraturia or nephrolith*).mp.
9 (calcium stone* or calcium phosphate stone* or calcium oxalate stone* or uric acid stone* or urate stone* or cystine stone* or struvite stone*).mp.
10 or/1-9
11 limit 10 to (controlled clinical trial or meta analysis or randomized controlled trial)
12 limit 10 to systematic reviews
13 11 or 12
14 exp meta-analysis/
15 exp randomized controlled trials/ or systematic review.mp.
16 exp controlled clinical trial/
17 or/14-16
18 10 and 17
19 13 or 18
20 limit 19 to English language

• Cochrane Central Register of Controlled Trials (CENTRAL) Search Strategy

1 (urolith$ or urolithiasis):ti,ab,kw in Clinical Trials
2 urinary calcul* or kidney calcul* or ureteral calcul* or renal calcul* or kidney stone* in Clinical Trials
3 renal colic in Clinical Trials
4 hypercalciuria in Clinical Trials
5 hyperoxaluria in Clinical Trials
6 hyperuricemia in Clinical Trials
7 cystinuria in Clinical Trials
8 hyperuricosuria or hypercitraturia or nephrolith* in Clinical Trials
9 calcium stone* or calcium phosphate stone* or calcium oxalate stone* or uric acid stone* or urate stone* or cystine stone* or struvite stone* in Clinical Trials
10 urolith* or Urolithiasis in Clinical Trials
11 (1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10)

C. Data Abstraction and Data Management

Screening of studies identified in literature searches will occur in two stages. First, search results will be preliminarily triaged. Titles and abstracts will be reviewed by two independent investigators and marked “include,” “exclude,” or “full text needed” if a determination cannot be made based on available information. Differences in triage decisions between the two investigators will be resolved by group discussion. The full text of articles identified for potential inclusion during the initial triage will be obtained. These studies will be distributed among investigators for secondary screening and data extraction. Full text will be evaluated by two investigators to ensure that the study meets the inclusion criteria. These two investigators will act as the primary and secondary abstractor/evaluators for their assigned studies. We will document the inclusion and exclusion status and the reason for exclusion in the project library of citations.

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Data fields to be extracted will be determined for each KQ. Data elements likely will include: author; year of publication; subject inclusion and exclusion criteria; intervention and control regimens; followup duration; participant baseline demographics, comorbidities, urine and blood test results, and stone characteristics; followup urine and blood test results; and event rates for final health outcomes, intermediate outcomes, adverse events, and adherence. The primary abstractor/evaluator will extract relevant data from studies that meet the inclusion criteria onto pretested extraction forms and, where possible, to evidence tables. Extraction forms and evidence tables will be reviewed and verified for accuracy by the secondary abstractor/evaluator.

D. Assessment of Methodological Quality of Individual Studies

The primary and secondary abstractors/evaluators will independently review each study included in the review. Study quality for the individual RCTs included in the systematic review will be evaluated by using criteria based on the domains recommended by the Cochrane Collaboration. These criteria include an assessment of the risk of bias within each study by specifically evaluating: 1) adequacy of allocation concealment, based on the approach developed by Schulz and Grimes; 2) blinding methods (participant, investigator, and/or outcome assessor); 3) data completeness (inclusion of all randomized participants in outcomes analyses, i.e., intention-to-treat); and 4) whether reasons for dropouts/attrition were reported (to judge whether those reasons could possibly be related to outcomes and were balanced between treatment groups). Studies will be assigned individual ratings of good, fair, or poor. A rating of good generally indicates that the trial reported adequate allocation concealment, blinding, analysis by intention-to-treat, and that reasons for dropouts/attrition were reported. Studies will be rated as poor if the method of allocation concealment was inadequate or not defined, blinding was not defined, analysis by intention-to-treat was not utilized, and reasons for dropouts/attrition were not reported and/or there was a high rate of attrition. The quality of RCTs and observational cohort studies reporting adverse events will be evaluated by using a subset of questions from the McHarm Scale. Discrepancies between the ratings of the primary and secondary abstractors/evaluators will be reconciled by consultation. When agreement cannot be reached during consultation, group discussion will be used to reconcile quality ratings. The ratings may be used to conduct sensitivity analysis of results, such as by including and excluding studies with an overall poor rating to assess the influence of poor studies on the results of the systematic review.

E. Data Synthesis

We plan to qualitatively synthesize the data obtained from included studies and abstracted into evidence tables. These data will be summarized in evidence summary tables relevant to the KQs. Assuming minimal clinical heterogeneity of patient populations, interventions, and outcomes, we then will perform a quantitative meta-analysis of all the main interventions and primary outcomes. Data will be analyzed by using Review Manager (RevMan) version 5.0 software. Random effects models will be used to generate pooled estimates of relative risks and 95 percent confidence intervals. Statistical heterogeneity will be summarized by using the $I^2$ statistic (50 percent indicates moderate heterogeneity and 75 percent or greater indicates high heterogeneity).

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For analyses of pharmacological treatments, results will be presented for each pharmacological class as a whole and separately for individual agents. For all treatments, subgroup analyses that will be performed if feasible include evaluation of treatment efficacy and adverse events according to: patient demographic and comorbid characteristics (age, gender, race, baseline chronic kidney disease, obesity, pregnancy, solitary kidney, urinary tract anatomic abnormality, past bariatric surgery, history of renal transplant, or other comorbid conditions [e.g., cardiovascular disease, diabetes, gout, hypertension, heart failure]); baseline diet characteristics (intake of fluids, calcium, animal protein, sodium, fruit and fiber, purine, oxalate, potassium, soft drinks); baseline stone characteristics (stone composition, frequency of past stone episodes, severity of past stone episodes, past shock-wave lithotripsy, or presence of residual stones/fragments); baseline biochemical measures from blood (uric acid, calcium, albumin, creatinine, potassium, bicarbonate) or urine (pH, volume, uric acid, oxalate, calcium, citrate, creatinine, sodium); study duration; patient treatment adherence; and followup blood and urine biochemical measures.

F. Grading the Evidence for Each Key Question

The overall strength of evidence for the RCTs will be evaluated by using methods developed by the AHRQ’s Evidence-based Practice Center Program as outlined in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews. For each of several important clinical outcomes within each comparison evaluated, the strength of the evidence will be evaluated based on four required domains: 1) risk of bias (internal validity); 2) consistency (similarity of effect sizes of included studies); 3) directness (single, direct link between intervention and outcome); and 4) precision (degree of certainty surrounding an effect estimate). The risk of bias—based on study design and conduct—will be rated low, medium, or high. Consistency will be rated as consistent, inconsistent, or unknown/not applicable (e.g., a single study). Directness will be rated as either direct or indirect, and precision will be rated as either precise or imprecise. A precise estimate is one that would yield a clinically meaningful conclusion. Other factors that may be considered in assessing strength of evidence include the dose-response relationship, the presence of confounders, the strength of association, and publication bias. Based on these factors, the overall evidence will be rated as:

1. **High**: High confidence that the evidence reflects the true effect; further research is very unlikely to change confidence in the estimate of effect.
2. **Moderate**: Moderate confidence that the evidence reflects the true effect; further research may change confidence in the estimate of effect and may change the estimate.
3. **Low**: Low confidence that the evidence reflects the true effect; further research is likely to change confidence in the estimate of effect and is likely to change the estimate.
4. **Insufficient**: Evidence either is unavailable or does not permit a conclusion.

An overall rating of high strength of evidence would imply that the included studies were RCTs with a low risk of bias and with consistent, direct, and precise domains.

G. Assessing Applicability
Applicability of studies will be determined according to the PICOTS format. While some conditions that affect applicability of studies are used as exclusion criteria in study selection (i.e., short followup times), others may only be identified through a detailed review of the studies. Specific study characteristics that may affect applicability will be noted by the study abstractors/evaluators in evidence tables. These characteristics may include, but are not limited to: non-U.S. settings; specialty clinic versus primary care settings; narrow eligibility criteria; stone recurrence rates different from those described by population studies of nephrolithiasis; and drugs or dosages not typically used in current practice.\textsuperscript{36}

V. References


Source: www.effectivehealthcare.ahrq.gov
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VI. Definition of Terms

Hypercalciuria: Elevated level of calcium in the urine.
Hypercalcemia: Elevated level of calcium in the blood.
Hyperuricemia: Elevated level of uric acid in the blood.
Hyperuricosuria: Elevated level of uric acid in the urine.
Hyperoxaluria: Elevated level of oxalate in the urine.
Hypermnatriuria: Elevated level of sodium in the urine.
Hypocitraturia: Low level of citrate in the urine.

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.

VIII. Review of Key Questions

Key questions were reviewed and refined as needed with input from Key Informants. In addition, the key questions were posted for public comment and finalized by the EPC after review of the public comments.

IX. Key Informants

Key Informants were selected to provide input to the EPC in development of key research questions that will inform healthcare decisions, as well as in identifying high priority research gaps. Key Informants are the end users of research, including patients, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Key Informants will not be involved in analyzing the evidence or writing the report and will have the opportunity to review and comment on the draft report only through the public review mechanism.

Key Informants must have disclosed any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. The Task Order Officer and
the EPC worked together to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

A Technical Expert Panel (TEP) will be selected to provide input on the Evidence Report. The TEP will be comprised of a multidisciplinary group of clinical, content, and methodological experts who will provide input in defining relevant study populations, interventions, comparisons, or outcomes, in refining the literature search strategy, and identifying particular studies or databases to search. The TEP also will recommend approaches to specific issues as requested by the EPC. Study questions, design and/or methodological approaches will not necessarily represent the views of individual TEP members. TEP members will not perform analysis of any kind, or contribute to the writing of the report. They may review and comment on the draft report only through the 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. The Task Order Officer and the EPC will work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers will be invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Their written comments will be considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report. 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 will be documented and published three 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.