Evidence-based Practice Center Systematic Review Protocol

Project Title:
Lower Limb Prosthesis

Initial publication date if applicable: March 1, 2017

Amendment Date(s) if applicable:

(Amendments Details–see Section VII)

I. Background and Objectives for the Systematic Review

An estimated 1.9 million people in the U.S. are living with limb loss, a number expected to double by 2050 mostly due to the rising prevalence of diabetes.[1,2] The management of lower limb amputees with respect to lower limb prostheses (LLPs) is a complicated problem. LLP candidates are a heterogeneous group with distinct needs dependent upon age, etiology of limb loss, level of amputation, comorbidities and health status, postoperative stage, and rehabilitation status. Many LLP options exist, comprising numerous permutations of components, the anatomy they replace, their sophistication, and other attributes, including those pertaining to cosmesis and comfort. In addition, patients may require multiple LLPs (initial, preparatory, definitive, or replacement prosthetics). Compared to the general population, LLP patients exhibit lower overall physical and emotional health (e.g., increased risk for cardiovascular disease,[3] anxiety, and depression[4]) and higher mortality (estimated 5-year mortality rates for amputees range between 50%[5] and 74%[6]; estimated 1-year mortality is 36% for amputees >65 years old[7]).

The current standard approach for matching patients to prostheses relies heavily on performance-based assessments, self-assessments, and wearable monitoring technologies that record patient activity;[8] although in practice prosthetists often rely on clinical judgment to match patients to prostheses. Numerous outcome measurement tools (OMTs) exist to assess the patient functional status, but no consensus "gold standard" assessment schema exists. One review in 2006 of LLP OMTs found that many measures exist (n=19), but few were used by more than one author (n=6).[9] Other reviews, including more recent ones, summarize between 9 and 17 tools that have been validated for or that are recommended for use with lower limb amputees.[10-13] The most recent of these reviews organized 17 outcome instruments used for adult lower limb amputees by construct measured (activity, quality of life, and patient satisfaction).[13] Many of these tools are not specific to amputees, but were designed for the general or other populations (e.g., elderly mobility impaired). Similarly, numerous instruments (or techniques) are used to assess current amputee function or status and tools have been developed to predict future outcomes, including successful use of LLPs. Constructs of reliability (e.g., test-retest, interrater, internal consistency) or validity (e.g., face, content, construct, criterion) of existing OMTs, assessment techniques, and prediction tools have been evaluated in the amputee population for the most frequently used measures.[9] However, it is unclear to what degree studies with functional and patient-centered outcomes use validated instruments and outcomes. It is also unclear whether the population of

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amputees included in validation (etc.) studies is generalizable to the population of participants in studies of LLP components and, in turn, whether these study populations are applicable to the more general population of users of LLPs.

LLPs replace the functionality of a missing limb to as great a degree as possible. Medicare covers custom fabricated LLPs in accordance with the Local Coverage Determination (LCD) for Lower Limb Prostheses. As for all items to be covered by Medicare, it must: 1) be eligible for a defined Medicare benefit category, 2) be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member, and 3) meet all other applicable Medicare statutory and regulatory requirements. A LLP is covered when the beneficiary: 1) will reach or maintain a defined functional state within a reasonable period of time; and 2) is motivated to ambulate. Potential functional ability is based on the reasonable expectations of the prosthetist and treating physician, considering factors including, but not limited to, the beneficiary's past medical history, the beneficiary's current overall health condition including the status of the residual limb and the nature of other medical problems. Some prosthetic components are limited to beneficiaries with a functional ability at or above a certain level.

As indicated by Medicare coverage guidance,[14] clinical assessments of beneficiary rehabilitation potential must be based on the classification levels listed in Table 1.

Table 1: Lower limb prosthesis function levels, per CMS (K levels)[14]

Level 0:	This patient does not have the ability or potential to ambulate or transfer safely with or without assistance and a prosthesis does not enhance their quality of life or mobility. Foot/Ankle assemblies not eligible for prosthesis. Knee units not eligible for prosthesis.
Level 1:	Has the ability or potential to use a prosthesis for transfers or ambulation on level surfaces at fixed cadence. Typical of the limited and unlimited household ambulator. Foot/Ankle assemblies: External keel, SACH feet or single axis ankle/feet. Knee units: Single-axis, constant friction knee.
Level 2:	Has the ability or potential for ambulation with the ability to traverse low level environmental barriers such as curbs, stairs or uneven surfaces. Typical of the limited community ambulator. Foot/Ankle assemblies: Flexible-keel feet and multi-axial ankle/feet. Knee units: Single-axis, constant friction knee.
Level 3:	Has the ability or potential for ambulation with variable cadence. Typical of the community ambulator who has the ability to traverse most environmental barriers and may have vocational, therapeutic, or exercise activity that demands prosthetic utilization beyond simple locomotion. Foot/Ankle assemblies: Flex foot and flex-walk systems, energy storing feet, multi-axial ankle/feet, or dynamic response feet. Knee units: Fluid and pneumatic control knees.
Level 4:	Has the ability or potential for prosthetic ambulation that exceeds basic ambulation skills, exhibiting high impact, stress, or energy levels. Typical of the prosthetic demands of the child, active adult, or athlete. Foot/Ankle assemblies: Any ankle foot system appropriate. Knee units: Any ankle knee system appropriate.

CMS = Centers for Medicare and Medicaid Services.

Medicare reimbursement policies require documentation of current functional capabilities and expected functional potential. Therefore, OMTs must both assess and predict function. However, this runs contrary to the Veterans Affairs/Department of Defense Clinical Practice Guideline for lower limb rehabilitation, which recommends that tools should assess what patients actually do, not what they can do.[15] Third-party coverage of LLP requires an additional index is applied to standardize the assessment findings. The Medicare Functional Classification Level (MFCL or K-Level) system (Table 1) broadly defines five classification levels that can be attained with an LLP and range from 0 (no ability to ambulate or transfer; LLP will not enhance mobility) to 4 (ability to excel with [an appropriate] LLP). The classification level assigned is used to determine the medical necessity of certain componentry, and thus to match the ultimate LLP to the beneficiary's clinical needs. However, in practice it is difficult for prosthetists to assess medical necessity for a patient to receive the most appropriate component (whether of higher or lower level or sophistication).

Furthermore, it is unclear to what extent measures of current function and status accurately predict future function. Variability in assigning or predicting the K-Level of prospective LLP recipients may inadvertently lead to inefficient LLP matching. This can occur if a person receives a too-low level LLP when a higher level LLP would enable better function, or if a person receives a too-high level LLP which might be unnecessarily complex for an individual who would have equivalent or better function with a simpler component. It is hypothesized that OMTs with high reliability and predictive validity may optimize the matching of patients to the K-Level they can eventually attain and, more importantly, to the component that would best suit their needs and maximally improve functional and other patient-centered outcomes. Despite the central role of OMTs in the selection of LLPs for Medicare beneficiaries, their utility in the prediction of patient outcomes remains unresolved.

The major contextual challenges pertain to the large heterogeneity in patient characteristics and attributes of the LLPs; the fact that it is unclear which patient characteristics and LLP attributes are important for determining the outcome of the matching of a patient to a specific LLP, and how to best measure them; the disagreements about what constitutes an optimal matching of patients with LLPs; and poor clinical outcomes and wasted resources associated with suboptimal LLP allocations.

Specifically, patients who are in need of LLPs are heterogeneous in terms of etiology of limb loss, amputation type (level of amputation, uni- or bilateral), age, comorbidities, frailty, general health status factors, expected life span, mental health status (e.g., depression, post-traumatic stress syndrome), family and social support, and many other factors, including whether they have fragile skin or allergies towards socket liners or other materials. These factors may affect their actual and perceived current and maximum attainable functional ability, and the likelihood that they will receive and use an LLP.[8,16]

Variability of LLPs is very large, as they are highly customized devices, comprising combinations of components that replace missing anatomy and function. Components of a given type can differ in terms of functional sophistication (e.g., articulated componentry may be passive, with undamped movement, have mechanical or hydraulic dampening, or have electronic control), materials used, weight, aesthetics, comfort, and other factors. A major question is how to match patients with LLPs to optimize functional and other patient-centered outcomes. Because there are many different patients and many possible

LLPs, there are numerous possible matchings. However, it is unclear which patient-level characteristics or LLP-level attributes predict a good matching.

The major methodological challenges pertain to the assessment of analytic validity (reliability) of assessment techniques and predictor tools and the clinical validity and utility of OMTs. OMTs are used as predictive tools (predictive tests). Predictive tests should be valued with respect to their ability to predict future outcomes. However, outcomes are determined by the whole patient management strategy which involves the baseline assessment, the LLP that a patient is given based on this assessment, and any additional care (e.g., physical therapy, rehabilitation) that the patient receives. It is not possible to assess the value of a baseline OMT assessment by itself, if the choice of LLP is influenced by the OMT assessment. Instead, one must evaluate the whole patient management strategy.

The optimal matching of LLPs to patients is a value-laden issue, and therefore a source of disagreement and a sensitive topic for the public. The current K-level classification system requires assignment to discrete functional levels to support medical necessity for LLPs. Concerns persist that K-Level classification may be too coarse and may modulate patient aptitude and clinical trajectory. Even under ideal conditions that reveal and accurately measure important patient-related and LLP specific indicators, controversy would persist over defining an "optimal" outcome. Finally, suboptimal matching of patients to LLPs may unnecessarily increase health care utilization, prevent attainment of maximal patient function, and defer realization of improved quality of life attainable with an appropriate prosthetic. Integral to the identification of good predictive tools that mitigate these issues is the study of OMTs and the relevant patient and LLP characteristics to decision making.

The purposes of this systematic review are to 1) identify validated patient assessment techniques, prediction tools and OMTs that have been validated for use in persons with lower limb amputation; 2) identify studies that compare the differential relative effect of LLP components based on LLP users' characteristics; 3) determine whether these studies use validated instruments and OMTs and whether the validation studies are applicable to the participants in these studies; 4) assess the strength of evidence for studies of differential comparative effectiveness of LLPs based on validated measures; 5) determine whether patient expectations align with their outcomes with LLPs; 6) evaluate whether patients are satisfied with the process of obtaining their LLPs; and 7) describe the long-term continued use of LLPs by those prescribed a prosthesis. This systematic review may also identify areas where evidence gaps exist related to the prescription of LLP so that recommendations may be made concerning the study designs and outcome measures that best inform patient oriented function, quality of life and service satisfaction in this realm.

This review's Key Questions and study eligibility criteria were designed to assist CMS to better understand the state of the evidence regarding how best to match patients with LLPs that would yield best outcomes for them, and related issues. It is important to note that this review does not fully cover the field of evaluation of LLPs. Specifically, it excludes from evaluation biomechanical and other non-patient-centered intermediate outcomes. It also does not attempt to review all evidence about comparisons between specific components. Instead, it largely focuses on those comparisons which provide within-study data to allow assessment about how components compare in different subpopulations of patients based on their characteristics. The review also focuses on

people who may be eligible to be covered by CMS, whether due to age or disability. Therefore the review is restricted to adults with an emphasis on those with dysvascular, cancer-, or trauma-related amputations, but excluding military amputees with battle-related trauma (who are generally covered by Department of Defense and/or Veterans Health Administration insurance). Furthermore, the review excludes studies from low-income or resource settings not applicable to the U.S.

II. The Key Questions

Preliminary Key Questions (KQ) and protocol were discussed in depth with a panel of key informants (stakeholders representing patients [amputees], clinicians, prosthetists, rehabilitation, and physical therapy), with the sponsor, and were publicly posted in December, 2016. Based on feedback from commenters and further discussion with the sponsor the Key Questions (and study eligibility criteria) were revised to improve clarity, focus the topics more closely with the sponsor's needs, and to evaluate measures and outcomes of interest to stakeholders.

KQ 1. What **assessment techniques** used to measure functional ability of adults with major lower limb amputation have been evaluated in the published literature?

1a. What are the measurement properties of these techniques, including: reliability, validity, responsiveness, minimal detectable change, and minimal important difference?

1b. What are the characteristics of the participants in studies evaluating measurement properties of assessment techniques?

KQ 2. What **prediction tools** used to predict functional outcomes in adults with major lower limb amputation have been evaluated in the published literature?

2a. What are their characteristics, including technical quality (reliability, validity, responsiveness), minimal detectable change, and minimal important difference?

2b. What are the characteristics of the participants in these studies?

KQ 3. What **functional outcome measurement tools** used to assess adults who use a LLP have been evaluated in the published literature?

3a. What are their characteristics, including technical quality (reliability, validity, responsiveness), minimal detectable change, and minimal important difference?

3b. What are the characteristics of the participants in these studies?

KQ 4. In adults who use a lower limb prosthesis, how do the **relative effects** on ambulatory, functional, and patient-centered outcomes **of different prosthetic components** or levels of components/prostheses **vary based on study participant characteristics**?

Prosthetic components include:

- Foot/ankle
- Knee
- Socket
- Liner
- Suspension
- Pylon
- Other

Study participant characteristics of interest include:

- K level
- Level of amputation
- Etiology of amputation
- Prior function (prior to new or replacement LLP)
- Current function
- Expected potential function/level of activity and activities (e.g., athletics, uneven surface walking)
- Time since amputation
- Initial vs. subsequent limb LLP
- Unilateral vs bilateral LLP
- Time since last assessment
- Age
- Comorbidities that may affect use of LLP (e.g., congestive heart failure, vascular dysfunction, skin ulceration/damage, visual dysfunction, peripheral neuropathy, local cancer treatment, other lower limb disease)
- Type, setting, and description of rehabilitation, physical therapy, training
- Periamputation surgery information, including surgical details, inpatient rehabilitation details, wound status
- Residence setting
- Use of assistive devices
- Comfort of existing prosthesis (for patients receiving replacement LLP)
- Psychosocial characteristics
- Family (etc.) support system
- Training and acclimation with LLP

4a. What **assessment techniques** that have been evaluated for measurement properties were used in these studies?

4a.i. How do the characteristics of the participants in eligible studies that used these specific assessment techniques compare to the characteristics of the participants in the studies that evaluated the assessment techniques (as per KQ 1b)?

4a.ii. What is the association between these pre-prescription assessment techniques and validated outcomes with the LLP in these studies?

4b. What **prediction tools** that have been evaluated for measurement properties were used in these studies?

4b.i. How do the characteristics of the participants in eligible studies that used these specific prediction tools compare to the characteristics of the participants in the studies that evaluated the prediction tools (as per KQ 2b)?

4b.ii. What is the association between pre-prescription assessment techniques and validated outcomes with the LLP in these studies?

4c. What **functional outcomes** that have been for measurement properties were used in these studies?

4a.i. How do the characteristics of the participants in eligible studies that used these specific functional outcomes compare to the characteristics of the participants in the studies that evaluated the outcomes (as per KQ 3b)?

KQ 5. How do the patients' pre-prescription **expectations of ambulation** align with their functional outcomes?

5a. How does the level of agreement vary based on the characteristics listed in KQ 4, including level of componentry incorporated into their LLP?

KQ 6. What is the level of patient **satisfaction with the process** of accessing a LLP (including experiences with both providers and payers)?

6a. How does the level of patient satisfaction vary based on the characteristics listed in KQ 4, including level of componentry incorporated into their LLP?

KQ 7. At 6 months, 1 year, and 5 years after receipt of a LLP, (accounting for intervening mortality, subsequent surgeries or injuries) what percentage of individuals…?

i. Maintain bipedal ambulation
ii. Use their prostheses only for transfers
iii Are housebound vs. ambulating in community
iv. Have abandoned their prostheses
v. Have major problems with prosthesis

7a. How do these percentages vary based on the following characteristics?

- Patient residence and setting
  - Living situation (e.g., homebound, institutionalized, community ambulation)
  - Setting for rehabilitation, physical therapy, or training (e.g., in-home or at facility)
- Patient characteristics
  - Age
  - Level of amputation
  - Number of lower limbs amputated (unilateral vs. bilateral)
  - Prior level of function (prior to onset of extremity disability)
  - Current level of function
  - Etiology of amputation
  - Time since amputation
  - Comorbidities (e.g., diabetes, CVD, PVD)
  - Operative treatment
  - Use of assistive device
  - Cosmesis of the prosthesis
  - Comfort of the prosthesis
  - Other
- Prosthetic componentry

7b. What were the reasons for suboptimal use of the prosthetic device?

Eligibility Criteria

Pertinent to all KQ:

Population

- Adults with lower limb amputation who are being evaluated for or already have a lower limb prosthesis (LLP)
  - Lower limb amputees who require or have a lower limb prosthesis
- **Exclude** if study includes only participants with battle-related trauma
- **Exclude** if study includes only congenital amputations (and not otherwise Medicare eligible)
- **Exclude** if study includes only children ≤18 years old

    - If a study has a mixed population (related to battle trauma, congenital amputations, or pediatrics) and they report subgroup data based on these factors, include analyses of relevant populations (exclude substudy data on excluded populations). If study reports only combined data (e.g., adults and children), include overall study, but note issue related to population.
- **Exclude** if study conducted in low income or low resource country

Intervention

- Custom fabricated lower limb prosthesis
- Specific prosthetic component, including foot/ankle, knee, socket, liner, pylon and suspension, or components with specific characteristics (e.g., shock absorbing, torque, multiaxial, computer assisted, powered, flexion, microprocessor)
- New or existing definitive or replacement prosthetics
- ***Exclude*** initial or preparatory prosthetics (used temporarily prior to definitive or replacement prostheses immediately after amputation surgery)
- ***Exclude*** studies comparing only rehabilitation, physical therapy, or training techniques or regimens
- ***Exclude*** evaluation of orthotics and of implanted devices

Comparators, Outcomes

- Variable by Key Question

Study Design

- Published, peer reviewed study
- Any language (that can be read by research team or machine translated)
- No publication or study date restriction
- ***Exclude*** case reports

Setting

- Patients homebound, institutionalized, community ambulation, any residence
- Clinical or laboratory setting (for evaluation of specific ambulatory function outcomes)
- Rehabilitation setting (e.g., physical therapy clinic, in-home)
- ***Exclude*** exclusively post-acute (post-surgical) setting or inpatient rehabilitation (immediately post-amputation)

KQ-Specific Criteria:

KQ 1-3

Population

- As per criteria pertinent to all KQ
- Also allow studies of amputees, whether or not they use LLPs (KQ 1 & 2)

Predictors/Tools/Tests/etc. (KQ 1 & 2)

- Assessment techniques (that are used prior to prescription) (KQ 1)
  - Tests, scales, questionnaires that assess current functional or health status
  - Include patient history and physical examination
  - Measures of physical function and functional capacity (e.g., parallel bar ambulation without LLP)
  - ***Exclude*** single factors (e.g., time since surgery, fasting blood glucose)
- Predictor tools (used prior to prescription to predict functional outcomes with prosthesis) (KQ 2)
  - Tests, scales, questionnaires
  - ***Exclude*** single factors (e.g., time since surgery, fasting blood glucose)

Outcomes (KQ 3)

- Functional, patient centered, or ambulatory outcomes per KQ 4

Study Design

- Any assessment of validity, reliability, reproducibility, and related characteristics
- ***Exclude*** studies of validation of translations of non-English scales, indexes, etc.
- Any study design
- No minimum sample size (except not case reports)
- No minimum followup time

KQ 4

Population, Interventions

- As per criteria pertinent to all KQ

Comparators

- LLPs with different components (e.g., feet/ankles, knees, sockets, pylons, liners, suspension), or that differ in other ways

Outcomes

- Functional or patient-centered outcomes (measured or related to status in the community)
    - Quality of life
    - Disability measures
    - Activities of daily living
    - Mobility measures, including use of prostheses only for transfers
    - Self-care
    - Pain
    - Fatigue post-use (e.g., end of day)
    - Daily activity
    - Time LLP worn per day
    - Falls
    - Satisfaction with LLP
    - ***Exclude*** (simple) preference
- Ambulatory functional outcomes
    - Gait speed, step count, walk distance
    - Uneven or wet surface, low lighting walking
    - Ramps and incline traversing
    - Step/stair climbing function
    - Ambulatory function measured in the community setting (eg, self-report or activity monitors)
    - Achievement of bipedal ambulation
    - Other patient-centered ambulatory function measures
    - ***Exclude*** biomechanical measures
- Adverse effects of LLP
    - Skin ulcers/infections, (injuries from) falls due to mechanical failure, etc.
    - Other problems with prosthesis

Study Design

- Direct comparison between any two components
- Must include an analysis or reporting of differences in relative effect between components by a patient characteristic of interest (see text of KQ 4) or sufficient participant-level data to make such an analysis
- No minimum sample size (other than no case reports)
- No minimum followup time

KQ 5

Population

- As per criteria pertinent to all KQ

Predictor

- Any measure of preprescription expectation of ambulation

Outcomes

- Functional, patient-centered, and ambulatory outcomes per KQ 4
- (Not adverse effects)

Study Design

- Any study design, including qualitative studies
- No minimum sample size (other than no case reports)
- No minimum followup time

KQ 6

Population

- As per criteria pertinent to all KQ

Intervention

- Accessing (or attempting to access) a LLP

Outcomes

- Satisfaction with the process of accessing a LLP

Study Design

- Any study design, including qualitative studies
- No minimum sample size (other than no case reports)
- No minimum followup time

KQ 7

Population

- As per criteria pertinent to all KQ

Intervention

- Prescription for a LLP

Outcomes

- Maintain bipedal ambulation
- Use of prostheses only for transfers
- Housebound vs. ambulating in community
- Abandonment of prostheses
- Major problems with prosthesis

Study Design

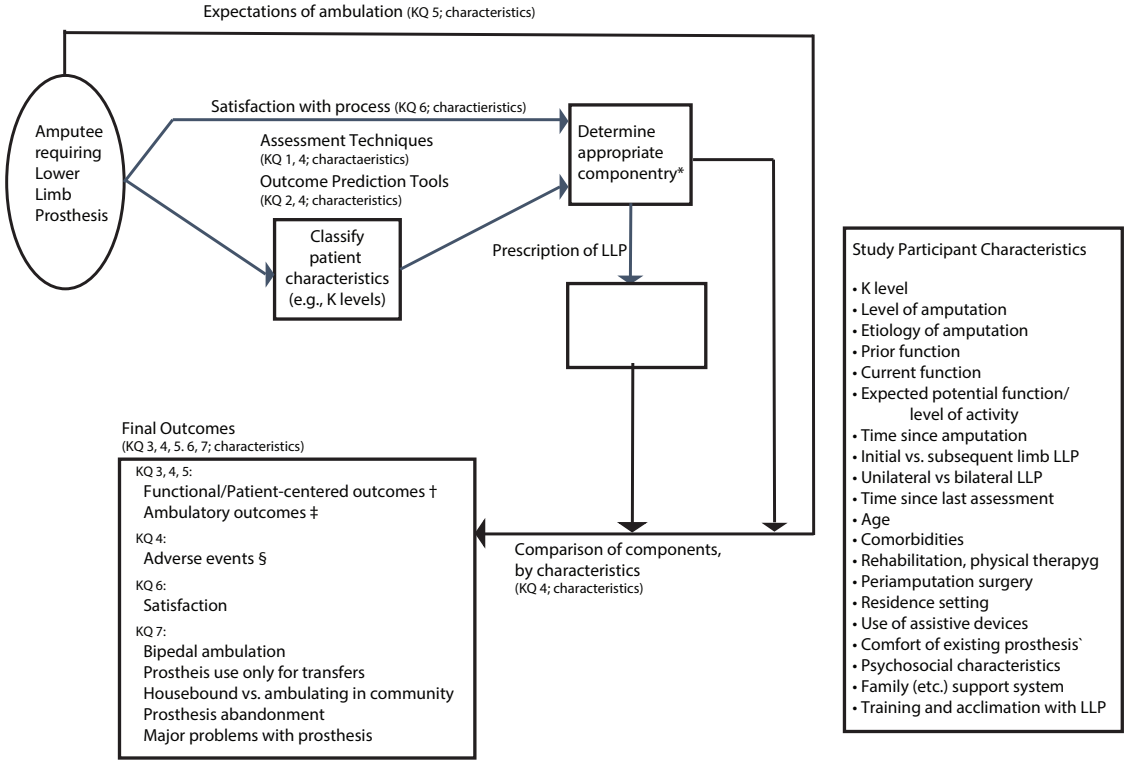
- Either longitudinal with followup since original lower limb prosthesis prescription or cross-sectional at timepoint after amputation or prescription

- Minimum followup time
  - ≥6 month followup from time of prescription, or
  - ≥1 year followup from time of amputation, if no data reported about time since prescription
- Minimum sample size
  - If subgroup analyses reported (based on bullet characteristics in text of KQ 7a), N≥10 per subgroup (thus, N≥20 total) [this number may change depending on available data]
  - If no subgroup analyses reported, N≥100 total [this number may change depending on available data]

III. Analytic Framework

The following analytic framework graphically illustrates the synthesis of the KQs and their elements

Figure 1. Analytic framework for assessment and assignment of lower limb prostheses, including Key Questions



IV. Methods

The Evidence-based Practice Center (EPC) will conduct the review based on a systematic review of the published scientific literature using established methodologies as outlined in the Agency for Healthcare Research and Quality's (AHRQ) Methods Guide for Comparative Effectiveness Reviews.[17]

Criteria for Inclusion/Exclusion of Studies in the Review – Please refer to Section II *The Key Questions*, where the Eligibility Criteria are listed after the KQs.

Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies to Answer the Key Questions: We will conduct literature searches of studies in PubMed, both the Cochrane Central Trials Registry and Cochrane Database of Systematic Reviews, EMBASE, and CINAHL/PSYCInfo databases to identify primary research studies and systematic reviews meeting our criteria. No publication date or language restrictions will be applied. We will peruse the reference lists of published relevant systematic reviews. Any comparative studies (KQ 4) or long-term followup studies (KQ 7) found from existing systematic reviews will be assessed and incorporated *de novo* from the original article. For KQ 1-3, we will summarize and, if new studies exist, update existing systematic reviews (about validation of instruments and measures). Peer and public review will provide an additional opportunity for experts in the field and others to ensure that no relevant publications have been missed. The search will be updated in all databases upon submission of the draft report for peer and public review.

All citations (abstracts) found by literature searches and other sources will be independently screened by two researchers. At the start of abstract screening, we will implement a training session, in which all researchers will screen the same articles and conflicts will be discussed. During double-screening, we will resolve conflicts as a group. All screening will be done in the open-source, online software Abstrackr (http://abstrackr.cebm.brown.edu/). All potentially relevant studies will be rescreened in full text to ensure eligibility. During abstract screening, liberal eligibility criteria will be used to minimize the risk of rejecting pertinent studies. Potentially relevant abstracts will then go through a phase of evidence mapping where specific data are tabulated. This process will allow us to focus and refine, if necessary, our criteria and the list of pertinent studies.

Data Extraction and Data Management: Each study will be extracted by one methodologist. The extraction will be reviewed and confirmed by at least one other experienced methodologist. Any disagreements will be resolved by discussion among the team. Data will be extracted into a customized form in Systematic Review Data Repository (SRDR) online system (http://srdr.ahrq.gov) designed to capture all elements relevant to the Key Questions. Upon completion of the review, the SRDR database will be made accessible to the general public (with capacity to read, download, and comment on data). The basic elements and design of the extraction form will be the similar to those used for other AHRQ comparative effectiveness reviews and will include elements that address population characteristics; descriptions of the interventions, exposures, and comparators analyzed; outcome definitions; effect modifiers; enrolled and analyzed sample sizes; study design features; funding source; results; and risk of bias questions.

Assessment of Methodological Risk of Bias of Individual Studies – We will assess the methodological quality of each study based on predefined criteria. For RCTs, we will use the Cochrane risk of bias tool,[18] which asks about risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other potential biases. For observational studies, we will use relevant questions from the Newcastle Ottawa Scale.[19] Quality/risk of bias issues pertinent to specific outcomes within a study will be noted and considered when determining the overall strength of evidence for conclusions related to those outcomes.

Data Synthesis – All included studies will be summarized in narrative form and in summary tables that tabulate the important features of the study populations, design, intervention, outcomes, and results. These included descriptions of the study design, sample size, interventions, followup duration, outcomes, results, and study quality.

We do not expect the evidence to be amenable to meta-analysis. However, if there are sufficient similar studies, we will conduct random effects model meta-analyses of comparative studies, if they are sufficiently similar in population, interventions, and outcomes. Specific methods and metrics (summary measures) to be meta-analyzed will depend on available, reported study data. Possible reasons for statistical heterogeneity will be explored qualitatively and, if appropriate data are available, we may also conduct metaregression analyses to evaluate study, patient, and intervention features and to evaluate dose-response.

Studies will be summarized semi-quantitatively, with descriptions of ranges of results/estimates across studies and descriptions of statistical significance of studies, emphasizing larger studies with better study design and lower risk of bias. Inconsistencies across studies will be highlighted, with attempts to explain the heterogeneity.

We will explore subgroup differences within and, as feasible, across studies. Study results will be categorized into those that employ validated instruments and measures and those that do not.

Grading the Strength of Evidence (SOE) for Major Comparisons and Outcomes: We will grade the strength of the body of evidence as per the AHRQ methods guide on assessing the strength of evidence.[20] Following the standard AHRQ approach, for each intervention and comparison of intervention, and for each outcome, we will assess the number of studies, their study designs, the study limitations (i.e., risk of bias and overall methodological quality), the directness of the evidence to the Key Questions, the consistency of study results, the precision of any estimates of effect, the likelihood of reporting bias, and the overall findings across studies. Based on these assessments, we will assign a strength of evidence rating as being either high, moderate, or low, or there being insufficient evidence to estimate an effect. The data sources, basic study characteristics, and each strength-of-evidence dimensional rating will be summarized in a "Summary of Evidence Reviewed" table detailing our reasoning for arriving at the overall strength of evidence rating.

Assessing Applicability: We will assess the applicability within and across studies with reference to U.S. adults receiving LLP. At a minimum, factors of interest to assess applicability will be the key potential modifiers listed in the Analytic Framework (e.g., age, amputation reason).

V. References

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VI. Definition of Terms

Assessment technique: A tool or other technique to assess patient status. For the purposes of this review, assessment techniques of interest are those used in clinical practice or in research settings to assess patient status as a guide to choosing the most appropriate prosthesis for that patient. The assessment technique may include both past history and markers of current status.

K Level, also known as **Medicare Functional Classification Level**: Five classification levels that can be attained with an lower limb prosthesis. The levels range from 0 (no ability to ambulate or transfer; prosthesis will not enhance mobility) to 4 (ability to excel with [an appropriate] prosthesis). See Table 1.

Lower limb prosthesis (LLP): A device that substitutes for a missing lower extremity (leg). This review is concerned with prostheses that replace the lower extremity after amputation at the hip, above the knee, below the knee, or above the ankle. It does not address "minor" prostheses of portions of the foot only. In addition it does not include implanted prostheses (that are permanently attached to a bone) or orthotic devices (a

device used to support or align a joint or body part as opposed to replacing a missing body part).

Outcome measurement tool (OMT): An instrument, index, questionnaire, inventory, or other metric that measures an assessment of an outcome. For example, the visual analogue pain scale is an OMT that assesses level of pain.

Predictor tool: A tool used or designed to predict future function based on a patient's past history or current status. For the purposes of this review, predictor tools of interest are those that include elements describing patient status prior to lower limb prosthesis prescription that predict function after prescription and use of the prosthesis.

Prosthetic components: The individual pieces that are compiled into a lower limb prosthesis. These include the foot/ankle, knee, socket, liner, suspension, and pylon.

VII. 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 preparation of the final report. Peer reviewers do not participate in writing or editing of 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 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.

VIII. EPC Team Disclosures

The EPC team has no conflicts to disclose

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X. Registration

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