Evidence-based Practice Center Systematic Review Protocol

Project Title: Serum-Free Light Chain Analysis for the Diagnosis, Management, and Prognosis of Plasma Cell Dyscrasias

I. Background and Objectives for the Systematic Review

Plasma cell dyscrasias (PCDs) are a spectrum of disorders characterized by the expansion of a population of monoclonal bone-marrow plasma cells that produce monoclonal immunoglobulins.[1] At the benign end of the spectrum is monoclonal gammopathy of undetermined significance (MGUS), where the plasma-cell clone usually does not expand. Multiple myeloma (MM) is a plasma cell disorder at the malignant end of the spectrum and is characterized by the neoplastic proliferation of a clone of plasma cells in the bone marrow with resulting end-organ damage, including skeletal destruction (lytic bone lesions), hypercalcemia, anemia, and renal insufficiency. Whereas monoclonal plasma cells generally secrete intact immunoglobulin, in about 20 percent of patients with MM these cells only produce light-chain monoclonal proteins (i.e., light-chain multiple myeloma [LCMM], formerly known as Bence Jones myeloma) and in 3 percent of patients they secrete neither light- nor heavy-chain monoclonal proteins that are detectable by immunofixation (i.e., nonsecretory multiple myeloma [NSMM]).[1] In two-thirds of patients with NSMM, a monoclonal protein can be identified by the serum-free light chain (SFLC) assay. Patients with LCMM develop complications related to tissue deposition of light chains, including amyloidosis. Amyloid light-chain (AL) amyloidosis is the most common form of systemic amyloidosis seen in the United States and is characterized by a relatively stable, slow-growing plasma-cell clone that secretes light-chain proteins that form

Table 1: Diagnostic criteria and clinical course of selected plasma cell dyscrasias (PCDs)[2]

Disorder	Disease Definition	Clinical Course
Monoclonal gammopathy of undetermined significance (MGUS)	▪ Serum monoclonal protein ≤ 3g/dL ▪ Bone marrow plasma cells ≤10% ▪ Absence of end-organ damage (bone lesions, anemia, hypercalcemia, or renal failure)	▪ Asymptomatic ▪ 1% per year progress to multiple myeloma or related PCD
Multiple myeloma	▪ Bone marrow plasma cells ≥10% ▪ Presence of serum and/or urinary monoclonal protein ▪ Evidence of end-organ damage (bone lesions, anemia, hypercalcemia, or renal failure)	▪ Median survival is approximately 4 years
Other forms of multiple myeloma: Light chain myeloma	▪ Malignant plasma cells produce free monoclonal light chains but no associated heavy chain/complete immunoglobulin	▪ 20% of multiple myeloma
Nonsecretory myeloma	▪ Serum monoclonal protein absent or only revealed by bone marrow immunostaining	▪ <1% of multiple myeloma
Smoldering multiple myeloma	▪ Serum monoclonal protein ≥3 g/dL and/or bone marrow plasma cells ≥10% ▪ Absence of end-organ damage (bone lesions, anemia, hypercalcemia, or renal failure)	▪ Asymptomatic ▪ 10% per year progress to myeloma
Systemic light-chain (AL) amyloidosis	▪ Amyloid-related systemic syndrome — organ involvement by tissue amyloid deposition (renal, liver, heart, gastrointestinal tract, or peripheral nerve involvement with positive amyloid staining by Congo red) ▪ Evidence of a monoclonal plasma-cell proliferative disorder	▪ Median survival is approximately 2 years

insoluble, Congo red-positive (on histological staining) fibrils in tissues that, in turn, lead to multiorgan dysfunction. Table 1[2] provides an overview of the diagnostic criteria and clinical course of selected PCDs.

Across the spectrum of PCDs, measurement of circulating monoclonal immunoglobulins is the mainstay for diagnosis, prognosis, and management.[3] The current standard for screening for elevated immunoglobulins and abnormal monoclonal proteins in a patient suspected of having a PCD is through both serum and urine protein electrophoresis (SPEP and UPEP, respectively) and serum and urine immunofixation (SIFE and UIFE, respectively). The standard tests have limited efficacy for the diagnosis of PCDs that are characterized predominantly by monoclonal light chains or by very few or nondetectable light- or heavy-chain monoclonal proteins. Free light chains, which have a serum half-life of 2 to 4 hours, are rapidly cleared by the kidney and are then metabolized in the proximal tubules of the nephrons.[4] In a healthy individual, little protein escapes into the urine, because the kidneys can metabolize from 10 to 30 g of free light chains per day. The normal plasma-cell production of free light chains is from 0.5 to 1.0 g/day.[5] The detection of free monoclonal light chains (i.e., Bence Jones protein) in the urine has traditionally been an important diagnostic marker for MM. In addition, it has been the mainstay of diagnosis for disorders such as AL amyloidosis and LCMM, in which the monoclonal protein consists exclusively of light chains. Table 2[6] provides an overview of the laboratory tests used to diagnose PCDs.

Table 2: Laboratory diagnosis of plasma cell dyscrasias[1]

Test Name	Use	Limitations
Serum protein electrophoresis (SPEP)	▪ Detect the presence of the monoclonal (M)-protein or monoclonal FLC components ▪ Densitometric quantification of the M-protein ▪ Correlates with tumor burden of 10^9 cells when positive	▪ Insensitive ▪ Lower limit of measuring range is 500–2000 mg/L ▪ Cannot detect low levels of M-protein
Urine protein electrophoresis (UPEP)	▪ Detect the presence of the M-protein or monoclonal free light chain components ▪ Quantitative	▪ Sensitive only in concentrated urine (100x) to 30 mg/L ▪ 24-hour urine collection needed
Serum or urine immunofixation electrophoresis (IFE)	▪ Identifies M-protein subtype after the M-spike is seen on SPEP — diagnosis of clonality ▪ Sensitivity for serum ~150 mg/L	▪ Not sensitive enough to detect slightly increased free light chains ▪ Qualitative result
Serum-free light chain (SFLC) assay	▪ Polyclonal Ab to light-chain epitopes normally sequestered in the intact molecule ▪ 95% reference interval for: - κ chains 3.3–19.4 mg/L - λ chains 5.7–26.3 mg/L - κ/λ ratio 0.3–1.2 ▪ Mainstay of diagnosis for nonsecretory myeloma	▪ 24-hour urine collection needed for AL amyloidosis, as monoclonal protein only identifiable in urine ▪ Adjunct to serum IFE, but not stand alone ▪ False positives and negatives known
Quantitative immunoglobulin	▪ Burden of disease and followup of plasma cell dyscrasias	▪ Less useful in biclonal gammopathies or nonsecretory disease
Urine free light chains	▪ Diagnosis and follow up of nonsecretory myeloma, monoclonal gammopathy of undetermined significance, and amyloidosis	▪ Less sensitive and more variable than SFLC testing ▪ More sensitive than urinary IFE and provides quantitative results

In 2002, a serum-free light chain assay (hereafter, SFLC assay) was developed to measure light-chain immunoglobulins in serum; a unique feature of this assay is that it recognizes an epitope on the free monoclonal light chains.[7] The SFLC assay (Freelite™ Assay, The Binding Site Ltd., Birmingham, United Kingdom) is based on a commercial reagent set of polyclonal antibodies and is performed by immunonephelometry on a number of automated laboratory instruments. This system was one of the first to be approved by the U.S. Food and Drug Administration and classified as an immunoglobulin (light chain-specific) immunological test system. It quantifies κ and λ light chains separately, with normal reference intervals of 3.3 to 19.4 mg/L and 5.7 to 26.3 mg/L, respectively. A major advantage of the SFLC assay is its sensitivity for detecting low concentrations of free monoclonal light chains—as low as <1 mg/L; the lowest concentrations SPEP and SIFE can detect are 1,000 mg/L and 150 to 500 mg/L, respectively.[7,8] A second potential advantage is the specificity afforded by examining the κ/λ ratio. This ratio remains normal in polyclonal hypergammaglobulinemia or in renal insufficiency where free monoclonal light chains are retained secondary to poor clearance. A PCD, however, secretes only one kind of free monoclonal light chain in excess, thereby disturbing the normal balance between κ and λ secretion and giving rise to a distinctly abnormal ratio.

Although recent narrative reviews have suggested several novel applications of the SFLC assay to aid in the diagnosis, monitoring, and prognostic assessment of PCDs, such applications have not been systematically reviewed. The International Myeloma Working Group has considered the use of the SFLC assay in four main areas for MM and related disorders and issued the following guidelines[9]:

1. In the context of screening, where the SFLC assay in combination with SPEP and SIFE yields high sensitivity and negates the need for 24-hr urine studies for diagnoses other than AL amyloidosis.
2. In the baseline measurement of free light chains, which is of major prognostic value for virtually every PCD.
3. For quantitative monitoring of patients with oligosecretory PCDs (including AL amyloidosis, NSMM, and LCMM).
4. According to the International Response Criteria,[10] the κ/λ ratio must be calculated to document a stringent complete treatment response.

However, these guidelines were not based on a systematic review, and the recommendations they made were not rated by strength of evidence.

While the guidelines suggest that using the SFLC assay as a screening and initial diagnostic tool for PCD could eliminate the need for urine tests, its diagnostic value could differ depending on the PCD, and specific diseases, such as AL amyloidosis, still require urine testing for diagnosis and monitoring. Much of the evidence regarding the use of the SFLC assay in diagnosis has come from studies of patients with known PCD, and its role in screening needs greater validation. The concentration of free light chains also appears to carry important prognostic information in both MGUS and PCDs, although a systematic review of the evidence is not available. Although the guidelines suggest the use of the SFLC assay for serial disease-monitoring among patients with oligosecretory disease (AL amyloidosis or NSMM), response criteria with respect to survival have not been validated. In patients whose PCD can be measured

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by SPEP or UPEP (MM with secretion of intact monoclonal protein), the role of the SFLC assay versus electrophoretic studies for serial disease-monitoring is unclear. The assessment of treatment response and remission by using the SFLC assay or the κ/λ ratio appears to differ between PCDs with or without measurable monoclonal protein. Potential applications of measuring the concentration of free light chains include defining early relapse, stringent complete response, or a partial response; the earlier prediction of drug failure; and the detection of light chain escape. Further, the SFLC assay may reduce the need for frequent bone marrow biopsies or other investigations or interventions if it correlates with bone marrow plasmacytosis or other disease-status markers, although the evidence varies.

In summary, it appears that there is considerable clinical uncertainty regarding the applications of the SFLC assay both within and beyond the 2009 International Myeloma Working Group consensus guidelines. These areas span diagnosis, therapeutic decisions and monitoring, diagnosis of response and remission among patients with diagnosed disease, and assessment of prognosis. Variability of the SFLC assay is also an important issue with direct relevance to patient care. Although standardization of results or reference intervals across assays was deemed to be beyond the scope of this review, a description of the degree of variation and any correlation with observed outcomes may be included. Other limitations of the SFLC assay may be associated with harms that have not been explicitly outlined and would need to be described. Cost savings and economic implications are also important areas of uncertainty beyond the scope of this review; however, a systematic review of the evidence of the comparative effectiveness of this test in different settings may help elucidate the issue,

II. The Key Questions

Question 1

Do the SFLC assay and the κ/λ ratio improve diagnostic accuracy for PCDs (MGUS, MM, NSMM, AL amyloidosis) when combined with serum electrophoresis and serum immunofixation and compared with the traditional tests of urine and serum electrophoresis and serum and urine immunofixation in a population of patients who have not been diagnosed with PCDs but have nonspecific symptoms associated with these diseases, whether those symptoms include kidney failure or not?

Question 2

When compared with traditional tests, how well does the SFLC assay independently predict progression to MM in patients with MGUS?

Question 3

In patients with an existing diagnosis of PCD (MM, NSMM, or AL amyloidosis), does the use of the SFLC assay result in different treatment decisions when compared with traditional tests?

a. Does the use of the SFLC assay affect the management of patients by allowing the earlier institution of specific therapies?

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b. Does the use of the SFLC assay influence the duration of treatment?
c. Does the use of the SFLC assay influence the type of treatment (e.g., radiation therapy)?

Question 4

In patients with an existing diagnosis of PCD (MM, NSMM, or AL amyloidosis) is the SFLC assay a better indicator of how the patient responds to treatment and of outcomes (overall survival, disease-free survival, remission, light chain escape, and quality of life) when compared with traditional tests?

Question 5

In patients with an existing diagnosis of PCD (MM, NSMM, and AL amyloidosis) does the use of the SFLC assay reduce unnecessary interventions?

Public Comments

The Key Questions (KQs) were posted on the Effective Health Care Program Web site for public comment from December 1–29, 2010. No comments were received for this topic.

Eligibility Criteria

- **Population(s)**

  Adults (≥18 years of age)

  - KQ 1: Patients who have not been diagnosed with a PCD but who have nonspecific symptoms (with or with out kidney failure) associated with these diseases.
  - KQ 2: Patients with MGUS.
  - KQs 3–5: Patients with an existing diagnosis of PCD (MM, NSMM, or AL amyloidosis) with and without measurable disease by traditional testing

- **Interventions**

  - KQ 1: SFLC assay and the κ/λ ratio in conjunction with SPEP.
  - KQs 2–5: SFLC assay.

- **Comparators**

  Traditional testing:

  - SPEP, UPEP, SIFE, and UIFE.
  - Size and type of serum monoclonal protein.

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- Bone marrow biopsy.
- Skeletal lesions.

- **Outcomes**

  - KQ 1: Diagnostic accuracy such as sensitivity, specificity, predictive values, likelihood ratios, and the area under the receiver operating characteristics curve.
  - KQ 2: Progression to MM.
  - KQ 3: Timing of treatment, duration of treatment, and type of treatment.
  - KQ 4: Overall survival; disease-free survival; response to treatment; remission, including complete remission and stringent complete remission; light chain escape, and quality of life.

    – **Response to treatment and remission.** Both have been categorized as "partial," "complete," or "stringent complete" based on the treatment-induced decline in monoclonal protein or light chain.[9,10]
    – **Light chain escape.** For unclear reasons, a subclone of malignant plasma cells expands, which is incapable of producing significant amounts of immunoglobulin heavy chain but retains the ability to make light chains.[9]

  - KQ 5: Unnecessary clinic visits, hospital stays, bone marrow biopsies, and bone scans.

- **Time**

  Any length of followup.[9.10]

- **Study Design**

  - KQ 1: Cross-sectional, RCT, and systematic reviews.
  - KQ 2: Cross-sectional, case-control, prospective cohort, RCT, and systematic reviews.
  - KQ 3: Cross-sectional, case-control, prospective cohort, RCT, and systematic reviews.
  - KQ 4: Cross-sectional, case-control, prospective cohort, RCT, and systematic reviews.
  - KQ 5: Cross-sectional, case-control, prospective cohort, RCT, and systematic reviews.

- **Setting**
  Any setting: primary or specialty care, in-facility or home, and inpatient or outpatient.

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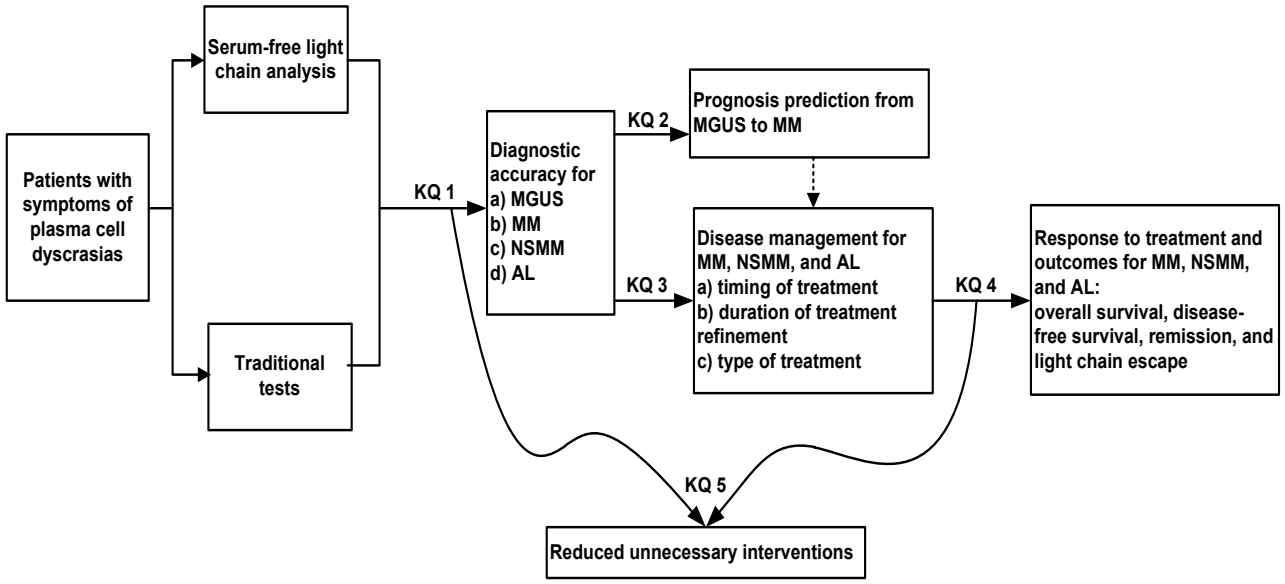
Figure 1. Analytic framework for serum--free light chain analysis for the diagnosis, management, and prognosis of plasma-cell dyscrasias



III. Analytic Framework

Abbreviations: AL amyloidosis = amyloid light chain amyloidosis; KQ = key question; LCMM = light chain myeloma; MGUS = monoclonal gammopathy of unknown significance; MM = multiple myeloma; NSMM = nonsecretory myeloma; PCD = plasma cell dyscrasia; SFLC assay = serum-free light chain assay; SPEP = serum protein electrophoresis; UPEP = urine protein electrophoresis.

Alternate Text: Figure 1 depicts the key questions described in the previous section within the context of the PICOTS (Populations, Interventions, Comparators, Outcomes, Timing, and Settings). In general, the figure illustrates how serum-free light chain analysis versus traditional testing (serum and urine electrophoresis and immunofixation) may result in better diagnostic accuracy, improve prognosis prediction, aid management decisions, improve overall outcomes, and reduce unnecessary interventions.

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IV. Methods

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

We will use the eligibility criteria for populations, interventions, comparators, outcomes, timing, and settings (PICOTS) as enumerated above. All publications between January 1, 2000 and the current date will be included. We do not expect to contact authors for additional data. We will not include single case reports; inclusion of case series will be based on the prevalence of the disease under consideration, lower thresholds will be applied for a rarer disease.

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

Appendix 1 at the end of this document has the proposed literature search strategy. This search will be conducted in MEDLINE® and the Cochrane Central Register of Controlled Trials. We will screen all abstracts available in English. Abstracts will be manually screened based on the eligibility criteria and exclusions cross-checked by a second member of the team. Any abstracts that are accepted will be reviewed by full text. For those articles not available in English, we will review the article in the native language, providing adequate expertise can be identified. A list of articles excluded due to language will be included in the final report. Full-text articles will be rescreened for eligibility. The reasons for excluding these articles will be tabulated. We will ask the technical experts and others to inform us of any potentially missing articles. All suggested articles will be screened for eligibility by using the same criteria as for the original articles. If necessary, we will revise the literature search to find articles similar to those missed. Additional articles will be retrieved from existing guidelines and narrative and systematic reviews and a search of other cancer-specific databases. When the draft report has been submitted, we will run an updated literature search (using the same search strategy) and will add these to the final report.

C. Data Abstraction and Data Management

Each study will be extracted by one experienced methodologist. The extraction will be reviewed and confirmed by at least one other methodologist. Any disagreements will be resolved by discussion in team meetings. Data extraction will be done into standard forms in Microsoft Word. The basic elements and design of the forms will be the same as multiple forms we have used for other comparative effectiveness reviews and will include elements that address population characteristics and sample size, study design, analytic details and outcomes. Prior to use, the form will be customized to capture all the relevant elements for the KQs. We will use separate forms for questions related to diagnostic test performance (KQ1), MGUS (KQ 2), and the other aspects of PCD treatment (KQs 3–5). We will test the forms on several studies and revise the forms as necessary before full data extraction of all articles is performed.

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We will extract basic demographic data such as age, sex, and race and any and all factors that may have a role in the outcome of PCDs. These will include type of PCD, anemia, light chain / monoclonal protein type and concentration, organ involvement, and other pertinent characteristics.

D. Assessment of Methodological Quality of Individual Studies

We will use methods for evaluating study quality that are standard within the Evidence-based Practice Center Program and are recommended by the Agency for Healthcare Research and Quality in its *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*, hereafter referred to as "the *Methods Guide*."[11] Briefly, we will rate each study as being of good, fair, or poor quality based on their adherence to well-accepted standard methodologies and adequate reporting.[11-13] The grading will be outcome-specific such that a given study that reports its primary outcome well but did an incomplete analysis of a secondary outcome would be graded of different quality for the two outcomes. Studies of different study designs will be graded within the context of their study design. Thus, RCTs will be graded good, fair, or poor, and observational studies will separately be graded good, fair, or poor. However, we expect retrospective studies to be of fair or poor quality due to the increased risk of bias with a retrospective study design.

E. 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. For questions regarding comparisons of diagnostic tests (KQ 1), we will consider doing Bland-Altman plots, which graph the differences in measurements against their average. This approach is recommended for analyses where neither test can be considered a reference (gold) standard. Analyses of sensitivity and specificity will also be undertaken where appropriate. For KQs 2–5 that evaluate the effect of an intervention on intermediate and clinical outcomes, we will consider performing meta-analyses where there are at least three unique studies that are deemed to be sufficiently similar in population and have the same comparison of interventions and the same outcomes. We expect to require input from domain experts to assess whether studies are too clinically heterogeneous for meta-analysis to be appropriate. We will perform only random-effects model meta-analyses.

F. Grading the Evidence for Each Key Question

We will follow the *Methods Guide*[11] to grade the strength of the body of evidence for each KQ with respect to four domains: risk of bias, consistency, directness, and precision.[11]

Briefly, we will define the risk of bias (low, medium, or high) based on the study design and the methodological quality of the studies.

We will determine the consistency of the data as no inconsistency, inconsistency present, or not applicable if there is only one study. We do not plan to use rigid counts of studies (e.g., 4 of 5 agree, therefore consistent), but instead we will evaluate the direction, magnitude, and

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statistical significance of all studies and make a determination. We will describe our logic where studies are not unanimous.

We will assess the precision (precise or imprecise) of the evidence based on the degree of certainty surrounding an effect estimate. A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions (e.g., both clinically important superiority and inferiority (i.e., the direction of effect is unknown), a circumstance that will preclude a conclusion.

We will assess the directness (direct or indirect) of the evidence, whether there is a single, direct link between the intervention(s) of interest and the health outcome under consideration. If the studies do not directly compare the tests of interest, we will use network analysis to estimate the comparative effect.

We will follow the *Methods Guide*[11] and use four strengths of evidence levels: high, moderate, low, and insufficient. These will be based on our level of confidence that the evidence reflects the true effect for the major comparisons of interest.

V. References

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VI. Definition of Terms

All terms requiring definition have been addressed in the background and objectives.

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

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

IX. Key Informants

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

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

X. Technical Experts

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

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

XI. Peer Reviewers

Approximately five experts in the field will be asked to peer review the draft report and provide comments. Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. The peer reviewer may represent stakeholder groups such as professional or advocacy organizations with knowledge of the topic. On some specific reports such as reports requested by the Office of Medical Applications of Research, National Institutes of Health there may be other rules that apply regarding participation in the peer review process. Peer review comments on the preliminary draft of the report are 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 or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical briefs, be published three months after the publication of the Evidence report.

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Potential 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.

It is our policy not to release the names of the Peer reviewers or TEP panel members until the report is published so that they can maintain their objectivity during the review process.

Appendix 1

Literature search

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <March 09, 2011>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to February 2011>, EBM Reviews - Cochrane Central Register of Controlled Trials <1st Quarter 2011>, Ovid MEDLINE(R) without Revisions <1996 to March Week 1 2011>
Search Strategy:

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1 Immunoglobulin Light Chain*.mp. or exp Immunoglobulin Light Chains/ (4166)
2 monoclonal light chain*.mp. (126)
3 serum free light chain*.mp. (145)
4 immunoglobulin-free light chain*.mp. (61)
5 Bence Jones protein.mp. or exp Bence Jones Protein/ (353)
6 1 or 2 or 3 or 4 or 5 (4498)
7 limit 6 to english language [Limit not valid in CDSR,CCTR; records were retained] (4070)
8 limit 7 to yr="2000 -Current" (2826)
9 remove duplicates from 8 (2819)

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