Methodological Approach

With the use of the framework advocated by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group, SEMPI panels aim to perform a systematic review and to develop evidence-based guidelines (referred to as Clinical Practice Guidelines (CPG) or alternately referred to as Appropriate Use Criteria (AUC) as preferred by CMS) to direct decision making for the diagnostic imaging of patients.

Standard Approach

1. DEFINE A CLINICAL PRACTICE GUIDELINE (CPG) TOPIC
    a. Topics will be medical conditions addressing signs and symptoms and procedures.
    b. Priority-setting criteria (from the Institute of Medicine) may include (in no specific order):
        i. Disease burden
        ii. Controversy
        iii. Cost
        iv. New evidence
        v. Potential impact
        vi. Public or Provider interest
        vii. Variations in care
    c. Topics should be either required by CMS or otherwise relevant, feasible, and important to patients.
    d. There should be a sufficient base of published evidence, if possible including one or more systematic reviews or meta-analysis
        i. If topic is deemed important and when there is NOT sufficient base of published evidence, the topic team will determine to use the alternative process that is focused on consensus and using all available published information, including "gray literature." See CONSENSUS APPROACH below.
    e. Each topic will be evaluated by a 'topic team' of 7 members chosen from the SEMPI multidisciplinary team of experts.

2. PROVIDE ABSTRACT
    The abstract summarizes the systematic review, e.g., "This review aims to determine the diagnostic accuracy of … in an adult population evaluated for cervical spine injury following blunt trauma."

3. PROVIDE BACKGROUND AND OBJECTIVES FOR SYSTEMATIC REVIEW
    a. Nature and burden of the condition
        i. "Neck pain is a common presenting complaint for …"
        ii. "Cervical spine injury (CSI) is a common etiology …"
        iii. Describe incidence
        iv. Describe consequence of undiagnosed injury
    b. Diagnoses of condition
        i. "Guidelines suggest …"
        ii. "Several clinical signs and symptoms have been described as suggestive of …, including …"
        iii. "The reliability and validity of clinical signs and symptoms for identifying … seems to be variable across studies, and few clinical findings appear to have adequate sensitivity and specificity when used in isolation"
    c. Importance of accurate diagnosis and impact on outcomes
        i. "As with all diagnostic tests, the modality used in the diagnostic investigation … indirectly affects outcome (e.g. time to treatment/surgery thus affecting pain, impact resource utilization, delays, perhaps decrease length-of-stay via early establishment of diagnosis, etc.)
    d. Specific issues impacting the diagnosis of the condition
        i. "The diagnosis of appendicitis is particularly challenging in some population subgroups, including …."
        ii. Describe issues: In appendicitis children and women of reproductive age need additional clinical criteria to provide the proper diagnosis and subsequent appropriate imaging
    e. Rationale for an evidence review
        i. "The reliable identification of patients with RLQ flank pain who need surgical intervention for appendicitis can improve clinical outcomes and reduce resource utilization."
        ii. "The review of guidelines and published systematic reviews indicates a lack of specific guidance for selecting diagnostic modalities, particularly in subgroups in whom it is a challenge establishing the diagnosis clinically"
        iii. "Existing systematic reviews do not adequately address the comparative effectiveness of alternative diagnostic approaches because they typically assess a single diagnostic modality, do not evaluate the comparative effectiveness of test, and focus almost exclusively on test performance outcomes without providing evidence on the impact of tests on patient-relevant outcomes"
        iv. "Thus, the current project will serve as a basis for the development of clinical practice recommendations for the …"
    f. Clinical focus questions
        i. "With input from clinical experts during review process, SEMPI have developed the following clinical questions to clarify the focus of the proposed systematic review:"

1) What is the accuracy of diagnostic tests, alone or in combination, for the condition?
    a) Does the performance or comparative performance of alternate diagnostic tests differ in different populations?
    b) What factors modify the test performance and comparative test performance of available diagnostic tests in these populations?
2) What are the direct harms of diagnostic tests, and what are the indirect harms of the test used to diagnose the condition?

4. TOPIC TEAMS
    a. Each CPG topic will be considered by a panel consisting of 7 members to form the SEMPI multidisciplinary team or panel. Members will fill the following team roles (a single individual may serve more than one role):
        i. Panel Coordinator/Leader
            1) In cooperation with Executive Director appoints members to topic team
            2) Ensures members are appropriately trained (see Training Verification below)
            3) Ensures compliance with the SEMPI Board COI policy (COI form available on website). Has Executive Director address member conflicts of interest (COI) to apply any needed restrictions
            4) Receives, organizes, and summarizes panel findings
            5) Serves as moderator for policy debates
            6) Drafts and finalizes panel recommendations and grades
        ii. Expert in GRADE methodology with expertise in systematic review methodology and clinical design research or quality improvement.
        iii. Practicing Professional (Primary Care) with interest/practice focus in topic area and must be in clinical practice and capable of providing patient perspectives.
        iv. Practicing Professional (Radiology/Imaging) with interest/practice focus in topic area and must be in clinical practice and capable of providing patient perspectives.
        v. Practicing Professional (Clinical Topic Expertise) with advanced training in the clinical topic and must be in clinical practice capable of providing patient perspective.
        vi. SEMPI Statistical Specialist with expertise in research methodology and statistics.
        vii. SEMPI CPG Specialist with expertise in clinical design research, methodology, statistical analysis or quality improvement.
    b. SEMPI will recruit additional multidisciplinary panelists to cover the various topics and to encourage diversity in the make-up of the panels. In past use of Nurse Practitioners, Doctors of Osteopathy, etc. have assisted in the

generalizability of the clinical content across many types of ordering professionals.

5. EDUCATION OF TEAM (Individualized as necessary)
    a. Methodology Education
        i. Norris, S., Analyzing multimodal interaction: A methodological framework. 2004, New York and London: Routledge.
        ii. Information regarding systematic reviews from http://handbook.cochrane.org/
        iii. GRADE Online Learning Modules – McMaster University These online learning modules are designed to help guideline developers and authors of systematic reviews learn how to use the GRADE approach to grade the evidence in systematic reviews, to create Summary of Findings Tables and GRADE Evidence Profiles, and to make recommendations from the evidence. There are two sets of modules: For authors of Cochrane systematic reviews and other systematic reviewers - For World Health Organization (WHO) guideline developers and other guideline developers. Each module covers a specific topic related to GRADE and can be viewed in sequence as presented here or, depending on your learning needs, viewed in any order. Most modules are approximately 20 minutes. Viewing is self-directed and anonymous. https://cebgrade.mcmaster.ca/
        iv. GRADE: Choosing a comparison and outcomes for the Summary of Findings Table is an important topic. http://fhsed.mcmaster.ca/onlineModules/GRADE/outcomes/
        v. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations is an important topic.
            1) Gordon H Guyatt, et. al (GRADE Working Group) https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2335261/
            2) Dr. Holger Schünemann lecture https://www.youtube.com/watch?v=x6MlqC7157E&feature=related
        vi. In person workshops on the GRADE system are encouraged.
    b. Bias Education
        i. Assessing Risk of Bias https://cebgrade.mcmaster.ca/RoB/index.html
        ii. Assessing Inconsistency https://cebgrade.mcmaster.ca/Inconsistency/index.html
        iii. Assessing Indirectness https://cebgrade.mcmaster.ca/Indirectness/index.html
        iv. Assessing Imprecision https://cebgrade.mcmaster.ca/Imprecision/index.html
        v. Assessing Publication Bias

https://cebgrade.mcmaster.ca/publicationbias/index.html

vi. Assessing Other factors and upgrading
https://cebgrade.mcmaster.ca/upgrading/index.html

c. Training Verification will be signed by each AUC panel member when training is completed.

6. CREATE FOCUSED RESEARCH QUESTIONS USING PICO CRITERIA
   a. Topic areas will be divided into appropriate, well-defined outcomes that are important to patients. Ambiguous terms will be defined.
   b. Formulating questions and choosing outcomes.
      https://cebgrade.mcmaster.ca/QuestionsAndOutcomes/index.html
      i. (P) – Population
         Example: "In cooperative adult blunt trauma patients with concern for neck injury …"
      ii. (I) – Intervention
         Example: "should CT scan of the cervical spine be performed …"
      iii. (C) – Comparators
         Example: "compared to physical exam alone (no imaging) …"
      iv. (O) – Outcome
         Example: "to identify an unstable cervical-spine injury"
         Considerations:
         1) What are you trying to improve with your intervention (decrease cost; reduce incidence of missed injury; provide a test that is easier to use, obtain or tolerate; reduce the number of imaging studies normally required, decrease morbidity/mortality, etc.)
         2) Once a list of outcomes is established, the team should then decide the ones that are directly important to patients. If needed, members may rate the outcomes from 1-9 with '9' being most critical to patients.

7. PERFORM SYSTEMATIC REVIEW OF CURRENT LITERATURE
   a. Define population and sub-groups
   b. Define interventions
      i. Clinical symptoms and signs (interview and physical exam)
      ii. Imaging tests
   c. Define comparators
      i. Alternate tests or clinical observation
   d. Define outcomes
      i. Test performance (e.g., sensitivity, specificity, accuracy, etc.)
      ii. Intermediate outcomes
         1) Impact on diagnostic process
         2) Impact on treatment
      iii. Patient-centered outcomes
      iv. Adverse effects of intervention(s)
         1) Direct harms of testing
         2) Indirect harms

e. Define timing
f. Define setting
    i. Predominately outpatient settings will be considered

8. SYSTEMATIC REVIEW METHODS
    a. Criteria for inclusion/exclusion of studies in the review
        i. SEMPI will use existing systematic reviews to identify single index test studies with test performance outcomes. Systemic reviews will be considered as potential sources of eligible studies if they meet the following criteria:
            1) Report the bibliographic databases searched and any additional sources of included studies
            2) Have used explicit criteria for selecting primary studies of the populations and index tests of interest
            3) Have examined test performance outcomes
            4) Provide a list of included studies that allows the retrieval of the corresponding full text publications
        ii. Based on database searches for primary studies and the studies included in previously published systematic reviews, SEMPI will compile a list of potentially eligible studies, to which SEMPI will apply the search criteria
        iii. Inclusion/exclusion criteria will vary by PICO question (outcome) in order to optimize the scope of this review and will be stated.
        iv. Study design categories
            1) Randomized controlled trials
            2) Prospective or retrospective diagnostic cohort studies-
            3) Nonrandomized comparative studies
            4) Single group (pre-post or time series) studies
            5) The following categories (for clinical experience) may be used if other literature is inadequate:
                a) Editorials
                b) Commentaries
                c) Narrative reviews
                d) Letters to the editor
    b. Searching for the evidence: literature search strategies for identification of relevant studies to answer the clinical focus questions
        i. A SEMPI search may be conducted in one or more of the following databases: MEDLINE, PubMed, the Cochrane Center Register of Controlled Trials, Google Scholar, Harvard Evidence Based Medicine Library, and Turning Research into Practice (TRIP) to identify either meta- analysis or primary research studies meeting the criteria.
        ii. Search publication dates will be defined for each systematic review.
        iii. Abstracts will be screened for eligibility utilizing a standardized screening process.
        iv. Potentially eligible citations will be obtained in full text and will be reviewed for eligibility on the basis of inclusion criteria. Disagreements on article eligibility will be resolved via consensus.

v. SEMPI will include only English-language studies
vi. Publications will be entered into the reference manager RefWorks

c. Data abstraction and data management
   i. Data will be extracted onto forms. The basic elements will include elements that address population characteristics, sample size, study design, descriptions of the index and reference standard tests of interest, analytic details, and outcome data. Forms will be modified to capture all elements relevant to the PICO question under investigation including intermediate outcomes, adverse events, and for factors affecting test performance among subgroups of patients.
   ii. A single reviewer will extract data from each eligible study. Extracted data will be reviewed and confirmed by at least one other team member, disagreements of which will be resolved by consensus involving a third reviewer.
   iii. Data will be entered into the SEMPI review template.
   iv. SUMMARY OF FINDINGS (Form).

SEMPI Grading QOE – Summary of Findings						
PICO:						
Author/Title/Year	**Design**	**Population**	**Intervention Vs Comparator**	**Results**	**Conclusion Summary**	**SEMPI QOE Rating**
Initial QOE Score across studies for PICO:						

d. Assessment of methodological "Risk of Bias" across studies
   i. SEMPI will assess the risk of bias for either the meta-analysis or across studies using the assessment methods detailed by the GRADE Study limitations (Risk of Bias).
   ii. SEMPI will not calculate "composite" quality scores. Instead, SEMPI will assess and report each risk criteria as 'Not Serious', 'Serious', or 'Very Serious'.
   iii. Studies are rated as being low, intermediate, or high risk of bias based on adherence to accepted methodological principles.
      1) Studies with a low risk of bias have the following features:
         a) Lowest likelihood of confounding due to comparison to a randomized controlled group

b) Clearly defined population, setting, intervention(s), and comparison group
c) Appropriate measurement of outcomes
d) Appropriate statistical and analytical methods and reporting
e) No inconsistencies in reporting
f) Clear reporting of dropouts with dropout rate <20%.
g) No apparent bias

2) Studies with moderate risk of bias have the following features:
   a) Susceptible to some bias but not sufficient bias to invalidate results
   b) Do not meet all the criteria for low risk of bias owing to some deficiencies, but none are likely to introduce major bias
   c) May not be randomized or may be missing information, making it difficult to assess limitations and potential problems
3) Studies with high risk of bias have the following features:
   a) Indications of bias that may invalidate the reported findings (e.g., observational studies not adjusting for confounders, studies using historical controls, or studies with very high dropout rates)
   b) Serious errors in study design, analysis, or reporting
   c) Large amounts of information may be missing

e. Grading Quality of Evidence - RISK OF BIAS for PICO Outcome Across Studies (Form)

SEMPI Grading QOE – Risk of Bias

PICO:

Initial QOE Grade for Outcome Across Studies:

High Moderate Low Very Low

High = Randomized controlled trials (RCTs), or overwhelming evidence from observational studies

Moderate = RCTs with important limitations, or exceptionally strong evidence from observational studies

Low = Observational studies, or RTCs with notable limitations

Very Low = Clinical experience and observations; observational studies with important limitations, or RCTs with several major limitations

Evaluate Outcome for Risk of Bias Across Studies

If Meta-Analysis (pooled)

Sensitivity_____(_CI, from_____ to_____)
Specificity_____ (___CI, from_____ to_____)

If Single Study

Sensitivity_____(_CI, from_____ to_____)
Specificity_____ (___CI, from_____ to_____)

If Multiple Studies

Sensitivity from_____to _____
Specificity from_____to _____

Criteria	**Assessment** (circle one)	**Reason** for Assessment (e.g. proportion, plausibility, limitations)
Negative Bias		
Risk of Bias (e.g. selection bias, blinding, attrition, incomplete data)	Not Serious Serious Very Serious	
Inconsistency	Not Serious Serious Very Serious	

Indirectness	Not Serious Serious Very Serious	
Imprecision	Not Serious Serious Very Serious	
Positive Bias		
Strength of association	Low Moderate High	
Overall Effect of Bias on Initial QOE Grade		

- Bias has no effect on initial QOE
- Bias is sufficient to downgrade the initial QOE grade
  Describe:
- Bias is sufficient to upgrade the initial QOE grade
  Describe:

Final QOE Grade for Outcome Across Studies:

High Moderate Low Very Low

High – Very confident the true effect lies close to that of the estimate of the effect
Moderate – Moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different)
Low – Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of effect)
Very Low – Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect)

f. Grading Quality of Evidence (QOE) for each PICO outcome
   i. For each reference, determine quality of evidence based on study design:
      1) Grade initial quality of evidence for each outcome
         a) High - Prospective, randomized trials
         b) Moderate - Clinical studies in which data were collected prospectively or retrospective analysis based on reliable data
         c) Low - Studies based on retrospectively collected data
         d) Very Low - Review articles, case reports, editorial, expert opinion
   ii. Evaluate for risk of bias for meta-analysis or across studies.
      1) Select: Not Serious, Serious, Very Serious
   iii. Determine overall effect of bias
      1) If the quality of evidence is affected by bias, describe the reason.
   iv. Determine final Grade of quality of evidence after taking bias into account for each study:
      1) High--Very confident that the true effect lies close to that of the estimate of the effect
      2) Moderate--Moderately confident in the effect estimate (the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
      3) Low--Confidence in the effect estimate is limited (the true effect may be substantially different from the estimate of effect
      4) Very Low--Very little confidence in the effect estimate (the true effect is likely to be substantially different from the estimate of effect)

9. GRADING QUALITY OF EVIDENCE (QOE)-EVIDENCE TO RECOMMENDATIONS (Form)

SEMPI Grading QOE-Evidence to Recommendations					
PICO:					
SEMPI Quality of Evidence (QOE) & Recommendation Strength					
Authors/title	Highlights	Initial QOE Category	Final QOE Category (effect of bias & limitations)	Recommendation (Strength & rating)	Reviewer Comments
Recommendation Rating:					
Justification:					
Rating Definitions: **Quality of Evidence:** High quality = **1**; Moderate quality = **2**; Low quality = **3**; Very low quality = **4** **Strength of Recommendation: A** = Strength of Recommendation from Consistent Evidence; **B** = Strength of Recommendation from Panel Consensus					
Conclusion:					
Recommendation:					

10. DEVELOP TABLE OF RECOMMENDATIONS
    a. In creating recommendations, consider:
        i. Quality of evidence
        ii. Benefits versus harms and burden
        iii. Patient values and preferences
        iv. Equity, feasibility, and acceptability
        v. Resource implications
11. STRENGTH (AND WORDING) OF RECOMMENDATION
    a. Strong (designated as 'A') -The recommended course of action is based

upon consistent evidence.

b. Consensus (designated as 'B') - The recommended course of action is based upon professional consensus given a lack of consistent evidence.

12. SYMBOLIC REPRESENTATIONS OF RECOMMENDATION QUALITY
    a. **Quality** of evidence
        i. High quality **1**
        ii. Moderate quality **2**
        iii. Low quality **3**
        iv. Very low quality **4**
    b. **Strength** of recommendation
        i. Strength of Recommendation from Consistent Evidence **A**
        ii. Strength of Recommendation from Panel Consensus **B**

    c. Thus, available SEMPI recommendations are shown symbolically as**: 1A, 2A, 1B,2B, 3A, 3B, 4A, 4B.** (See complete listing of Grade representation and descriptions in table below.)

    d. Panelists use Review Comments for any remarks.

SEMPI Recommendation	
GRADE	**Description**
1A	Strong recommendation for the intervention based on high quality evidence
2A	Strong recommendation for the intervention based on moderate quality evidence
3A	Strong recommendation for the intervention based on low quality evidence
4A	Strong recommendation for the intervention based on very low quality evidence
1B	Strength of Recommendation from Panel Consensus for the intervention based on high quality evidence
2B	Strength of Recommendation from Panel Consensus for the intervention based on moderate quality evidence
3B	Strength of Recommendation from Panel Consensus for the intervention based on low quality evidence
4B	Strength of Recommendation from Panel Consensus for the intervention based on very low quality evidence

13. JUSTIFICATION FOR RATING—KEY POINTS FOR RECOMMENDATION
    a. Statement made by the full panel as a summary
    b. Intended to be clear and succinct

Consensus Recommendation

When evidence-based literature/empirical evidence is incomplete, or available evidence is controversial or not completely accepted, and the topic is deemed important, then SEMPI panels may utilize the Consensus Approach. Consensus recommendations provide a basis for decision-making and is considered evidence-based, taking into consideration the best available evidence, patient values and preferences, resources, and clinical expertise from practice. Important patient outcomes defined as desirable/undesirable, the usefulness of test and clinical utility is acknowledged as being guiding factors. Even if the evidence base might remain suboptimal, expert consensus is developed by incorporating findings from rigorous reviews of available evidence, using the same transparent and explicit methods as those for recommendations derived solely from evidence-based literature. The intention of consensus recommendation is to do more good than harm for those practicing while evidence is continuing to be gathered.

Recommendations created via the Consensus process are completed using "formal" SEMPI panel process along with all supporting documentation (studies, bias assessment, grading assessment, discussion, etc.) for evaluation and verification. Differences of opinion will be handled per the standard methodology. Final recommendations will be based on consensus opinion and will be graded as such. Transparency as to the quality of "evidence" and "strength" of recommendation is fundamental to the SEMPI Recommendation.

Multiple factors affect the decision-making process when evaluating the appropriateness of ordering imaging studies. These include current community standards, availability, patient preference and expectations, radiation exposure, adverse reactions to contrast agents and prior imaging results. Further, such factors are not always quantifiable and frequently vary across therapeutic settings. Panelists review available literature to recommend appropriate imaging studies in specific clinical scenarios but realize that these other variables impact the decision-making process and are not necessarily addressed by published literature.

Review Process—Annually

SEMPI has a clinical philosophy that is quality-focused, patient-centered, and physician-directed. Importantly, the SEMPI team's methodology, outlined in detail above, works to achieve this philosophy by following the Institute of Medicine's 10 Steps for Best Medicine and drawing on the expertise and data, of affiliated organization(s), for example Sage HMS. SEMPI guidelines and criteria are vetted in a repeatable process: thorough literature search, content outline reviewed by a multi-disciplinary panel, subject to panel approval, and an annual review.

The Annual Review, in which guidelines are reaffirmed or updated, is an ongoing process. New literature/clinical evidence is assessed by the clinical team to ensure that it corresponds to the clinical question. Based on new literature identified or if an existing recommendation needs to be reevaluated, the clinical expert panel may initiate a partial review or full CPG development process.

In addition to the above outlined review process certain additional events will require a comprehensive or focused review of existing content or require development of new content. A triggered review may encompass an entire CPG (Clinical Practice Guideline), a PICO in a related CPG or require development of new content.

Following are possible occurrences when a comprehensive review will be considered:

1. CMS directives
    a. New rules/requirements
    b. Change in priority areas
        i. Addition of new diagnostic topics
        ii. Deletion of any existing topics
        iii. Modification or Replacement of terminology/verbiage
2. Customer request to develop content for a clinical topic area
3. Previously referenced articles or guidelines in existing CPG's are updated, superseded or expire.
4. Customer feedback or errors reported by customers (e.g. patient safety issues)

Any changes in the documentation are reflected in each CPG's documentation, including the forms for Summary of Findings, Risk of Bias, and Quality of Evidence to Recommendation. If no panel reviews are considered necessary for annual changes, due to lack of changes from the literature review, lack of code changes or regulatory requirements, then the multidisciplinary panel will be notified for agreement to continue with the content as previously approved.

Reviewed or edited Clinical Practice Guidelines will be identified with updated date. Before any change is available on the SEMPI website, a copy of the original version will be archived.