The University of Pennsylvania Health System (UPHS) Center for Evidence-based Practice (CEP) was established by the Chief Medical Officer in 2006 to promote the integration of evidence into practice and to provide decision support for administrators and clinicians (including physicians and nurses) developing policy and practice in the Penn healthcare system. More information about the center can be found in references 3 and 5.

CEP is committed to pragmatically following best practices in gathering and analyzing evidence. This document is intended to provide an overview of CEP products and methods in the interest of transparency.

**CEP evidence products**

CEP offers a variety of evidence products to meet the varying needs of its stakeholders. Products are differentiated by the depth of searching and analysis. Evidence Reviews make up a majority of CEP reports. Most of the rest are Evidence Advisories.

**Evidence Review:** A rapid systematic review of clinical evidence on a focused topic, carried out using streamlined methods to find and summarize the best available evidence. These reports include evidence tables, quality assessment of the evidence, meta-analysis where the quantity of combinable studies is sufficient, and GRADE analysis for reviews where patient-centered clinical outcomes are available.

**Evidence Advisory:** A report using systematic methods to review and analyze a limited range of information sources: usually secondary sources such as existing clinical practice guidelines or systematic reviews. Evidence tables are included, but *de novo* analysis of study results is beyond the scope of this type of report.

**Evidence Inventory:** A systematic search of the literature and tabulation of identified studies that describes available evidence on a topic, typically stratified by study design, population, or intervention (see reference 2). Articles are not critically appraised, so there are no conclusions about the results of clinical studies or the quality of the evidence. One of the primary goals of an Evidence Inventory is to help stakeholders determine whether a full Evidence Review on a topic would be likely to find sufficient data to support a decision.

**Annotated Bibliography:** A systematic search of the literature and reference list of selected articles addressing a specific question. Articles are not critically appraised but they may be categorized by study design, patient population, or other characteristics that will help the reader find articles that are most relevant to his or her clinical question.

**Acquisition and triage of topics**

The Center Director receives inquiries from UPHS stakeholders including physicians and nurses, clinical department leaders, health system administrators, committees charged with purchasing and formulary decisions, and others. These inquiries are often made directly to the Director, but
may also be made through Center analysts and liaisons. A few reports are commissioned by outside partners. CEP faculty and staff communicate with requestors to clarify the specific issue or question to be addressed, the anticipated use of the evidence report, and desired time frame for the review, and then the inquiry is introduced at the weekly CEP meeting so CEP clinical and research staff can share their knowledge and suggestions.

Preliminary investigations may be done to understand the feasibility and scope of a proposed review topic, and the Center Director (or the analyst) will communicate the results to the requestor to help the requestor refine the proposal. In some cases, a client inquiry can be satisfactorily addressed with information that is already available, such as an evidence-based guideline, a recent high-quality systematic review or a technology report from the ECRI Institute.

Once the preliminary scope of the investigation is decided, the Center Director formally adds the topic to the CEP work queue, assigns it to a lead analyst, and designates a project director/clinical director to oversee the project.

Report authorship

The key personnel involved in the research and writing of CEP reports are the Lead Analyst and the Project Director. The Project Director is usually the CEP Director, Co-director, or one of the physician liaisons. The Project Director is responsible for ensuring the quality and clinical validity of the report, and ensuring that the scope of the report addresses the question at hand. The Lead Analyst drafts the protocol, designs and carries out searches, selects references for inclusion, abstracts and analyzes data, and writes the bulk of the report. The Lead Analyst also manages internal review of reports under the supervision of the Project Director, who is responsible for ensuring that reviewer comments are satisfactorily addressed.

Authorship of reports and of manuscripts derived from reports will normally include the Lead Analyst as first author and the Project Director as last or senior author. Project requestors and other persons with significant participation in the development of the protocol and review of the draft report are recognized as co-authors. Additional persons who participate only in clinical and technical review of the draft report are identified on the last page of the report but are not named as co-authors.

Conflict of interest disclosures

CEP analysts and staff (including the Lead Analyst and Project Director of every report) are not permitted to work on any project where they or an immediate family member have a financial or employment relationship with a manufacturer, supplier or other party that would present the appearance of a conflict of interest. All CEP personnel are required to disclose any such relationships when they occur. Conflict of interest disclosures for all CEP faculty and staff are updated annually. Additional disclosures are filed as required when CEP reports are submitted for publication in the peer-reviewed literature.

Topic requestors and other co-authors of CEP reports are required to disclose any financial relationships that are potentially relevant to the topic of the review. Persons whose only contributions to a report are minor technical or clinical review comments are acknowledged but not listed as co-authors, and not required to complete disclosure forms.
Physicians on faculty of the University of Pennsylvania Perelman School of Medicine are required to file financial disclosures annually with School of Medicine administration. Faculty financial disclosures can be searched at http://www.med.upenn.edu/fapd/conflict-of-interest.html.

**CEP funding**

The Center for Evidence-based Practice is supported by institutional funds administered through the Office of the UPHS Chief Medical Officer. All CEP reports are funded internally, with the exception of reports done for partners such as the Children’s Hospital of Philadelphia.

CEP holds or has held contracts and subcontracts from federal government agencies including the Centers for Disease Control and Prevention and the Agency for Healthcare Research and Quality. These contracts support specific projects which are separate from CEP’s regular production of evidence reports. Funding of such extramural reports is disclosed in the report.

CEP does not accept funds from drug or device manufacturers.

**Protocol development**

Once the topic is assigned to an analyst, the analyst develops a draft review protocol that specifies the question to be answered. The protocol follows the PICOTS (population, intervention, comparison, outcomes, timing, setting) structure. The protocol also specifies information sources to be searched, planned methods for evaluating the quality and quantity of evidence and methods for quantitative synthesis of study results where possible. Preliminary searches may be done at this point to get a rough estimate of the amount and type of evidence that is available; this information helps the analyst and Project Director decide what type of report will be produced (Evidence Review/Evidence Advisory/Evidence Inventory).

The draft protocol is submitted to the Project Director for review and approval. Once preliminary approval is secured, the protocol is shared with the requestor for review and approval. Other clinical stakeholders may be included as reviewers at this stage.

**Protocol adjustment**

In the interest of expediting reviews and ensuring they are responsive to client requests, the scope of reviews may need to be changed after approval of the review protocol. The need for such post-hoc revisions can be reduced with careful design of the initial scope, particularly by defining populations and study types to be prioritized, and pathways for broadening the review in the event that the evidence base is too small or weak to support any conclusions. Protocol changes made after initial approval that narrow the scope of the review should be disclosed in the final report.

**Local information**

CEP Evidence Reviews and Evidence Advisories may start with a brief summary of existing UPHS policies and/or guidelines that are relevant to the report topic. A summary of previous CEP reports on related topics is also included. The policy section allows UPHS decision-makers to see whether current policy is in agreement with published guidelines and clinical evidence.
Sometimes UPHS financial and/or clinical information may be included in a report, so findings of the evidence review can be placed into local context. (See reference 4 for examples.) If a report contains confidential or sensitive information, that information may be redacted from copies of the report made available to outside requestors, or the report may not be made available to outside requestors.

**Literature searching: General**

Designing and conducting effective searches for evidence is a challenging task, which cannot be fully taught in a general methods document like this. Searches for CEP reviews also must be tailored to the specific needs of the requestor, the timeframe in which the review needs to be completed, the nature of available evidence, and the quality of its indexing in the major bibliographic databases. Therefore the following guidance is presented as a starting point and not as a strict protocol. Methods will necessarily differ, to a greater or lesser degree, in many CEP reports. When development of a search strategy is specifically challenging or additional sources of information are needed, the Penn Biomedical Library liaisons, who are part of the CEP team, are consulted.

For most report topics, searches will begin with a search for existing literature syntheses (guidelines and systematic reviews) and then be followed by a search for primary studies (randomized controlled trials, observational studies, etc.). Literature searches for Evidence Reviews, Evidence Advisories and Evidence Inventories will be systematic and comprehensive and designed to capture as many relevant studies as possible. Literature searches for Annotated Bibliographies will be systematic, but not necessarily comprehensive, as the goal of this type of report is to present a selection of articles that address a particular issue for Penn Medicine stakeholders. These studies are informative and may provide important perspectives, but their validity and reliability are not evaluated or confirmed by the CEP analyst. Literature searches must include a minimum of two database sources.

**Literature searching: Guidelines**

A search for guidelines should include multiple sources. At minimum, a search for guidelines will include MEDLINE, and NICE Evidence Search. Other databases to consider include Guidelines International Network (G-I-N) and Web sites of important US clinical specialty societies. Professional societies in Canada, Europe, Australia, and Japan as well as global societies are often checked for guidelines. Searches for guidelines can be incorporated into the main searches of bibliographic databases such as EMBASE and CINAHL when appropriate.

See supplemental documents for filters and other standard search syntax used with major databases.

**Literature searching: Reviews**

Searches for systematic reviews are carried out in, at minimum, the Cochrane Library (which includes the Cochrane Database of Systematic Reviews (Cochrane), NICE Evidence Search (which incorporates the former Database of Abstracts of Reviews of Effects and the former Health Technology Assessment database), and MEDLINE. Reports from the Canadian Agency for Drugs and Technologies in Health (CADTH) should be searched when the topic involves a drug, device, diagnostic test, or procedure. The Lead Analyst and Project Director will decide
whether a search for reviews in other bibliographic databases should be conducted. Searches for reviews in MEDLINE and other bibliographic databases may be incorporated into the main searches of these databases when appropriate. When the scope of the report is to include economic factors, the NHS Economic Evaluation Database should also be searched, though it too is no longer being updated.

See supplemental documents for standard search syntax used with major databases.

**Literature searching: Primary studies**

At minimum, searches for primary literature should encompass both the MEDLINE (OVID or PubMed interface) and either the EMBASE or CINAHL databases. EMBASE includes numerous non-MEDLINE journals, particularly from Europe and other non-US sources. EMBASE also has greater coverage of conference proceedings. For CEP report topics related to nursing or the allied health sciences, CINAHL should be searched; for topics relating to mental health or psychology, PsycINFO should be searched. In addition, the Cochrane Central Register of Controlled Trials (CENTRAL: Wiley interface is preferred) should also be searched if comparative studies are expected to be found.

**Search development**

After drafting a tentative search strategy, the person tasked with developing the literature search should submit the draft strategy to the project director for comment and approval. The search strategy is not normally submitted to the requestor for approval.

OVID MEDLINE searches should include both the main MEDLINE file (1946-present) and the MEDLINE In-Process & Other Non-Indexed Citations file. Searchers should be aware that searches that rely on index terms (i.e. one or more dimensions of the search is based entirely on index terms without an OR statement joining to a keyword search) will miss references from the In-Process file.

MEDLINE searches should include both index terms and keywords for relevant concepts, unless a preliminary search determines that index terms are lacking or unreliable. It is our experience that searches based only on index terms have inadequate sensitivity because NLM bibliographers may not capture all of the most relevant concepts when indexing articles. OVID qualifiers .mp (multi-purpose) or .ti,ab,kw (title, abstract, keyword) are both acceptable in keyword searching.

EMBASE search strategies should be developed with specific reference to the EMTREE indexing structure, as it differs in some important aspects from the MeSH indexing used in MEDLINE and PubMed. EMBASE indexing is more reliable, but inclusion of keywords for free-text searching in EMBASE searches is still suggested.

When adapting MEDLINE or EMBASE search strategies for use in CENTRAL, search elements relating to study design should be left out, as the CENTRAL database is pre-screened for controlled studies. This can allow for a broader search on other axes such as population or intervention.

CEP does not have a minimum or maximum number of database hits to screen.
Date restrictions

Literature searches may be restricted to specified periods of time so that evidence considered in the review does not reflect obsolete versions of a technology or outdated practices of care. Such restrictions should be documented *a priori* in the review protocol.

Language restrictions

CEP reviews are typically limited to articles published in the English language. Multiple studies suggest that the reliability of systematic review conclusions is often not adversely affected by limiting searches to English-language literature (see reference 1).

In order to broaden the evidence base, the analyst may include non-English literature at his or her discretion, so long as he or she is able to sufficiently translate the article (with or without automated translation software) so as to understand the population, methods, and results, and adequately assess threats to the validity of the results and conclusions. If so, the languages of articles that will be included or excluded should be documented in the report.

Full versus abstract publications

CEP data analyses and evidence tables exclude evidence from studies published only in abstract form, even if their abstracts are published in a peer-reviewed journal. Abstracts rarely provide sufficient information about study methods and outcomes to allow us to adequately assess the reliability of the results.

If the evidence from studies published in full form is weak or insufficient, results from studies published in abstract form may be reported in the text of the review for purposes of corroborating findings from the published studies. In this case, the weakness of evidence from abstract-only publications should be called to the reader’s attention.

Study size

By default, the minimum sample size for comparative studies to be included in a CEP review is 10 patients per group. Smaller studies are at increased risk of having non-representative samples of patients. The study size threshold may be increased if the evidence base is particularly large, or reduced if the evidence base is very small.

Study design (primary studies)

The study designs eligible for inclusion in CEP reports depend on the type of CEP report (Annotated Bibliography, Evidence Inventory, Evidence Advisory, or Evidence Review) as well as the topic/question of the report. For reports that aim to summarize the literature on efficacy or effectiveness, the randomized controlled trial (RCT) design will be prioritized. Non-randomized controlled trials with comparison groups will be sought as a second-line priority and analyzed if there is not sufficient RCT data to answer the research question. Hedges are often used to filter searches by study design (see reference 7).

Reference database and search documentation

CEP presently uses RefWorks software to manage references and prepare bibliographies for each report. The full results of each primary literature search (a listing of all hits in the final search)
should be retained in one form or another: either as a downloaded reference list (RIS format) or in the bibliographic database (RefWorks).

Final search strategies and a count of hits from each database are included in each report, along with counts of how many articles were marked for retrieval and how many articles were ultimately included in the evidence tables. A full PRISMA diagram describing the disposition of references is not included in CEP reports, as a means of expediting review.

**Duplicate detection**

RefWorks has a duplicate detection function with good sensitivity and specificity, but all marked duplicates are verified by the analyst before deletion. Records of deleted duplicates are retained either in the database or on paper.

**Title/abstract screening**

Title/abstract screening is done by a single analyst rather than by two independent analysts, in order to expedite review. Records of which references were excluded at this stage are maintained, but providing the specific reason for each exclusion is not necessary.

**Full-text retrieval**

It is expected that with the online resources and interlibrary loan, all articles marked for retrieval will be retrieved and screened. If any articles are unable to be retrieved, this should be documented in the report. Copies of all full-text articles (in electronic or paper form) are maintained with project files.

**Full-text screening**

Full-text screening is also done by a single analyst rather than by two independent analysts, in order to expedite review. Reasons for each exclusion at this stage should be recorded on paper or in the database, but do not need to be included in the report.

**Data abstraction**

Data abstraction is done by a single analyst rather than by two independent analysts, in order to expedite review. Data may be abstracted directly into the evidence tables, into a spreadsheet or computer database, or on paper. In all cases, the abstraction forms should be maintained with project files.

**Preferred methods for meta-analysis**

Most CEP meta-analyses involve datasets from clinical trials comparing the results of two groups in terms of whether or not patients had a specific outcome or adverse event. Our standard tool for meta-analyzing this data is RevMan (Cochrane Collaboration), though other validated tools including Comprehensive Meta Analysis and Open Meta-Analyst are also acceptable. Selection is at the analyst’s discretion, considering the differences in analysis and graphing capabilities and ease of use of those different tools.

Binary data should be analyzed using a random effects model. Results should be reported in full, including summary effect size and 95% confidence interval, and heterogeneity as measured with
the $I^2$ statistic (considered significant at 30-50% or more). A forest plot including results of individual studies and the summary results is included in the report.

Continuous data are also analyzed using a random effects model. Where possible, results are combined in their original metric, but if results are reported in different ways standardized mean differences are meta-analyzed. Results are reported in full, including forest plot, summary effect size and 95% confidence interval, and heterogeneity as measured with the $I^2$ statistic (considered significant at 30-50% or more).

Diagnostic data are analyzed using a two-dimensional model: either the bivariate approach (Reitsma) or logistic regression (Littenberg-Moses). Results are reported as summary ROC curves and selected points from the curve in the clinically-relevant range of thresholds. Area under the ROC is not reported.

**Quality assessment of published guidelines**

CEP has developed a guideline appraisal instrument based on the IOM publication “Clinical Practice Guidelines We Can Trust.” (see reference 6). The current version of this instrument is included with the supplemental documents.

**Quality assessment of published systematic reviews**

CEP uses a modified AMSTAR scale to assess the quality of systematic reviews. This streamlined scale was developed in-house and reviewed by external methodological experts. A copy of the scale is included with the supplemental documents.

**Quality assessment of randomized controlled trials**

CEP uses a modified Jadad scale to assess the quality of randomized controlled trials. This scale was developed in-house. A copy of the scale is included with the supplemental documents.

**GRADE summary**

The evidence for each outcome is graded by the analyst for overall quality and given a rating of high, moderate, low, or very low based on the system proposed by the GRADE Working Group (http://www.gradeworkinggroup.org/). Quality assessments are based on the nature of the evidence as well as its validity, directness, consistency, precision and other factors. Summaries of GRADE methods for evaluating evidence on interventions and for evaluating evidence on diagnostic tests are included with the supplemental documents.

**Internal review**

The first draft of the report is reviewed by the Project Director, who is responsible for ensuring that the review methods are sound, conclusions are supported by evidence, and the content of the report is accurate. The Lead Analyst revises the report in response to the reviewer comments, and the review loop continues until the Project Director is satisfied with the draft.

Then the report is circulated to the requestors for review and comment. Additional internal reviewers, specifically clinicians from UPHS entities, may also be invited to review the report at this time. The Project Director determines whether or not revisions to the report are sufficiently responsive to reviewer comments and, if necessary, decides whether reviewers have been given...
sufficient time to review and comment on reports. The Project Director then gives approval for the report to be finalized. Final reports are converted to PDF files before dissemination, to maintain the integrity of the contents.

There normally is no external (non-UPHS) review of draft reports because this adds substantially to the time needed to complete a report. Also, the local reviewers are more responsive to questions about their comments and more willing to participate in additional review loops as necessary to improve the report.

**Report dissemination and implementation**

Once final, CEP reports are disseminated by email to all key stakeholders across UPHS as identified by the clinical liaisons. Select reports are also presented by either directors or analysts at in-person meetings to decision makers, and integrated into clinical decision support tools and quality improvement initiatives.

CEP reports are prepared primarily for the purpose of informing clinical and policy decisions at UPHS. However, many of the topics of CEP reviews are of interest to a much broader audience. In the interest of improving the quality and safety of healthcare everywhere, full text of most CEP reports will be made available (in PDF form) on request to persons outside UPHS. Exceptions will be made, at the discretion of the Director, for reports containing confidential or proprietary information such as cost and operational data.

Bibliographic information and summaries of CEP reports are submitted annually for indexing in the Health Technology Assessment database, and a listing of all completed reports is published on the CEP public internet site. Selected reports are submitted for publication in the peer-reviewed literature, especially reports that address topics of general interest, have sufficient evidence to synthesize, and have no recent published systematic reviews in the peer-reviewed literature.

**Version control**

Revisions to a CEP report may become necessary if errors are discovered in the report as published, if important new evidence comes to light, or if evidence relied on for the conclusions of the report is retracted or corrected.

In the event that revisions to a CEP report become necessary after the report is published to the CEP web site, the following procedures should be followed. The lead analyst will report the situation to the center director, who will determine how to proceed.

If the changes are minor, and purely typographical or grammatical in nature, and results or data in tables are not changed, no notice of revision is necessary. If changes affect data, results, or conclusions, or if there is a substantive revision to the text, the reason for and nature of the change should be stated in a note to readers on the first interior page of the report with the heading “Correction” or “Update” as appropriate.

In all cases, a bullet symbol (•) will be inserted after the project number (e.g. R236•) in the cover page footer to denote a revised version of the report. A copy of the revised report shall be sent to all persons who received the original report.
References


