MEDICAL EFFECTIVENESS ANALYSIS AND RESEARCH APPROACH

The California Health Benefits Review Program (CHBRP) is charged by the California Legislature with estimating the medical effectiveness, public health, and cost implications of proposed health insurance benefits-related legislation (bills). CHBRP analyses present three types of information: (1) the medical effectiveness of screening, diagnostic, treatment, and other health services addressed in the legislation; (2) the financial impacts of the legislation; and (3) the impact on public health. This document describes the research approach used to analyze medical effectiveness.

The purpose of this document is to maximize transparency of CHBRP's approach to analyzing medical effectiveness.

CHBRP's initial approach to analyzing bills was described in a special edition of *Health Services Research* (Philip et al., 2006). This document and additional updates to the medical effectiveness analysis approach can be found on CHBRP's website.[1]

Details of the approach to analyzing medical effectiveness are found in the following sections below:

Background

As noted above, CHBRP analyses California health insurance benefits-related bills that may impact the benefits covered by state-regulated health insurance. California bills are introduced in

[1] Available at: http://chbrp.com/analysis_methodology/medical_effectiveness_analysis.php

either the California Senate or the Assembly, and are referred to by the house of origin and number, so CHBRP's analyses focus on Senate Bill (SB) X or Assembly Bill (AB) X. Throughout this document, examples from CHBRP's completed analyses are used to illustrate methods. The full analyses are found on CHBRP's website.[2]

Health insurance benefits-related bills considered by the California Legislature may impact health insurance plans and policies regulated by the Department of Managed Health Care (DMHC) or the California Department of Insurance (CDI). It is important to recall, however, that not all health insurance is subject to state law. For example Medicare and self-funded employer sponsored insurance are subject only to federal law. Additional information about Californians' enrollment in the various types of health insurance (that may or may not be subject to state law) is available in CHBRP's *Estimates of Sources of Health Insurance in California.*[3]

Preparing to Conduct the Literature Search

A. CHBRP staff at the University of California, Berkeley receive a request from the California State Legislature to analyze a health insurance benefit-related bill. An electronic copy of the bill is made available to all CHBRP faculty and staff.

B. CHBRP staff work with contracted faculty and researchers at UC campuses to determine who will work on the medical effectiveness, cost, and public health analyses.

C. CHBRP staff complete a phone call with the bill author's staff (and sometimes the bill sponsor) to clarify the bill author's intent. The items discussed in the phone call are derived from a bill author questionnaire that contains standard questions as well as questions specific to the bill that have been posed by CHBRP faculty and staff. The medical effectiveness team reviews the responses to the bill author questionnaire and uses them to refine the specifications for the literature search.

D. The medical effectiveness team, in consultation with other CHBRP faculty and staff, identifies a content expert for the bill. This person is often an expert in a relevant clinical specialty who is knowledgeable about current clinical practice, as well as clinical controversies associated with the bill. The content expert is also usually familiar with clinical epidemiology, health services research, or evidence-based medicine. For some bills, two content experts may be retained to ensure that the team obtains expertise in several areas relevant to the bill. Examples include bills that would have required coverage for oral chemotherapy drugs (SB 161 [2009] and SB 961 [2010]), and for diabetes-related complications (SB 1104 [2010]). For these bills, both a physician and a pharmacist were retained to provide expertise on pertinent diseases and the medications used to treat them.

E. The content expert reviews the legislative language and assists the medical effectiveness team in clarifying the meaning of the clinical terms used in the bill or relevant literature. For example, in reviewing the literature pertaining to the analysis of AB 1549 (2003), which addressed management of childhood asthma, the content expert explained what physicians mean by "treatment action plans" and the differences between types of action plans (i.e., peak flow-based vs. symptom-based).

[2] Completed analyses can be found here: http://chbrp.org/completed_analyses/index.php
[3] Available under Resources at: http://chbrp.com/other_publications/index.php#revize_document_center_rz44

F. **Developing a Logic Model.** The medical effectiveness team generates a logic model for the bill. The logic model shows the hypothesized linkages between the enacted bill and the changes in utilization (i.e., what impacts on healthcare utilization the bill might have) and the hypothesized linkages of the changes in utilization to health outcomes.

Below is an example of a logic model that could have been constructed for SB 999 (2016), a bill that would have required DMHC-regulated plans and CDI-regulated policies to cover a 12-month supply of hormonal contraceptives. The logic model shows how answers to five research questions posed by the medical effectiveness team that analyzed SB 999 drive conclusions regarding the impact of this bill. The five research questions are:

Research Question 1. Does an increase in dispensed self-administered hormonal (SAH) contraceptives result in reductions in unintended pregnancy, and other related outcomes, such as abortion rates, poor birth outcomes, infant morbidity and mortality, and poor child health status?

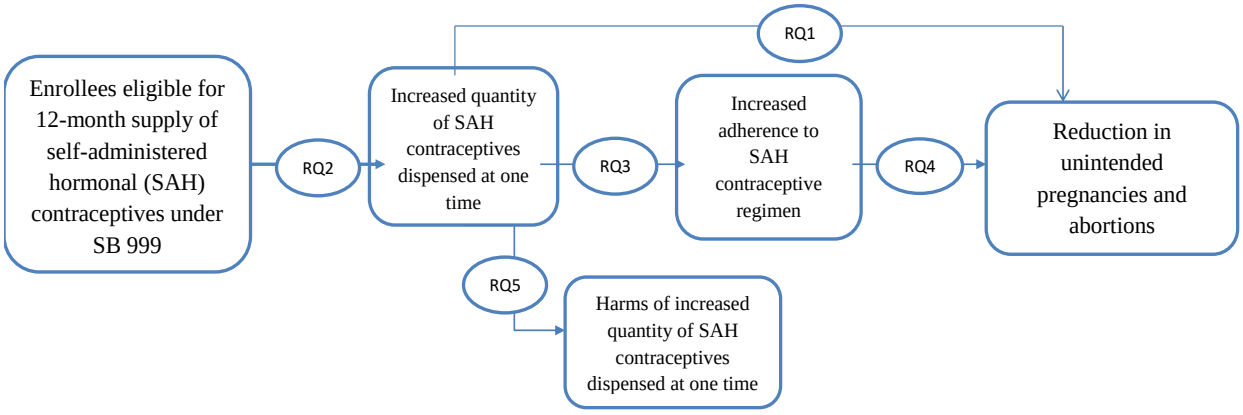
Research Question 2. Does coverage of a 12-month supply of SAH contraceptives increase the quantity dispensed at one time?

Research Question 3. Does an increase in contraceptives dispensed improve adherence to SAH contraceptive regimens?

Research Question 4. Does improved adherence to SAH contraceptive regimens result in reductions in unintended pregnancy, and other related outcomes, such as abortion rates, poor birth outcomes, infant morbidity and mortality, and poor child health status?

Research Question 5. What are the harms (undesirable outcomes) associated with dispensing of a 12-month supply of SAH contraceptives?

Figure 1. Logic Model for the Analysis of SB 999 (2016)



G. **Tabulating Components of Complex Bills.** If a bill would mandate coverage for multiple treatments or modalities of care or for treatments that multiple populations use or that are

used for multiple purposes, the medical effectiveness team may find it helpful to create a table that lists each category of treatment, modality of care, population, etc. The information in the table can be used to guide the development of the literature search specifications and can help the medical effectiveness team organize the results of the literature search. Below is an example of a table that could have been constructed for AB 447 (2017), a bill that would have required coverage of continuous glucose monitors for three subgroups of persons with diabetes and two types of continuous glucose monitors.

Table 1. Summary of Evidence of Medical Effectiveness of Continuous Glucose Monitors

	Retrospective	Real-time
Type 1 Diabetes	Preponderance of evidence – not effective	Inconclusive evidence
Type 2 Diabetes	Inconclusive evidence	Limited evidence – not effective
Gestational diabetes	Limited evidence – effective	Insufficient evidence

Source: California Health Benefits Review Program, 2017.

H. **Developing the Literature Search Specifications.** The medical effectiveness team works with the content expert and medical librarian to define the scope of the literature search for medical effectiveness and develop a plan for analyzing the literature. The medical effectiveness team prepares a draft literature search specifications memo and circulates it to the medical librarian, the CHBRP staff lead, and the public health team members working on the bill. The team members quickly review and comment on the draft. The public health sections of the memo contain "boilerplate" terms that the public health team members working on the bill edit to reflect their literature search needs. The medical effectiveness team revises the memo to incorporate the input received and submits a final version to the medical librarian. (The cost team will prepare a separate set of specifications for the librarians for a search of literature pertinent to the cost analysis.) While developing the literature search specifications memo, in collaboration with the content expert, the medical effectiveness team:

1. Identifies the type of intervention(s) the bill addresses (e.g., is the intervention a screening, diagnostic, or monitoring test, a procedure, or a treatment?) and the type(s) of literature needed to analyze the impact of the bill on patient outcomes and utilization of health care services.
2. Identifies the types of studies that contain information pertinent to the intervention(s). For example, if the bill were about osteoporosis treatment, studies about the effectiveness of osteoporosis treatments would be included, but studies of the effects of primary prevention of osteoporosis would be excluded.
3. Identifies the outcomes that the literature review will assess. If the bill references specific outcomes, these outcomes will be included in the review. If the bill does not mention

specific outcomes, the team and the content expert will identify outcomes most relevant to the bill. There is a preference for outcomes that are meaningful and recognizable to consumers, including patient-reported outcomes, over physiological outcomes. Outcomes of particular interest to CHBRP include mortality, morbidity, quality of life, ability to perform everyday activities, and absences from school and work due to illness.

4. The medical effectiveness team may use the following general inclusion/exclusion criteria:

    a. Include only studies for which an abstract has been published. The tight time frame for production of CHBRP reports (no more than 60 days from legislative request to completed analysis) compels the team to rely on abstracts as a screen to determine whether articles should be included in a literature review. Although some articles that do not have abstracts present research findings, most are commentaries, editorials, and letters to the editor that do not present the results of medical effectiveness studies and, thus, would not be included in CHBRP's literature reviews.

    b. Include only abstracts in English. The timeframe for CHBRP reviews is too short to obtain translations of medical literature published in other languages.

    c. Limit the search to the population affected by the bill. For example, for the analysis of AB 1549 (2005), which concerned management of childhood asthma, "children" were defined as persons aged 0 to 18 years and studies in which a large proportion of the subjects were older than 18 years were excluded.

    d. Limit the search to the past 20 years. The team may shorten the time period, if there is a large body of literature on the topic and/or if the content expert has indicated that treatment has changed considerably over the past 20 years. The team may lengthen the time period it if there are few published studies.

    e. In cases in which CHBRP is asked to analyze a bill that is similar to a bill on which the program has previously issued an analysis, the search is limited to literature published since the previous analysis was issued.[4]

5. The team determines the databases to be searched.

    a. Peer-reviewed literature

    The following databases that index peer-reviewed literature are typically searched: The Cochrane Library, MEDLINE (PubMed), and Web of Science. Other specialized databases of peer-reviewed literature, such as CINAHL EMBASE, PsycINFO, and Scopus may be searched if they are likely to contain articles relevant to the bill.[5]

[4] For example, in 2009 CHBRP was asked to analyze a bill (SB 158) that would mandate coverage for the human papillomavirus (HPV) vaccine. This bill was identical to a bill (AB 1429) CHBRP analyzed in 2007. Because CHBRP had conducted a comprehensive search of literature published through 2006 for AB 1429, the search for SB 158 was limited to literature published from January 2007 through March 2009.

[5] Some material published in peer-reviewed journals has not been peer-reviewed. In particular, journals may publish guidelines issued by organizations whose work is of interest to their readers without peer review. For example, *Obstetrics & Gynecology* publishes guidelines issued by the American College of Obstetrics and Gynecology, and *CA: A Cancer Journal for Clinicians* publishes American Cancer Society guidelines. Some of these guidelines are based on opinion and may provide weaker evidence than peer-reviewed journal articles and some documents in the grey literature. As discussed in *Selecting Articles for Inclusion in the Review*, the medical effectiveness team applies

Cochrane reviews are authoritative, peer-reviewed systematic reviews that can be treated as a "gold standard" with regard to the rigor of the methods used to review the medical literature. Cochrane reviews are often narrow in focus and, thus, most helpful for analyses of bills that address a limited set of services. For bills that address multiple treatments, Cochrane reviews supplement systematic reviews that address broader ranges of services, such as those conducted by the National Institute for Health and Clinical Excellence (NICE)[6] and the Agency for Healthcare Research and Quality's Evidence-based Practice Centers (AHRQ EPCs).

b. Grey literature

CHBRP also searches the grey literature, which consists of material that is not published commercially or indexed systematically in bibliographic databases. The grey literature is primarily composed of technical reports, working papers, dissertations, theses, business documents, and conference proceedings. The CHBRP medical effectiveness team draws upon grey literature from government agencies, scientific research groups, and professional societies for its reviews. Systematic reviews are among the types of grey literature most frequently analyzed for CHBRP reviews.

The medical effectiveness team has grouped the sources of grey literature into two hierarchical tiers based on the strength of the evidence.

First tier of the grey literature

The first tier of the grey literature includes systematic reviews and meta-analyses issued by authoritative organizations whose primary mission is to conduct objective analyses of the effectiveness of medical interventions that are used to develop evidence-based clinical practice guidelines. NICE and the US Preventive Services Task Force (USPSTF) are two of the most useful sources in this category, because these organizations commission systematic reviews that explicitly state their research questions, use standardized methods to assess the strength of evidence, and distill detailed findings into a small number of major conclusions. Other sources in this category include: the AHRQ EPCs, the Centers for Disease Control and Prevention Advisory Committee on Immunization Practices (CDC ACIP), the International Network of Agencies for Health Technology Assessment (INAHTA), the National Institutes of Health (NIH), the Scottish Intercollegiate Guidelines Network (SIGN), and the World Health Organization (WHO). These sources are searched by the medical effectiveness team if they address the health care services for which a bill would mandate coverage (e.g., search the USPSTF website when analyzing bills on screening tests). Systematic reviews and meta-analyses issued by these organizations are incorporated into CHBRP's literature review as described in *Selecting Articles for Inclusion in the Review* below. CHBRP relies most heavily on literature syntheses

---

the same hierarchy of evidence to all literature regardless of whether it appears in peer-reviewed journals or the grey literature. In addition, the medical effectiveness team and the content expert apply their knowledge of pertinent guidelines, journals, etc., when selecting literature for inclusion in the literature reviews.

[6] NICE commissions other organizations, such as the National Collaborating Centre for Women's and Children's Health, to produce evidence-based guidelines on some topics.

that present major findings from rigorous analyses of the evidence in a clear and concise manner.

Second tier of the grey literature

The second tier of grey literature consists of clinical practice guidelines issued by medical and scientific societies. They are often based on expert opinion, although some are evidence-based. The merit of these guidelines stems from the authoritative reputation of the societies. Such guidelines include those issued by AACE (American Association of Clinical Endocrinologists), AAP (American Academy of Pediatrics), AAPD (American Academy of Pediatric Dentistry), ACOG (American College of Obstetricians and Gynecologists), ADA (American Diabetes Association), APA (American Psychiatric Association), and the National Comprehensive Cancer Network (NCCN). Decisions about searches of professional society websites for guidelines are made on a case-by-case basis. Decisions are based on the following criteria: knowledge of the medical effectiveness team and content expert regarding guidelines issued by pertinent professional societies, the strength of evidence available from other sources, and whether the bill explicitly references a guideline or is derived from a guideline. See section *Selecting Articles for Inclusion in the Review* below for details.

c. Clinical practice guidelines

CHBRP has developed the following criteria to determine whether and how clinical practice guidelines should be incorporated into its medical effectiveness reviews.

Bills that reference clinical or national practice guidelines

In cases where:

- A bill mandates coverage for an intervention that is "consistent with national guidelines,"; or
- A guideline is an obvious source of bill language; or
- A guideline is specified in the bill.

The medical effectiveness team will select studies for inclusion per CHBRP's hierarchy of evidence (discussed in *Selecting Articles for Inclusion in the Review* below) and will also will assess relevant guidelines.

Bills that DO NOT reference clinical practice guidelines

The medical effectiveness team will follow CHBRP's hierarchy of evidence, which ranks clinical practice guidelines below other sources of evidence regarding medical effectiveness. Systematic reviews and meta-analyses that are part of a guideline may be reviewed separately per the hierarchy of evidence. If a guideline appears to be evidence-based and relevant to the issue, the medical effectiveness team may reference it in the text. In a case where little or conflicting information about the issue is available, the medical effectiveness team may cite guidelines with appropriate caveats noted (i.e., strength of evidence, guideline author, etc.).

For bills for which the medical effectiveness team determines that clinical practice guidelines should be reviewed, the National Guideline Clearinghouse (NGC) is always searched to identify summaries of pertinent guidelines. The medical effectiveness team uses NGC's summaries to screen guidelines and retrieves the full text of guidelines it selects for inclusion in the literature review.

Web sites maintained by organizations that issue clinical practice guidelines are also searched, because NGC has several important limitations. NGC relies on voluntary submissions and, as a consequence, does not index all guidelines. Some of the most authoritative guidelines are not indexed by NGC. For example, as of 2017, clinical guidelines from the American Diabetes Association are not indexed with NGC. In addition, the quality of the evidence presented in guidelines indexed by NGC varies. Some guidelines are based on systematic reviews of peer-reviewed literature, whereas others are based on expert opinion. In addition, NGC's summaries of guidelines are not as authoritative or as exhaustive as the full guidelines.

G. The medical effectiveness team, content expert, and medical librarian take into account primarily the literal meaning of the bill's language when developing the strategy for the literature search but may also consider the bill author's stated intent (when the intent does not appear to contradict or be unsupported by the literal meaning).

1. Some bills address coverage for multiple types of services (e.g., medical treatment, medical supplies, physical therapy, and counseling). In such cases, the literature search will be designed to retrieve literature on all types of services relevant to the bill.

2. For some bills, the medical literature may be assessed in segments because it addresses a wide range of diseases and conditions. For example, if a bill addressed cancer screening, the team would need to analyze literature on screening of multiple types of cancer (e.g., breast, colorectal, lung, and prostate separately).

3. Screening, diagnostic, monitoring, and treatment interventions require different analytic approaches. For example, a treatment is typically designed to cure a disease or improve function, and designing trials to assess how well the treatment works may be relatively straightforward. On the other hand, a screening test might indicate an increased risk of a disease. This may lead to recommendations for one or more types of preventive interventions. The interventions may vary in their effectiveness, and the disease, which may or may not manifest even if the result of the screening test is positive, may be treated in various ways.[7] Thus, an effectiveness assessment of an intervention will have to be built upon information available from various parts of the "evidence chain." To assess each of these links, information needs to be collected over a long period of time. Testing and treatment options continually change over time, and studies that directly address all effectiveness questions pertinent to a bill may not exist.

4. Some bills may concern the terms of coverage for different types of services rather than coverage for specific health care services per se. Examples include SB 572 (2005), which

[7] For example, a screening test may indicate that a person has high cholesterol. Based on this result, his or her physician may recommend exercise, dietary changes, and/or medication. These preventive interventions may or may not lower the person's cholesterol or prevent him or her from developing heart disease. If he or she develops heart disease, his or her physician may recommend one of several treatments which may or may not be successful.

addressed parity in coverage of physical and mental health services, and SB 1198 (2008), which concerned parity in coverage for durable medical equipment. For parity bills, the medical effectiveness analysis focuses on evidence of the effects of parity, such as the effects of reduction in cost sharing on utilization of health care services and health status, to the extent literature is available on these topics. Other bills that have addressed the terms of coverage include AB 1826 (2010), which would have prohibited "fail-first protocols" for pain medication. For this bill, the medical effectiveness team reviewed the literature on the impact of "fail-first protocols."

5. Some bills address more treatments or conditions than the medical effectiveness team can analyze within 60 days. For example, AB 219 (2013), a bill regarding coverage for oral anti-cancer medications, would have affected coverage for 54 medications that are used to treat over 50 cancers. In such cases, the medical effectiveness team assigned to a bill will work with other members of the analysis team to develop a feasible research approach. For AB 219, the medical effectiveness team provided readers with general descriptive information regarding oral anti-cancer medications but did not analyze the literature on the effectiveness of any of these medications.

Conducting the Literature Search

A. The medical librarian conducts the search and contacts the medical effectiveness, cost, and public health team members working on the bill regarding questions as they arise.

B. The medical librarian provides the initial search results to the medical effectiveness and public health teams in EndNote to the maximum extent feasible. All citations to peer-reviewed literature should be included in the EndNote file. EndNote is software to manage and organize citations and references for academic writing.

C. The medical librarian records all search terms, including Medical Subject Headings (MeSH) terms and key words.

D. The team assesses the extent to which the results of the literature search address the questions and issues underlying the bill, consulting the content expert as needed. If the initial literature search returns few results, the search criteria will be reexamined, and the medical librarian will run additional or modified searches, or the lead analyst on the medical effectiveness team will search articles from the reference lists of articles that have already been retrieved to determine if they contain any additional articles pertinent to the bill.

Deciding Whether to Retrieve Articles

A. At least two medical effectiveness team members review all abstracts returned by the search to identify articles for which the full text will be retrieved.[8] Criteria for excluding articles may include: (1) duplicate studies: (2) study subjects who are not representative of Californians who would be affected by the bill: and (3) articles that describe interventions but do not assess their effectiveness.

[8] This approach risks excluding useful articles based on their abstracts. This risk is necessary, given the short time frame for CHBRP reports. However, abstracts often overstate, rather than understate, authors' findings.

B. For utilization outcomes, only studies conducted in the United States are selected. When an outcome is likely to depend on specific aspects of the US health care system, such as the effect of pediatric asthma education on emergency department visits, the results may be affected by policies and norms of "usual care" that differ in other countries. However, if the outcome of interest concerns health status, international studies may be included.

C. Once a full-text article is retrieved,[9] the team reapplies the initial inclusion/exclusion criteria to ensure the study is relevant to the bill.

D. There may be instances in which the full text of an article cannot be retrieved quickly enough to meet the timeline for a CHBRP review. In these instances, the team relies on the published abstract. Reliance on an abstract may omit information relevant to a CHBRP review, including some of the study's results and information about the characteristics of the study population. The team keeps a log of articles that appear relevant, but for which full text was not available in time for inclusion in the draft report circulated for review. If articles arrive after the due date for the draft report, they will be examined to determine whether they would substantively alter the team's conclusions. If the conclusions would change, the report is revised accordingly.

Selecting Studies for Inclusion in the Literature Review

A. Hierarchy of Evidence

In general, the medical effectiveness team faculty and staff adhere to the following hierarchy of evidence when determining which articles to include in a review:

1. High-quality meta-analyses[10]—particularly those included in the Cochrane Library.
2. Systematic reviews—particularly those performed by authoritative organizations, such as the AHRQ, NICE, USPSTF, and other government agencies (e.g., NIH, CDC, and the Centers for Medicare & Medicaid Services).
3. Well-implemented randomized controlled trials (RCTs) and cluster RCTs.[11]
4. RCTs and cluster RCTs with major weaknesses.

---

[9] The team retrieves full-text articles available on the Internet through the University of California libraries. If an article is not available online, but is available in hard copy at the UCSF, UCD, or UCI library, a team member retrieves the article from the library. If an article is not available at UCSF, UCD, or UCI, the team requests the article through interlibrary loan, from the journal's website, or a commercial document delivery service.

[10] "High-quality" meta-analyses are meta-analyses that have clear objectives and hypotheses, apply appropriate inclusion/exclusion criteria, assess meaningful outcomes, and use sound methods to find, select, and evaluate studies and to generate pooled estimates of an intervention's effects. In general, results of meta-analyses of randomized controlled trials (RCTs) are likely to produce more valid estimates than meta-analyses of observational studies, because randomization of subjects reduces the risk of selection bias. In addition, meta-analyses with large numbers of observations (i.e., where the sum of observations from all studies included in a review is large) are likely to yield more valid estimates than meta-analyses with small numbers of observations because they have greater power to detect effects. (Cochrane, 2005; Egger et al., 1998; Egger et al., 1997; Flather et al., 1997)

[11] "Cluster RCTs" are studies in which subjects are randomized in groups rather than as individuals. This research design is typically used in situations in which the intervention is administered to groups of subjects or in which randomization at the individual level may lead to contamination of the control group (i.e., inadvertent exposure to the intervention).

5. Nonrandomized studies with comparison groups and time series analyses.
6. Case series and case reports.
7. Clinical practice guidelines and narrative reviews.[12]

B. Implementing the Hierarchy of Evidence

1. If published meta-analyses and/or systematic reviews are available, the team generally uses them as the principal source of information for the review. The remainder of the review is then limited to individual studies published after the articles included in the meta-analyses and/or systematic reviews. For example, if a meta-analysis was published in June 2011 and included studies published up to December 1, 2010, the team would focus on individual studies published on or after December 1, 2010.
2. The team reviews published meta-analyses and/or systematic reviews for consistency. If there are several meta-analyses and/or systematic reviews that reach different conclusions, the team will consult with the content expert to identify possible explanations (e.g., the inclusion/exclusion criteria of the meta-analyses and/or systematic reviews vary, one or more meta-analyses and/or systematic reviews do not use rigorous methods). In some cases, the results of one or more meta-analyses and/or systematic reviews may be discounted. The rationale for discounting is discussed in the report.
3. If no applicable meta-analyses and/or systematic reviews are available, the medical effectiveness team proceeds down the hierarchy of evidence.
4. Where meta-analyses and/or systematic reviews are available, narrative (unsystematic) reviews are excluded from CHBRP's medical effectiveness reviews. However, when literature regarding a disease and intervention is sparse, the medical effectiveness team includes narrative reviews (e.g., AB 163 [2009] on amino-acid based elemental formula; AB 30 [2007] on inborn errors of metabolism).
5. Strict adherence to the hierarchy of evidence may not be possible or advisable in all cases. For example, if a bill addresses coverage for a new screening test and there are meta-analyses of the sensitivity and specificity of the test, but only nonrandomized studies of the test's effects on utilization and clinical outcomes, the meta-analyses cannot fully substitute for the nonrandomized studies. The rigor of the former studies must be balanced against the relevance of the latter.[13]

---

[12] Clinical practice guidelines are ranked below other sources of evidence because strength of the evidence on which they are based varies widely. Some guidelines contain recommendations based on meta-analyses, systematic reviews, or multiple RCTs, whereas others are based solely on expert opinion. This wide variation exists across organizations that issue guidelines and among guidelines issued by individual organizations. For example, a study of guidelines issued by the American College of Cardiology and the American Heart Association found that most recommendations contained in these guidelines were based on expert opinion and only that 11% were based on evidence from meta-analyses or multiple RCTs. (Tricoci et al., 2009)

[13] CHBRP's analysis of AB 259 (2009), a bill that would allow women to obtain services from a certified nurse midwife (CNM) directly without a physician's referral, illustrates the trade-off between rigor and relevance. Most RCTs on the effectiveness of midwives that have been conducted in developed countries were carried out in Australia, Canada, New Zealand, and the United Kingdom. Midwives in these countries work within health care systems that are quite different from that of the United States. The level and type of education mandated for midwifery practice in these countries also differs from that required of CNMs in the United States. The medical effectiveness team decided that its literature review for this bill should go beyond RCTs to also include

C. Use of Grey Literature

1. The hierarchy of evidence is applied in a consistent fashion to both the peer-reviewed literature and the grey literature. Systematic reviews and clinical practice guidelines are the most frequently cited types of grey literature.
2. The medical effectiveness lead is responsible for searching pertinent sources of grey literature and should prioritize sources that are most likely to publish high-quality literature syntheses. For further discussion of literature search methods, see *Conducting the Literature Search.*
3. Grey literature and peer-reviewed literature about the medical effectiveness of an intervention may contain varying levels of detail. For example, some organizations that develop clinical practice guidelines, such as the USPSTF, publish summaries in peer-reviewed journals and the full guidelines and associated systematic reviews as grey literature. In such cases, the grey literature version of the guideline is reviewed to obtain additional detail not found in the peer-reviewed version.

D. Selecting Studies for Inclusion in the Utilization Literature Section

1. The medical effectiveness team and the cost team will independently review the literature identified in the medical effectiveness/public health and cost literature searches that address the impact of coverage on utilization and select studies for inclusion in their respective sections. In the event that the teams use different criteria for selecting literature to include in the report write-up, a discussion of these discrepancies will be included in the cost section.

Reviewing the Literature

A. The medical effectiveness team will generally not have time to undertake as detailed a review of the methods and quality of individual studies as the authors of a meta-analysis can.

B. Some of the full-text articles retrieved may ultimately be excluded from the review if the medical effectiveness team, in consultation with the content expert, determines that the study is not relevant to the bill, is not generalizable to the population addressed by the bill, or has major methodological problems that affect the validity of its findings.

C. If the medical effectiveness team is analyzing a complex bill and has prepared a table to indicate relevant types of treatments, treatment modalities, uses of treatments, and/or populations, the team may group relevant abstracts into the categories in the table prior to reviewing the literature. This can be done in EndNote using the "Groups" function or in an Excel spreadsheet. In the case of AB 447 (2017), as demonstrated in the Table 1 above, there are six categories, one for each combination of three types of diabetes and two types of continuous glucose monitors.

observational studies with comparison groups that were conducted in the United States. Although the observational studies are weaker methodologically (in particular, they may be subject to selection bias), their findings are more generalizable to the providers to which the bill would apply (i.e., CNMs) than non-U.S. studies.

D. As indicated in *Preparing to Conduct the Literature Search* above, in the cases where (1) a bill may mandate coverage for an intervention that is "consistent with national guidelines", (2) a guideline is an obvious source of bill language, or (3) a guideline is specified in the bill, the medical effectiveness team will select studies for inclusion per CHBRP's hierarchy of evidence and also will assess relevant guidelines.

Rating the Strength of the Evidence

A. In a conference call or group meeting, the medical effectiveness team members review the results of relevant studies for each outcome and decide collectively, based on the weight of the evidence available, on the effectiveness of the intervention across three dimensions. If a bill is relevant to multiple populations, the medical effectiveness team assesses whether the evidence is similar across as many populations as analytic time allows. Similarly, if the bill addresses multiple treatments, treatment modalities, or uses of a treatment, the team examines whether the evidence is consistent across as many treatments, modalities, or uses as analytic time allows.

B. In making a "call" for each outcome measure, the team considers the number of studies as well the strength of the evidence. To grade the evidence for each outcome measured, the team uses a grading system that has the following categories:

- Research design;
- Consistency of findings; and
- Generalizability of findings to the population whose coverage would be affected by a bill.

Each of these categories is described below along with the criteria that are used to classify studies within each category. Once studies have been classified within categories, a conclusion about the medical effectiveness of an intervention can be made. The language used to describe the medical effectiveness team's overall conclusion regarding the medical effectiveness of the intervention is also discussed.

1. Research Design

This category contains information about the strength of the research designs of individual studies that evaluate an intervention's effect on an outcome of interest. Studies are assigned to one of five levels adapted from ranking systems developed by the American College of Chest Physicians and the North American Spine Society (Cook et al., 1992; NASS, 2006). ***The levels refer to the strength of the research designs of individual studies. They do not refer to the overall strength of the evidence regarding an intervention's effect on an outcome.*** Level I studies have the strongest research designs and Level V studies have the weakest research designs. The five levels are as follows:

- Level I: Well-implemented RCTs and cluster RCTs (Strong RCTs);

- Level II: RCTs and cluster RCTs with major weaknesses (Weak RCTs);
- Level III: Nonrandomized studies that include an intervention group and one or more comparison groups and time series analyses;
- Level IV: Case series and case reports; and
- Level V: Clinical practice guidelines and narrative reviews.

Level I groups RCTs and cluster RCTs because either research design may be more or less appropriate than the other depending on the intervention studied. The RCT design is more appropriate than the cluster RCT design when an intervention is delivered to individuals and is provided in such a manner that the control or comparison group is unlikely to be inadvertently exposed to the intervention. Conversely, the cluster RCT design is more appropriate when an intervention is delivered to groups of individuals or in situations in which the control or comparison group could be contaminated.[14]

Well-implemented RCTs and cluster RCTs" are defined as studies that have: (1) sample sizes that are sufficiently large to detect statistically significant differences between the intervention and control groups (100 or more subjects); (2) low attrition rates (less than 20%); (3) made use of intent-to-treat methods;[15] and (4) intervention and control groups that are statistically equivalent prior to the intervention, with respect to baseline measures of the outcome and important factors associated with the outcome. To be considered well-implemented, a cluster RCT must also use appropriate statistical methods to determine whether observations are clustered at the level at which randomization occurs and, if so, to adjust for clustering. Such adjustment is necessary to ensure that the statistical significance of findings is not overstated.

Level II includes RCTs and cluster RCTs that have major weaknesses, such as small sample sizes, high attrition rates without use of intent-to-treat methods, or intervention and control groups that are not statistically equivalent at baseline and, in the case of cluster RCTs, do not test for clustering of observations and adjust for clustering if it is present.

[14] For example, the RCT design can be easily used for studies of pharmaceuticals because drugs are dispensed to individuals and because drugs and placebos can be made to appear identical. However, the RCT design is problematic for health education classes taught to children in schools, because children who receive the intervention and their teachers may interact with children in the control group and their teachers. Such interaction could involve sharing of knowledge about self-management that might lead to changes in self-care behavior among children in the control group, which would limit the study's ability to discern differences between the intervention and control groups. In such cases, a cluster RCT design under which schools rather than children are randomized would be more appropriate than an RCT design.

[15] Intent-to-treat analysis addresses the problem of attrition bias by preserving randomization. If a study has a high rate of attrition, the persons in the intervention group who receive the full treatment may be systematically different from persons who drop out of the study. For example, persons who believe the treatment is not helpful may be more likely to drop out. In such cases, analyzing data only for those persons who completed the study could lead researchers to overestimate the effectiveness of the treatment. Intent-to-treat analysis eliminates this bias because all subjects are included in the groups to which they were randomized regardless of whether they received the full treatment. Some experts in intent-to-treat analysis believe it is sufficient to analyze data only for those subjects for whom complete data are available, whereas others believe that data should be imputed for subjects for whom data are missing (Cochrane, 2005).

Levels III through V are used to classify studies in which subjects are not randomly assigned to either an intervention or a comparison group. Studies that do not randomize subjects are not as well designed as RCTs for assessing the efficacy of an intervention (i.e., detecting causal inference), because they do not control for selection bias.[16]

Level III encompasses time series analyses and nonrandomized studies that have intervention and comparison groups. Time series studies analyze multiple observations on subjects before and after exposure to an intervention, which enables researchers to separate the effects of interventions from other factors that influence trends in outcomes over time. Nonrandomized studies with comparison groups include quasi-experimental studies, cohort studies, case-control studies, and before-after studies. In cases in which most studies of an outcome are nonrandomized studies with comparison groups, the effectiveness team will parse these studies to distinguish studies with stronger and weaker research designs.

Level IV studies are those without comparison groups. This level encompasses cross-sectional studies of a single group of subjects exposed to an intervention and case reports on individual subjects exposed to an intervention.

Level V consists of clinical practice guidelines and narrative reviews.

Meta-analyses and systematic reviews are assigned to the research design level to which most of the studies reviewed correspond. For example, the meta-analyses included in the effectiveness review on Alzheimer's drugs for SB 415 (2004) would be classified as Level I, because most of the studies synthesized in these meta-analyses were well-implemented RCTs. In contrast, a systematic review of multiple types of prosthetic ankle-foot mechanisms that was examined for the report on AB 2012 (2006) would be classified as Level IV, because most studies included in that review were cross-over studies that compared the effects of two or more prosthetic ankle-foot mechanisms on a single group of subjects.

A research design level is assigned to each piece of evidence included in a medical effectiveness review for a CHBRP analysis. The pieces of evidence are aggregated by level for each outcome assessed and the aggregate results of the evidence presented by these articles are reported in a summary figure that appears in the effectiveness section of the report.

The numbers of pieces of evidence at each level reflect the studies included in a medical effectiveness review and not necessarily the totality of studies on the topic. For some bills, CHBRP relies primarily on meta-analyses, systematic reviews, RCTs, or cluster RCTs, and does not consider studies lower in the hierarchy.

2. Consistency

   CHBRP evaluates consistency of findings from the evidence across three dimensions:

[16] Selection bias is a formal term used to characterize situations in which the intervention and control groups are not equivalent except for exposure to the intervention due to some consistent factor that is not measured.

- Statistical significance;
- Direction of effect; and
- Size of effect.

a. Statistical Significance

Statistical significance is an important consideration in assessing the effectiveness of an intervention. If a finding is statistically significant, one has greater confidence that it did not occur by chance. CHBRP considers a finding to be statistically significant if there is a 95% or greater probability that a difference in outcomes between the intervention and control or comparison groups did not occur by chance (i.e., if the p value is 0.05 or less). The 95% confidence interval is a conventional threshold for determining statistical significance. Most studies report the results of formal tests of statistical significance, although some case reports and studies with very small samples do not.

Each study that assesses an outcome will be assigned to one of three categories:

- Finding was statistically significant; or
- Finding was not statistically significant; or
- Results of a test of statistical significance were not reported.

The studies are then grouped by the three categories and the numbers of studies in each category are reported in the effectiveness section of the report.

In cases in which most studies of an outcome report have strong research designs and report the 95% confidence intervals around point estimates of effects, the medical effectiveness team also examines the 95% confidence intervals to determine how similar the results are across studies.

b. Direction of Effect

The direction of the relationship between an outcome and a test, treatment, or service indicates whether the intervention has a desirable effect on the outcome. A desirable effect may be an increase or a decrease in an outcome depending on the nature of the outcome and the intended effect of the intervention. For example, one would expect a drug for Alzheimer's disease to improve cognitive outcomes, whereas one would expect a biological medication for rheumatic disease to reduce joint pain and swelling. In some cases, there may be no relationship between an outcome and a test, treatment, or service.

For each outcome, studies that address the outcome are categorized into three groups based on the direction of the effect:

- Test, treatment, or service associated with desirable outcomes for the intervention group; or
- Test, treatment, or service had no effect or negligible effect; or

- Test, treatment, or service associated with undesirable outcomes for the intervention group.

The "no effect or negligible effect" category includes studies in which the Test, treatment, or service had no effect on the outcome and studies in which the effect was very small, regardless of whether it was statistically significant. Examples of negligible effects found in studies previously reviewed by CHBRP include a 1% difference in severity of asthma symptoms (AB 264 [2006]), a 2% difference in scores on an instrument measuring cognitive functioning of persons with Alzheimer's disease (SB 415 [2005]), and a 0.7% difference in the performance of hearing aids (SB 1223 [2006]).

Once individual studies have been coded, they are grouped by the three categories. The numbers of studies in each category (i.e., desirable outcomes, no or negligible effect, and undesirable outcomes) are reported in the effectiveness section of the report.

c. Size of Effect/Clinical Significance

Policymakers need to know whether a test's, treatment's, or service's effect on an outcome is large enough to be meaningful to patients and/or their caregivers.[17] The minimum clinically meaningful effect depends on the disease or condition addressed in a bill, the outcome of interest, and the manner in which the outcome is measured. In general, the minimum clinically meaningful effect is greater for diseases and conditions for which effective treatments are widely available than for terminal or severely debilitating illnesses for which no other treatments exist. With respect to measurement, a difference of two points may be very meaningful for an outcome measured by a single question on a five-point Likert scale, but probably is not meaningful for an outcome measured by an instrument that has multiple items and a maximum score of 100 points. For all outcomes assessed, the medical effectiveness team consults the content expert to determine whether minimum clinically meaningful effects have been established through research or expert opinion.[18]

The measures used to assess clinical significance vary across outcomes depending on the availability of research on minimum meaningful differences and the measures used in studies of the intervention in question.

[17] Statistical significance and the size of an effect are related, but not synonymous. For example, the apparent effect in a diet study may be large, e.g., a 20-pound weight reduction, but measured with such imprecision due to small sample size that it could also be a weight increase. Perhaps more importantly, a very large study might show statistically significant effects that are not meaningful. For example, with a sufficient number of cases, a new diet might show convincingly that it achieves an average weight reduction of one pound—perhaps statistically significant, but not a meaningful effect.

[18] An example of a research-based approach to determining minimum meaningful effects is the American College of Rheumatology (ACR) Response Rate clinical scoring system that was used in many of the studies synthesized in CHBRP's report on SB 913 (2005), which would have mandated coverage for biological medications for rheumatic disease. Under the ACR-20 instrument used in many of these studies, a medication was determined to have a meaningful effect if patients experienced a 20% reduction in the number of tender joints, the number of swollen joints, laboratory test results, and patient and physician assessment of severity of disease.

CHBRP cites the effects reported in studies included in its reviews. Some studies report continuous outcomes (e.g., differences in means or medians), whereas others report binary outcomes (e.g., percent changes, relative risks, odds ratios). Statistically significant point estimates are cited in the text. Where minimum clinically meaningful effects have been established, the team will note in the text whether the effects reported by the studies included in the review meet or exceed minimum clinically meaningful effects.

The medical effectiveness team's conclusions regarding the statistical significance, direction, and size of effects are based on findings reported in studies published in peer-reviewed publications. These conclusions may be overstated in cases in which there is bias in the reporting of research findings. Forms of bias include publication bias, multiple publication bias, citation bias, and language bias. Studies have found that some journal editors are more likely to accept studies with statistically significant and favorable findings, and that some researchers are more likely to submit statistically significant findings for publication. Multiple publication bias arises when researchers publish findings for a group of patients multiple times, as was the case in the literature CHBRP analyzed on transplantation services for persons with human immunodeficiency virus (AB 228 [2005]). Citation bias occurs when studies with statistically significant findings are cited more frequently than studies with nonsignificant findings and, thus, more easily retrieved when searching for studies. Language bias is an especially important challenge for CHBRP, because CHBRP reviews are limited to studies published in English. Studies conducted in countries in which English is not the primary language are more likely to be published in English-language journals if their findings are statistically significant.[19]

The extent and nature of bias probably vary across topics. The problem is probably greatest where most studies are funded by industry (Lundh et al., 2017) and where most studies have weak research designs. However, except for the few topics on which empirical studies have been published the magnitude and consequences of bias are unknown. The 60-day timeframe for CHBRP analyses precludes the team from undertaking its own research to determine whether unpublished studies (i.e., studies not published by commercial publishers or issued by government agencies, professional associations, or other organizations) exist and assess their impact on the team's conclusions.

The team inserts a brief paragraph in every CHBRP report that states that our conclusions are based on the best available evidence from peer-reviewed and grey literature. The paragraph also indicates that unpublished studies are not reviewed because the results of such studies, if they exist, cannot be obtained within the 60-day timeframe for CHBRP reports.

3. Generalizability

   Generalizability refers to the extent to which a study's findings can be generalized to a population of interest. For CHBRP, the population of interest is the segment of California's diverse population to whose health insurance the bill's requirements would

[19] The information presented in this paragraph was derived from the following sources: Cochrane, 2005; Lee et al., 2006; Sutton et al., 2000a; Sutton et al., 2000b

be relevant. Although some studies enroll persons who are very similar to the population addressed by a bill, others enroll different populations (e.g., adults vs. children) or populations with different health care needs than many persons to whom a test, treatment, or service is typically provided (e.g., persons who are less severely ill or do not have co-morbidities). Findings from studies that enroll persons who are different from the population most relevant to a bill are less useful in determining whether a bill would benefit Californians, even if the studies are well-designed and report statistically and clinically significant findings that favor the test, treatment, or service. However, concerns about generalizability must be balanced against the need to provide information about medical effectiveness to the Legislature. It is unrealistic to restrict literature reviews only to studies that enroll Californians similar to populations addressed by the bill because doing so could lead to an undersampling of studies of a treatment or technology.

The medical effectiveness team addresses generalizability in two ways. First, the team selects studies for inclusion in reviews that are most likely to be generalizable to the population a bill would address. To the extent possible, the parameters for the literature search are set to retrieve studies that enroll persons similar to those to which a bill would address. For example, the search for AB 264 (2006), a bill requiring coverage for pediatric asthma education, was limited to studies that enrolled children. Once the literature search is completed, the team takes generalizability into account when selecting studies for inclusion in the review. For AB 264, the team included only studies conducted in the US, because several of the most important outcomes concerned use of health care services. For AB 259 (2009), the medical effectiveness team decided that its literature review for this bill should go beyond RCTs conducted in other developed countries to include observational studies with comparison groups that were conducted in the United States because the findings from the US studies were more likely to be generalizable to California.

Once studies are selected for inclusion in a review, the team screens them to assess the degree of generalizability to the population a bill would address. Findings regarding the generalizability of studies are summarized in the text of the report. It is unlikely that a review would include studies that are not at all generalizable to the population that would be affected by a bill, because such studies should have been excluded from the review.

4. Conclusion

The last step in evaluating the evidence of medical effectiveness involves making an overall conclusion regarding the strength of the evidence based on research design, consistency of findings, and generalizability of findings to the population whose coverage would be affected by the bill. The following terms are used to characterize the body of evidence regarding the medical effectiveness of the test, treatment, or service on the outcome:

- *Clear and convincing evidence*.
- *Preponderance of evidence*.
- *Limited evidence*
- *Inconclusive evidence*

- *Insufficient evidence*

Table 2. Summary of the Medical Effectiveness Grading System

	Clear and Convincing	Preponderance	Limited	Inconclusive	Insufficient
Number of Studies	≥3 studies	≥3 studies	<3 studies	Any	Any
Research Design	Multiple RCTs	RCTs, quasi-experimental studies, cohort and case-control studies that have contemporaneous comparison groups, and cross-sectional studies	Cohort and case-control studies with historical comparison groups or before-and-after designs	Any	Uncontrolled observational studies or expert opinion
Consistency	≥60% have similar findings re statistical significance, direction of effect, and size of effect	≥60% have similar findings re statistical significance, direction of effect, and size of effect	Studies have similar findings re statistical significance, direction of effect, and size of effect	Studies disagree re statistical significance, direction of effect, and size of effect	Any
Generalizability	Most are highly generalizable	Most are generalizable	Generalizability is limited	Any	Any
Cumulative Impact of Evidence	Additional RCTs would not alter conclusion	Conclusion could be altered by additional strong evidence (well-implemented RCTs with large sample sizes)	Conclusion could be altered by additional evidence	No conclusion can be determined	No conclusion can be determined

Source: The California Health Benefits Review Program, 2018.
Key: RCTs = randomized controlled trials.

a. Criteria for Grading Bodies of Evidence as "Clear and Convincing"

Bodies of evidence are graded as "Clear and Convincing Evidence" if all of the following conditions are met:

- **Research Design:** There are multiple RCTs of the intervention (meta-analyses or systematic reviews of these RCTs are not required, although having such syntheses would strengthen the evidence regarding an intervention's effect).
- **Consistency:** Over 60% of studies have similar findings with respect to statistical significance, direction of effect, and size of effect.[20]

[20] The conclusion could be that the intervention has a desirable or detrimental effect on a pertinent outcome or that it does not affect the outcome.

- **Generalizability:** The studies are highly generalizable to the intervention in question and the population whose benefit coverage would be affected by a bill.
- **Cumulative Impact of Evidence:** It is unlikely that publication of additional RCTs would change the medical effectiveness team's conclusion about the effectiveness of the intervention.

Use of the grade "Clear and Convincing Evidence" is limited to bodies of evidence that include RCTs because even the best designed and implemented nonrandomized studies cannot fully control for selection bias. The requirement for at least three RCTs recognizes that multiple studies are needed to determine whether there is a consistent pattern of findings across studies. The minimum number of RCTs is set at three because identification of a larger number of RCTs does not necessarily mean that the evidence is stronger. A smaller number of well-implemented RCTs with large sample sizes may yield more compelling evidence than a larger number of poorly implemented RCTs with small sample sizes.

Assessing generalizability inherently requires some level of judgment. The medical effectiveness team considers studies highly generalizable if the intervention assessed is similar to the intervention for which a bill would mandate benefit coverage and if the population studied is similar to the population whose benefit coverage would be affected.

Determining whether publication of additional RCTs would change the medical effectiveness team's conclusion about the effectiveness of an intervention is admittedly a judgment call. In some cases, such as bills that would mandate coverage for tobacco cessation (e.g., AB 1738 [2012]), the volume of evidence from RCTs is so large and the findings are so consistent that one can easily conclude that publication of additional RCTs would not alter the conclusion regarding the intervention's effects. Other cases are not so clear cut.

b. Criteria for Grading Bodies of Evidence as "Preponderance of Evidence"

Bodies of evidence are graded as "Preponderance of Evidence" if all of the following conditions are met:

- **Research Design:** There are at least three studies with research designs include RCTs, quasi-experimental studies, cohort and case-control studies that have contemporaneous comparison groups, and cross-sectional studies.
- **Consistency:** The majority of studies (> 60%) have similar findings with respect to statistical significance, direction of effect, and size of effect.[21]
- **Generalizability:** The studies are generalizable to the intervention in question and the population whose benefit coverage would be affected by a bill.

If most studies are RCTs, the studies are highly generalizable, and it is unlikely that publication of additional RCTs would change our conclusion about the effectiveness

[21] The conclusion could be that the intervention has a favorable or detrimental effect on a pertinent outcome or that it does not affect the outcome.

of the intervention, the grade of "Clear and Convincing Evidence" should be assigned instead of "Preponderance of Evidence."

c. Criteria for Grading Bodies of Evidence as "Limited"

Bodies of evidence are graded as "Limited Evidence" if the following criteria are met:

- **Research design:** Cohort and case-control studies with historical comparison groups or before-and-after designs.
- **Consistency:** Studies have similar findings re statistical significance, direction of effect, and size of effect.
- **Generalizability:** Limited.

The "Limited Evidence" grade is assigned to studies with historical comparison groups or before-after (i.e., pre-post) designs. In these sorts of studies, outcomes prior to implementation of an intervention are compared to outcomes after the intervention is implemented. Such research designs are weak because they do not enable researchers to rule out the possibility that changes in an outcome are due to a "secular trend" (i.e., something that changes over time other than the intervention).

Bodies of evidence are also graded as "Limited" if less than three pertinent studies are identified. The choice of three studies as a cut off is admittedly arbitrary but useful for identifying outcomes for which the medical effectiveness team has limited evidence from which to draw conclusions about the impact of a test, treatment, or service. The medical effectiveness team may waive this requirement but should only do so if there are two well-designed RCTs with large sample sizes that enrolled populations that are very similar to the population whose coverage would be affected by the bill.

d. Criteria for Grading Bodies of Evidence as "Inconclusive"

Bodies of evidence are graded as "Inconclusive Evidence" if the following criteria are met:

- **Research design:** Any.
- **Consistency:** Studies disagree with respect to statistical significance, direction of effect, and size of effect.
- **Generalizability:** All levels.

The grade "Inconclusive" is used regardless of whether the evidence comes from RCTs or from *controlled* nonrandomized/observational studies. In cases in which the only available evidence is from *uncontrolled* observational studies, the grade "insufficient evidence" is always used regardless of whether or not findings are similar across studies.

e. Criteria for Grading Bodies of Evidence as "Insufficient"

Bodies of evidence are graded as "Insufficient Evidence" if the following criteria are met:

- **Research Design:** The only published studies of the intervention are *uncontrolled* observational studies (i.e., case series or case studies) or there are no published research studies of the intervention (i.e., the only evidence available is based on expert opinion or narrative reviews).
- **Consistency:** All levels.
- **Generalizability:** All levels.

The rationale for assigning the grade of insufficient evidence to bodies of evidence that include only uncontrolled observational studies is that without a comparison group, one cannot know whether outcomes that occur in an intervention group are due to the intervention versus another factor. Case studies are even less sufficient than case series because they include only one person. When only one person is studied, one cannot determine whether outcomes are similar across persons who receive the intervention.

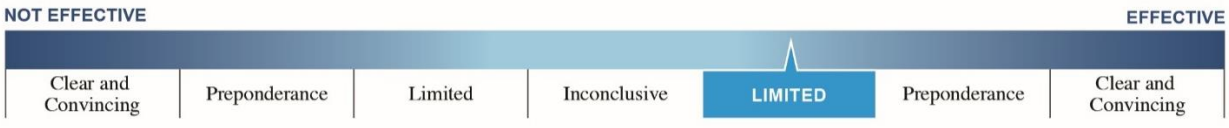
Bodies of evidence that consist solely of narrative reviews are also classified as "insufficient evidence" because the literature searches for such reviews are not conducted systematically. There is no way for the medical effectiveness team to know whether the authors have synthesized all available evidence versus intentionally picking and choosing studies that support their opinions regarding the effectiveness of an intervention.

5. One way to understand these groupings is to imagine that after the assessment was completed a new well-designed RCT was published with findings contrary to those of the report. Such a single contradictory study would do little to change the overall assessment of findings labeled as "clear and convincing," but might call into question findings previously labeled as "preponderance of evidence," and might become the basis for reevaluating findings previously labeled "limited" or "inconclusive."

In addition to the written discussion of evidence included in the medical effectiveness section of each CHBRP analysis, the medical effectiveness team also includes graphic representations of the medical effectiveness of as many interventions and outcomes were addressed. Figure 2 provides an example of this graphic from the analysis of SB 172 (2017). This figure was one of nine presented in the analysis. For complex analyses, Table 1 is a way to assist the reader in understanding the overall findings.

Figure 2. Embryo Cryopreservation

There is limited evidence that embryo cryopreservation is effective in preserving fertility among women undergoing cancer treatment from two cohort studies and one retrospective study of 248 women of which 63 retrieved cryopreserved embryos.



Identifying and Assessing Harms

When assessing the medical effectiveness of a treatment for which a bill would mandate coverage, the medical effectiveness team should consider the treatment's potential harms as well as its potential benefits. Some treatments that yield substantial benefits also carry substantial risks of harm. In other cases, the harms associated with a treatment may outweigh the benefits.

The medical effectiveness sections of CHBRP reports should include findings about the harms of a treatment except in cases in which the team has not carried out a traditional medical effectiveness analysis, such as bills on cost sharing for multiple prescription drugs. The summary of findings regarding harms should focus on the absolute risk of harm to persons who receive a treatment, to the extent that literature on absolute risk of harm is available. The absolute difference in the risk of harm to persons in the intervention and comparison groups is more important than the relative difference in the risk of harm because the absolute risk difference captures the magnitude of the difference in risk. A difference in relative risk may be statistically significant but the relative difference may not be clinically significant if the absolute risk of harm is very low in both intervention and comparison groups (e.g., 3% in the intervention group and 2% in the comparison group). However, if the only literature available presents findings about relative risk of harms, the medical effectiveness team should summarize that literature.

For CHBRP reports on bills that would mandate coverage for a screening or diagnostic test, the medical effectiveness team should summarize evidence regarding harms associated with the screening or diagnostic test, the rates of false positive and false negative results, the invasiveness of diagnostic procedures used to determine whether a person has a disease or condition, and the likelihood of over-diagnosis and overtreatment. Over-diagnosis and overtreatment refer to identification of asymptomatic disease, which results in unnecessary and potentially ineffective or harmful treatment.

When assessing the harms associated with a treatment, the medical effectiveness team should be cognizant that the sample sizes of RCTs may sometimes be too small to detect harms. Even if a medical effectiveness team identifies multiple RCTs that address the benefits of a treatment, the team may need to review findings from large observational studies to identify harms associated with the treatment. This is particularly true of harms that are rare and serious because RCTs may not be adequately powered to detect such harms.

The CHBRP medical effectiveness team should not make its own judgements about whether the harms outweigh the benefits or vice versa. The team should only summarize existing guidance/recommendations reputable sources, such as the US Preventive Services Task Force and other organizations that issue evidence-based guidelines for clinical practice.

The medical effectiveness team should confer with the Cost and public health teams to ensure that the harms that the medical effectiveness team assesses are aligned with the Cost & public health teams' plans for their analyses. For example, if the Cost team is planning to estimate the cost of a downstream procedure associated with something covered by the mandate (e.g., radical mastectomy for women identified as BRCA mutation carriers as part of mandated screening), the medical effectiveness team needs to make sure that the harms (and benefits) associated with that downstream event are captured in the medical effectiveness section.

Summarizing the Quantifiable Evidence for Specific Outcomes

A. Where feasible, the medical effectiveness team also reports pooled estimates of the effects of the intervention on select medical effectiveness outcomes. These estimates may be used by the cost and public health teams to assess a bill's impact on utilization of health care services and its effect on public health. Below is a summary of this process. For more information about how the estimates are generated, refer to Appendix A.

B. In some cases, the medical effectiveness team reports quantitative estimates from meta-analyses or individual studies.

   1. Quantitative estimates from recent high-quality meta-analyses are used whenever possible, because the authors of meta-analyses may have greater expertise and more time to thoroughly review the pertinent literature than CHBRP's medical effectiveness team, and may use more sophisticated statistical methods to generate quantitative estimates of effects.[22] In cases in which a meta-analysis has been published, the team asks the content expert to assess whether the meta-analysis adequately addresses current practice in the prevention, diagnosis, or treatment of the disease(s) or condition(s) addressed by the bill.

      a. Many meta-analyses (particularly those included in the Cochrane Library) report their results as standardized mean differences (SMDs), which is a unitless measure. To obtain values in meaningful units consistent with those assessed in individual studies, such as the number of physician visits, the team extracts data from the individual studies included in a meta-analysis.

   2. In some cases, a single study may be much more rigorous[23] than other studies that analyze an outcome.[24] The point estimate from such a study is likely to be more accurate than a point estimate derived from pooling this study with less rigorous studies. When deciding whether to use the point estimate from a single study, the medical effectiveness team also considers whether the study enrolled persons who are representative of the population addressed by the bill.

C. The medical effectiveness team generates its own new quantitative estimate of an intervention's effect on an outcome if the following conditions are met:

---

[22] Findings from systematic reviews that present a qualitative assessment of the literature without an accompanying meta-analysis are excluded because they do not provide quantitative estimates of treatment effects.

[23] "Rigorous" can encompass a variety of characteristics of a study such as selecting a sample that is sufficiently large to provide adequate power to detect differences between the intervention and control or comparison groups, designing the sampling procedure to maximize the likelihood that the intervention and control or comparison groups are equivalent at baseline, using appropriate statistical methods to adjust for lack of equivalence, implementing procedures to prevent contamination of the intervention and control groups, and concealing allocation to the intervention and control groups to the maximum extent feasible. The assessment of "rigor" in this case is considered within the context of studies that address the questions needed for the review. Thus, a methodologically rigorous study that focused only on a narrow subset of the population to whom the mandate or repeal would be applied would not necessarily "trump" other studies.

[24] For example, CHBRP relied on a single study in its analysis of the literature on the effect of high-deductible health plans on use of preventive services for the 2006 analysis of AB 2281. The medical effectiveness team found that the literature consisted of one, large, rigorous RCT, the RAND Health Insurance Experiment (HIE), a few small RCTs, and a number of retrospective observational studies. The RAND HIE was a highly generalizable study that enrolled children and non-elderly adults with low or moderate household incomes from six urban and rural communities across the United States into various types of health plans, including a high deductible plan.

1. The outcome is relevant to consumers and policymakers. For all bills, the team determines which outcomes will be assessed in consultation with the members of the analytic team for the bill, the content expert, and State Legislature staff responsible for a bill.
2. There are no recent high-quality meta-analyses on the topic or the findings of the most recent studies differ significantly from findings of studies synthesized in meta-analyses.
3. There is not a single large, well-implemented RCT that is much more rigorous than other studies that assess an outcome and that analyzes subjects who are representative of the population addressed by the bill.
4. The studies that measure the outcome are methodologically rigorous. RCTs generally provide the best estimates of an intervention's effect on an outcome, because they provide the greatest assurance that a change in the outcome is due to the intervention and not some other factor. If the majority of studies of an outcome are RCTs or cluster RCTs, the team only pools estimates from RCTs. If a majority of the relevant studies are observational studies, a biostatistician is consulted to assess the appropriateness of pooling the observational studies with one another and with RCTs that assess the outcome. Quantitative estimates are not generated if the only pertinent studies do not randomize subjects, have very small samples, and/or do not include control groups.

Quantifying Harms

As noted previously, the ME team should confer with the Cost and PH teams to ensure that the harms that the ME team assesses are aligned with the Cost & PH teams' plans for their analyses. If the Cost & PH teams plan to generate quantitative estimates of the effects of harms (and benefits) of downstream procedures, the ME team needs to summarize quantitative data from the literature regarding the risk of harm.

As noted at the beginning of this document, its purpose is to maximize the transparency of CHBRP's approach to analyzing medical effectiveness. This document, as well as companion methodology pieces on CHBRP's approach to analyzing impacts on public health, benefit coverage, utilization, and costs, can be found at www.chbrp.org. Further questions about CHBRP's methodology and analyses should be directed to info@chbrp.org.

APPENDIX A: GENERATING QUANTITATIVE ESTIMATES FOR SPECIFIC OUTCOMES

If the criteria for a quantitative estimate are met, the medical effectiveness team uses the following procedure to calculate these estimates. Example calculations used below are from the 2006 CHBRP analysis of AB 264.

In general, pool results only from studies in which similar comparisons are made. There are two major types of medical effectiveness studies: (1) studies that compare a group of subjects who receive an intervention to a group that receives either no intervention or a placebo; and (2) studies that compare groups of subjects who receive different interventions (e.g., two different drugs used to treat persons with Alzheimer's disease, chiropractic services vs. surgery for low back pain) or receive the same intervention at different intensities (e.g., different dosage, different number of visits). Estimates from studies that make these two different types of comparisons should not be combined, because combining them is likely to generate pooled results that reflect neither an intervention's effectiveness relative to no intervention nor its effectiveness relative to a different or more/less intensive intervention. The team consults with the content expert if its members have difficulty making such distinctions. The team always calculates pooled estimates for studies that compare an intervention group to a group that receives a placebo or no intervention. Studies that compare two different interventions may be pooled, if there are multiple studies that compare the same two interventions.

For all studies, review pre-intervention data on the outcome of interest to ascertain whether the intervention and control or comparison groups are equivalent at baseline. Estimates should be pooled only if both pre- and post-intervention data are reported and appropriate multivariate methods are used to adjust for significant baseline differences between the intervention and control groups.[25] If the intervention and control or comparison groups are not equivalent, differences in outcomes may be due to differences between the two groups prior to exposure to the intervention rather than to the intervention. Randomization does not necessarily produce equivalent intervention and control groups, particularly when the sample size is small.[26] Observational studies are even more vulnerable to selection bias, especially if researchers do not use multivariate analytic methods to adjust for baseline differences between the intervention and comparison groups.

If a study reports an overall "adjusted" effect of an intervention that takes into account important differences that may exist between the intervention and comparison groups, that estimate is used to calculate the pooled estimate of effects across studies.

[25] Use of multivariate methods mitigates selection bias only if the additional variables added to an analysis are the only factors other than the intervention that are likely to affect the outcome of interest. This method does not eliminate the possibility that there may be unmeasured variables that are associated with the outcome but not correlated with any of the other variables included in the analysis. However, studies that make an effort to adjust for baseline differences are preferable to studies that ignore them.

[26] Randomization of subjects only produces equivalent groups if the trial is repeated many times or if the sample is very large. Well-executed RCTs with small samples may have non-equivalent intervention and control groups just by chance.

If a study does not report an overall "adjusted" measure of the effect, the medical effectiveness team calculates the proportionate effect attributable to the intervention and then applies it to the overall study population (intervention plus comparison group).

Studies with baseline and post-intervention data

Raw data from the study are inserted into a spreadsheet. A sample calculation for Krishna and colleagues' study (2003) as used in the analysis of AB 264 (2006)appears in Table 2 below. This study assessed the effects of an asthma education intervention on a variety of outcomes, including the number of days children with asthma were absent from school.

Baseline data and post-intervention data for the study appear in Table 2. In this instance, the intervention group had a somewhat higher rate of school absences (7.90) at baseline than the control group (6.40). The difference for the intervention group (-6.50) equals the post-intervention rate (1.40) minus the baseline rate (7.90).

Baseline data for the intervention and comparison groups (7.15) are averaged. (Implicitly, averaging assumes that the two groups are the same, as they would be if randomization were successful, and that any observed differences are due to chance variation.) If the study reports the numbers of cases in each group, they are used as weights. If not, the two groups are assumed to be of equal size.

Table A.1. Calculating the Overall Effectiveness of an Intervention: Proportionate Reduction in School Absences

Trial: Krishna et al., 2003	**Intervention Group**	**Control Group**	**Average**
Baseline	7.90	6.40	7.15
Post-intervention	1.40	5.40	
Difference	-6.50	-1.00	
% difference	-82.3%	-15.6%	
Expected difference	-5.88	-1.12	
Expected reduction in days absent			-4.77
Expected days absent in the control group			6.03
Proportionate reduction in days absent in intervention group			-79.0%

Source: The California Health Benefits Review Program. (2006). *Analysis of Assembly Bill 264, Pediatric Asthma Self-Management Training and Education Services.*

- The % difference (-82.3%) = difference (-6.50)/baseline (7.90). This is the observed percentage reduction in the intervention group.

- Expected difference (-5.88) = % reduction in the intervention group (-82.3) times the baseline average for all subjects (7.15)
- Expected reduction in days absent (-4.77) = the expected difference in the intervention group (-5.88) – the expected difference in the control group (-1.12)
- Expected days absent in the control group (6.03) = baseline average (7.15) + expected difference in the control group (-1.12).
- Proportionate reduction in days absent in intervention group (-79.0%) = expected reduction in days absent (-4.77)/expected days absent in the control group (6.03). This last calculation compares the results for the intervention and control groups. Even if the intervention group experiences a reduction in days absent, this calculation may appear to indicate an increase in the number of absences in the intervention group, if the control group experiences a greater reduction in absences than the intervention group.

Studies with post-intervention data only

For studies that publish only post-intervention data, the proportionate reduction = (control – intervention)/control (see Table 3).

Table A.2. Calculating Proportionate Reduction in School Absences with Post-Intervention Results Only

Trial		Intervention Group	Control Group	Difference
Fireman et al., 1981	Post-intervention	0.5	4.6	-89.1%

Source: The California Health Benefits Review Program. (2006). *Analysis of Assembly Bill 264, Pediatric Asthma Self-Management Training and Education Services*.

Calculating the weighted average

Next, a weighted average calculation is made to estimate the overall proportionate reduction in days absent for the intervention groups in the studies being pooled. The results for each study are weighted by sample size so that results from studies with more subjects will be weighted more heavily. Table 4 illustrates the weighted average for the effect of asthma education on school absences.

Table A.3. Calculating the Weighted Average to Find the Overall Proportionate Reduction in School Absences

Trial	Total Subjects	% Reduction	(Weighted)
Clark 2004	835	0.0%	0
Christiansen et al., 1997	42	-19.8%	-0.3
Evans et al., 1987	204	-3.8%	-0.3
Fireman et al., 1981	26	-89.1%	-1.0

Trial	Total Subjects	% Reduction	(Weighted)
Horner 2004	44	18.3%	0.3
Morgan 2004	937	-50.1%	-19.6
Perrin et al., 1992	56	-79.1%	-1.8
Persaud et al., 1996	36	-15.8%	-0.2
Rubin et al., 1986	54	-0.9	0.0
Velsor-Friedrich 2004	102	-28.0%	-1.2
Wilson et al., 1996	59	-60.0%	-5.0
Total	**2395**		**-25.7%**

Source: The California Health Benefits Review Program. (2006). *Analysis of Assembly Bill 264, Pediatric Asthma Self-Management Training and Education Services*.

After a new, pooled estimate of the effect of an intervention on an outcome has been completed, a sensitivity analysis is conducted to determine whether the pooled estimate is highly sensitive to the results of one or two studies. If one or two studies have samples that are much larger than those of other studies with which they are pooled, the pooled estimate will be dominated by the results of those studies. Pooled estimates may also be sensitive to studies with anomalous results, regardless of sample size, particularly if the total number of studies pooled is small.[27] Sensitivity analyses are performed by omitting each study sequentially, repeatedly recalculating the pooled estimate, and comparing the pooled estimate obtained when all studies are included to the pooled estimate obtained when a study is omitted. If one or two studies to which a pooled estimate is highly sensitive are large, well-implemented RCTs, the medical effectiveness team may choose to rely on estimates reported in these studies rather than on the pooled estimate from the larger group of studies. If the studies in question are not large, well-implemented RCTs, the team reports the pooled estimate but also reports the results of the sensitivity analysis.

[27] For example, in the analysis of AB 264 (2006) the pooled estimate of the effect of pediatric asthma self-management education on mean hospitalizations for asthma is highly sensitive to the results of the one study of this outcome that found no association between the intervention and the outcome. All other studies found a reduction in mean hospitalizations. If the study with anomalous results were omitted from the pooled estimate, the estimated size of the effect would be 15 percentage points greater.

REFERENCES

Christiansen SC, Martin SB, Schleicher NC, Koziol JA, Mathews KP, Zuraw BL. Evaluation of a school-based asthma education program for inner-city children. *J Allergy Clin Immunol*. 1997;100:613-617

Clark NM, Brown R, Joseph CL, Anderson EW, Lu M, Valerio MA. Effects of a comprehensive school-based asthma program on symptoms, parent management, grades, and absenteeism. *Chest*. 2004;125:1674-1679.

Cochrane Handbook for Systematic Reviews of Interventions 4.2.5, Chichester, UK: John Wiley & Sons, 2005, p. 97-99.

Cook DJ, Guyatt GH, Laupacis A, Sackett DL. Rules of Evidence and Clinical Recommendations on Use of Antithrombotic Agents (Third ACCP Consensus Conference on Antithrombotic Therapy). *Chest*. 1992;102(4):305S-311S.

Egger M, Schneider M, Smith GD. Meta-analysis: Spurious precision? Meta-analysis of observational studies. *British Medical Journal* 1998;316:140-144.

Egger M, Smith GD, Phillips AN. Meta-analysis: Principles and procedures. *British Medical Journal* 1997;315:1533-1537.

Evans D, Clark NM, Feldman CH, et al. A school health education program for children with asthma aged 8-11 years. *Health Educ Q*. Fall 1987;14(3):267-279.

Fireman P, Friday GA, Gira C, Vierthaler WA, Michaels L. Teaching self-management skills to asthmatic children and their parents in an ambulatory care setting. *Pediatrics*. Sep 1981;68(3):341-348.

Flather MD, Farkouh ME, Pogue JM, Yusuf S. Strengths and limitations of meta-analysis: Larger studies may be more reliable. *Controlled Clinical Trials*. 1997;18:568-579.

Horner SD. Effect of education on school-age children's and parents' asthma management. *J Spec Pediatr Nurs*. 2004;9:95-102.

Krishna S, Francisco BD, Balas EA, Konig P, Graff GR, Madsen RW. Internet-enabled interactive multimedia asthma education program: A randomized trial. *Pediatrics*. 2003;111:503-510.

Lee KP, Boyd EA, Holroyd-Leduc JM, Bacchetti P, Bero LA. Predictors of publication: characteristics of submitted manuscripts associated with acceptance at major biomedical journals. *Medical Journal of Australia*. 2006; 184:621-626.

Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcomes. *Cochrane Database of Systematic Reviews*. 2017.

Morgan WJ, Crain EF, Gruchalla RS, et al. Results of a home-based environmental intervention among urban children with asthma. *New England Journal of Medicine*. 2004;351:068-1080.

North American Spine Society. Levels of evidence for primary research question. www.spine.org/forms/LevelsofEvidenceFinal.pdf. Accessed on October 4, 2006.

Perrin JM, MacLean WE Jr., Gortmaker SL, Asher KN. Improving the psychological status of children with asthma: A randomized controlled trial. *J Dev Behav Pediatr*. 1992;13:241-247.

Persaud DI, Barnett SE, Weller SC, Baldwin CD, Niebuhr V, McCormick DP. An asthma selfmanagement program for children, including instruction in peak flow monitoring by school nurses. *J Asthma*. 1996;33:37-43.

Philip S, McLaughlin CG, Gluck ME, eds. Informing Legislative Decisions on Health Benefit Mandates: The California Health Benefits Review Program [Special issue]. *Health Services Research*. 2006;41:991–1158.

Rubin DH, Leventhal JM, Sadock RT, et al. Educational intervention by computer in childhood asthma: A randomized clinical trial testing the use of a new teaching intervention in childhood asthma. *Pediatrics*. 1986;77:1-10.

Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F. *Methods for Meta-Analysis in Medical Research*. Chichester, UK: John Wiley & Sons, LTD, 2000.

Sutton AJ, Duval SJ, Tweedie RL, Abrams KR, Jones DR. Empirical assessment of effect on publication bias on meta-analyses. *British Medical Journal*. 2000; 320:1574-1577.

Tricoci P, Allen JM, Kramer JM, Califf RM, Smith SC. Scientific evidence underlying the ACC/AHA clinical practice guidelines. *Journal of the American Medical Association*. 2009; 301:831-841.

Velsor-Friedrich B, Pigott TD, Louloudes A. The effects of a school-based intervention on the self-care and health of African-American inner-city children with asthma. *J Pediatr Nurs*. 2004;19:247-256.

Wilson SR, Latini D, Starr NJ, et al. Education of parents of infants and very young children with asthma: A developmental evaluation of the Wee Wheezers program. *J Asthma*. 1996;33:239-254.

Acknowledgements

This document was prepared by the members of CHBRP's medical effectiveness team, which consists of CHBRP task force members and contributors, as well as members of CHBRP's staff.

Contributors include Janet Coffman, MPP, PhD, Margaret Fix, MPH, Mi-Kyung Hong, MPH, Wade Aubry, MD, Chris Tonner, MPH, Patricia Franks, and Ed Yelin, PhD, all affiliated with the University of California, San Francisco's Philip R. Lee Institute for Health Policy Studies, and Adara Citron, MPH, and John Lewis, MPA, of the CHBRP staff at the University of California, Berkeley.