

## Chapter 7

### Applying Evidence-Based Pharmacotherapy to Formulary Decisions

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This chapter provides insights into how an evidence-based approach is vitally important to help inform the decisions reached by formulary managers and pharmacy & therapeutics committees. Specifically, it explains (1) what a formulary system is, (2) the advantages and disadvantages of utilizing a formulary system, (3) the qualities of an effective system, including details about an evidence- and value-based approach, (4) how to conduct scientific, clinical and economic drug reviews, and (5) how to effectively – and efficiently -- use various resources available to ensure high quality of the information used to support formulary decisions. A glossary of terms is included at the end of this section.

#### The Formulary

A formulary is a list of therapeutic agents available for caring for patients. It is also sometimes referred to as a “preferred drug list.” Formularies may also include guidance or stipulations concerning the use of drugs. The users of a formulary are generally insurers, health care systems or drug benefit management companies (known as pharmacy benefit managers or more frequently referred to as PBMs). Formularies help manage appropriate use of therapeutic agents and, in some instances, are also used to manage drug-related health plan insurance benefits.

Formularies are considered to be “open” or “closed,” and these terms may be somewhat loosely applied. Essentially, the concept of whether a formulary is “open” or “closed” concerns restrictions. Just as it sounds, an open formulary is one in which there are no or few limitations, so it frequently may simply list drugs and their alternatives which are available for use by a practitioner. A closed formulary is more restrictive and selectively includes agents – and may or may not include limitations or stipulations concerning their use.

#### The Formulary System

A formulary system provides for the processes for establishing and managing the formulary. Ideally, the system includes processes, tools and structures (usually a pharmacy administration department and/or a “Pharmacy & Therapeutics Committee”, referred to as a “P&T committee”), for –

- Evaluating and selecting drugs for formulary inclusion;
- Creating educational materials regarding formulary products;
- Evaluating use of the formulary products, (e.g., measuring and analyzing drug utilization and managing the reporting of adverse events); and,
- Keeping up-to-date on changes such as new understandings about drug safety or effectiveness, changes in brand versus generic status or the emergence of new alternatives which may provide value, as examples.

#### Formulary System Outcomes

Evaluating drugs for formulary inclusion can result in several kinds of decisions:

- Approval or disapproval of specific agents to be included in a formulary, including any recommendations or messages to users of the formulary.
- Decisions concerning restrictions of use or exceptions (e.g., quantity or refill limits, protocols guiding use of the agents, restriction of the agent to being a “second-line therapy” for patients failing on drugs established as “first-line” therapies -- meaning the drugs to be utilized first in treating the patient, or prior authorizations – often referred to as “prior auths” or edits -- in which a clinician has to get approval before a drug can be dispensed). This may be done when the patent on a brand-name drug expires. Bioequivalence is frequently assumed (i.e., it is assumed that the generic agent is equivalent to the brand-name drug). In some cases the effects of other components of the generic preparation (e.g., the vehicle in a dermatological preparation) may vary and result in outcomes that differ from those reported for brand-name agent.
- Decisions concerning equivalence or substitutability such as –
  - Generic substitution (i.e., determining which generics can be considered equivalent to which brand name drugs). Generic substitution involves replacing one agent with a different agent with the same chemical structure and bioequivalence.
  - Therapeutic substitution (i.e., substituting agents with different chemical structures, but with similar clinical benefits).

- Class effect (i.e., “equipotency,” meaning deciding which agents are to be considered sufficiently similar as to be able to group them into one drug family – or “drug class” as if they are, for all intents and purposes, clinically the same – although some other factors, such as cost, may vary).
- Decisions concerning pricing or coverage.

### **Formulary Development**

Frequently formularies are developed by pharmacy administration departments either working alone or in concert with a pharmacy and therapeutics committee whose role it is to make formulary management decisions, along with performing other formulary management functions. Pharmacy and therapeutics committees primarily consist of physicians and clinical pharmacists, but may also include other health care professionals and administrators or organizational medical leaders. Decisions are frequently made by vote or through a “determination of findings,” often with selected members specifically designated to participate in the decision-making process. Often, in practice, the actual decision-making is strictly limited to physicians; however, the clinical pharmacy staff who support a P&T committee by reviewing drugs and making recommendations to the committee often play the most crucial role in the determination of formulary decisions in that P&T committees will frequently base decisions on the recommendations of the supporting clinical pharmacist staff.

These recommendations come documented as detailed reviews, analyses and recommendations often for a single agent – which are called monographs – or drug reviews looking at a group of drugs to assess similarities and differences. Monographs and other relevant drug review information are generally prepared by clinical pharmacists and address such items as clinical considerations, FDA information, approved indications, applicable patient population, exclusions, efficacy, safety (including issues such as tolerability and the potential for psychological and physical dependency), dosing, drug interactions, adherence issues, cost, restrictions and available alternatives.

Frequently P&T committees are highly reliant upon these assessments as their primary – and often sole -- source of information. This means that it is critically important that the clinical pharmacist reviewer be extremely well versed in the concepts, methods, processes, skills and tools that can help ensure quality formulary decisions.

### **Formulary Development Considerations**

Formularies need to be developed with an eye to addressing the health needs of the populations served, ensuring that the formulary is complete and that selected agents represent value. By value, we mean the sum consideration of the overall net gains and net losses in health care outcomes, patient satisfaction, clinician satisfaction, utilization, cost and other important factors which we have euphemistically termed “other triangulation” issues as a catch-all phrase for the wide array of other kinds of considerations which need to be taken into account when making formulary decisions. Examples include legal issues, liability and risk management, community standards, accreditation and regulatory requirements, public relations, and marketing. These other factors can have as great an impact on formulary decisions as patient need, benefit, safety and cost.

For example, let us imagine a hypothetical situation in which a multimillion dollar lawsuit was awarded to Patient X whose complaint was that Drug Y resulted in her baby having birth defects. At the time this verdict was rendered, the only evidence available was from observational studies from which cause and effect conclusions cannot be drawn. In spite of insufficient evidence to conclude that Drug Y caused the birth defects, the health care providers in the city where this legal judgment was rendered elected to remove Drug Y from the formulary anyway because of legal concerns. This is an example of triangulating other important factors, along with evidence, in rendering a formulary judgment.

Another example would be in which a fully-informed patient with a high profile illness – such as a brain tumor – is pressing for a treatment for which there is no evidence of benefit, but there are a great risk of harms and a high cost impact. Situations such as this one can result in high profile media stories that can be very negative. In a circumstance such as this, because of placing a high value on avoiding bad publicity, a health care system or insurer might choose to make a business decision in favor of covering the agent, fully aware that their action would set a precedent. These examples illustrate how a wide range of factors may be taken into account in determining overall gains and overall losses to reach a net view.

As we stated at the outset of this chapter, an evidence-based approach is vitally important to help inform formulary decision-making – so much so that we dedicate considerable emphasis on this in greater detail in its own section, **Use of Science in Clinical Decision-making**, which follows. Cost and utilization are extremely important factors as well and often play a significant role in formulary decisions. U.S. health expenditures in 2006 reached \$2.1 trillion, which translates to \$7,026 per person or 16 percent of the nation's Gross Domestic Product.<sup>1</sup>

Estimates have been made that at least 20 to 50 percent of all prescriptions, visits, procedures and hospitalizations in the United States are considered inappropriate as a result of overuse, underuse, non-use and mis-use of what has been demonstrated to be effective and beneficial care.<sup>2, 3, 4</sup> This translates into hundreds of billions of dollars of waste annually. Many health care systems today are struggling financially, and their resources are extremely limited, which can have an impact on what services can be provided to which patients, at what cost to the patient and of what quality. A good formulary management system has thoughtful ways of making cost and utilization part of the equation to attempt to address excessive or misapplied spending. Because poor financial management can result in the lack of provision of needed care to patients, cost can be considered a patient “harm” too.

Thus, in addition to being evidence-based, a formulary management process should be value-based as well, triangulating all meaningful factors into the decision-making process to achieve the best outcomes by applying a net view.

### **Advantages and Disadvantages of Formularies and of the Formulary System**

There are perceived advantages and disadvantages of formularies and of the formulary system. The primary objection made against formularies by clinicians and patients is that they limit choice, and doctors may resent what they may perceive as impingements on their judgment, along with any inconvenience imposed by the restrictions and resulting administrative procedures such as prior authorization.

However, given estimates that twenty to fifty percent of all health care delivered is inappropriate, we believe that much of this inappropriate care can be attributed to the use by health care decision makers such as prescribers and those making formulary decisions of invalid and misleading information, which can be found in even the best medical journals. The unfortunate truth is that, as of this writing, the majority of physicians, clinical pharmacists, nurses, and other health care professionals – along with many of those providing information to these practitioners, such as researchers, publishers and other medical information content providers -- lack even basic skills in being able to differentiate a good study from a poor one. This lack of critical appraisal skills even extends to many medical experts, professional medical societies, editors, reviewers and research funders. A crucial advantage of a well thought-out formulary is that it can help improve patient care if it has resulted from a well designed and well functioning formulary system and is constructed from evidence-based principles to help assess whether scientific information is valid and whether the results of valid studies will be useful in clinical practice.

Another factor in considering the pros and cons of a formulary and a formulary management system is cost and complexity. The staffing and management of formulary administration is expensive, as is the cost of involvement of others in formulary decisions. The management of national formulary systems, for example, can result in considerable expense and complex logistics in bringing together many members from around the country on a regular basis. Yet, while having a rigorous system for formulary management is expensive due to the high caliber of staff needed and the labor-intensiveness of this endeavor, a key advantage of having a formulary management system is that it can help achieve more optimal use of resources for the health care system as a whole.

In a review of health care for employees of King County in Washington State, a comparison of an open drug system versus a closed formulary system showed a very large and inappropriate use of drugs, especially anti-depressant drugs, in the open system. The open system was managed through common strategies used by prescription benefit managers such as prior authorization, negotiated discounts and/or rebates, which frequently are cost offsets pharmacy systems receive when purchasing large quantities of drugs based on volume of use. In the closed system, the drugs were evaluated using an evidence-based review process considering effectiveness, safety, need and cost. The cost was one-third less in the closed formulary system which was part of a health care organization with a national reputation for very high quality health care.<sup>5</sup> The implications from this research are that the right structures and work processes, through a formulary system, can help improve care and help achieve optimal use of resources. These structures and processes can help achieve good choices through a focus on use of the best available valid and useful evidence along with a value-centered approach and may also include a good drug utilization review (DUR) system which continuously monitors drug usage and evaluates new evidence. Such monitoring and continuous quality improvement is a hallmark of evidence- and value-based care done correctly.

A formulary system can also *potentially* provide legal protection in setting community standards for physicians and other prescribers who utilize the system correctly in that they might be afforded greater protection by being considered part of the norm, and if the system is successfully evidence-based, they are likely to benefit because of the grounding of decisions on evidence. In these days of high risk of medical malpractice litigation – whether warranted or not – there are instances in which this kind of protection might be important not only to practitioners of medical care, but for health care systems and their patients served as well. There are no guarantees when dealing

with medical-legal issues, but a formulary system – especially one which is based on good use of science, combined with medical appropriateness -- can potentially help mitigate such risk.

### **The Use of Science in Clinical Decision-making**

Formulary management outcomes are best accomplished by an evidence-based approach. The main purpose of science in evaluating drugs is to inform us of two very important things: 1) what agent results in what outcome (i.e., cause and effect), and 2) since medicine is probabilistic, what is the probability that a specific outcome will occur (i.e., what number of people treated in a specific period of time will realize a particular benefit or a particular harm)? It is by effective and appropriate use of evidence-based medicine (EBM) that these questions are addressed by pharmacy administration departments and P&T committees in making decisions about which agents will be included on the formulary and under what circumstances.

An evidence-based approach means that a systematic approach has been taken to find and obtain the best available scientific evidence and that the science used in the decision-making process has been effectively evaluated for appropriateness of study design, validity and usefulness. Applicability is a special consideration within the usefulness evaluation.

- By appropriateness of study design, we mean the appropriate kind of study methodology is matched to a specific type of clinical question. This is important because using the wrong type of study design can result in misleading information. For drug therapy, this means reliance upon well-done randomized controlled trials (RCTs) – or valid and useful systematic reviews of RCTs -- because *only* RCTs can demonstrate cause and effect. (Tip: An easy way to distinguish between observational studies and true experiments, such as RCTs, is to determine whether the patient or his or her physician chose a treatment or not, or whether the intervention was assigned. If chosen, this is an observational study; if assigned, it is an experiment.)
- By validity, we mean “closeness to truth,” which means that the studies have been scrutinized to determine whether bias, confounding and chance may possibly explain study results. Bias, confounding and chance can invalidate a study: if there are many or major threats to validity, the study should be considered to be lethally flawed and should not be used for health care decisions. Many studies, while not lethally flawed, have so many threats to validity that we remain uncertain about what the science tells us. As of this writing, very few research studies – regardless of where published -- achieve an excellent grade for quality. Sometimes this is a result of poor research design, execution or reporting. However, sometimes this is because of extenuating factors such as high loss to follow-up for a population that is highly mobile or as a result of ethical challenges – it would be unethical to do a study where people are randomized to smoke, for example. Even if when an investigator does his or her utmost to design a high quality study under such challenging and limiting circumstance such as these, the natural laws of science still prevail – and a study is only as good as it is valid and as its results are useful. The fact is that there are some research questions we will never be able to answer well, if at all. This is a critically important point. The lack of good evidence-based practice as a culture, the lack of critical appraisal skills, time pressures and the need for clinical solutions often all operate in concert to work against an objective analysis of the quality of the medical science. This is so important that we will talk about this in greater detail when we address evidence versus “judgments.”
- By usefulness, we mean that the results will be meaningful which includes the size of the study results and what we might expect for outcomes outside the research setting (i.e., effectiveness). Also, another important consideration is that the science be “clinically significant,” meaning that it is directly found to achieve desired outcomes in things that matter to patients in five areas -- morbidity, mortality, symptom relief, functioning and health-related quality of life. Utilizing research which does not have direct proof for these outcomes can increase the risk of harms to patients as well as drive up costs and add to waste.
- By applicability, we mean the considerations and the conditions for use of an agent, which may entail determinations of how the drug will be used and for which subpopulations of patients and under what circumstances, taking into account such things as likelihood of patient adherence to treatment and the patient perspective on benefits, risks, harms, cost, uncertainties and alternatives, as examples.

It is incumbent upon clinical pharmacists to possess strong critical appraisal skills to be able to assist decision-makers in selecting drugs and in determining appropriate use of these drugs to help guide quality and value-based care for patients and for the health care systems that serve them.

## The Evidence- and Value-based Approach

EBM can be defined as, “a set of principles and methods intended to ensure that -- to the greatest extent possible -- medical decisions, guidelines, and other types of policies are based on and consistent with good evidence of effectiveness and benefit.”<sup>6</sup> An evidence- and value-based approach should be taken in all aspects of formulary management including the creation of process steps as well as how those steps are executed. This extends to establishing criteria for decision-making; finding, evaluating and synthesizing the most useful information; developing monographs or drug reviews; and, managing committee deliberations and formulary adjustments.

The principal drivers of this approach are these – application of solid EBM methods, consideration of value, and a thoughtful differentiation between the two. In the next section -- **Scientific, Clinical and Economic Drug Review Processes: A Method** – we will describe specific steps in greater detail.

### 1. **Solid EBM methods are applied.**

The drug review process starts with a systematic search of the medical literature followed by a judicious selection process of the literature to be considered and then entails ensuring critical appraisal has been conducted for scientific validity (closeness to truth) and usefulness, including applicability.

Many processes are hampered by lack of skills not only in critical appraisal as we have mentioned, but also in effective and efficient information retrieval. Pharmacists need to know which sources to search, how to perform a focused search and how to increase or decrease the sensitivity and specificity of their search. They also can benefit from time saving strategies which we will discuss in greater detail.

### 2. **Value is taken into account**

Potential impacts of clinical practice change resulting from formulary decisions are assessed as part of the decision-making process. This includes health care outcomes, patient and provider satisfaction, cost and utilization and other triangulation issues.

### 3. **Evidence does not get confused with non-evidentiary considerations**

The review of the evidence is separated out from other considerations, such as “beliefs,” cost and other triangulation issues which need to be considered when making a judgment regarding overall clinical value.

While this may seem obvious, in our experience, this is where *many* committees or reviewers fail – and this is *especially* likely to occur when the research is poor or the evidence is lacking. This occurs for a host of reasons including 1) widespread lack of EBM skills coupled with a lack of awareness that this is even a problem;<sup>7</sup> 2) a bias toward “approved” drugs since, if they are FDA-approved, there *must* be overall value in using them; 3) cultural influences and attitudes which include consumerism and a bias equating “new” with “improved;” 4) influence from “experts” (who might not, in fact, be expert in the evidence); 5) sloppy, incorrect and misleading language about evidence; 6) “rooting” for the investigator -- usually out of trust, respect and goodwill; and, 6) “rooting” for the intervention -- usually due to a hopefulness for a clinical solution addressing a need. The end result is a tangle where the actual evidence gets lost or is believed to be better than it is which results in evidence being misrepresented as the basis for a conclusion when in fact opinion or other value considerations are actually basis of the decision.

To elaborate on a few of these problems, we will start with the “experts.” As we’ve stated before, the vast majority of physicians lack critical appraisal skills. Yet physicians in specialties other than primary care (i.e., the “subspecialties”) are considered “experts.” And yet, one can only truly be considered “expert” if one truly understands what will and won’t work clinically. David Eddy did an illuminating study in which he framed questions for “experts” in many subspecialties and, instead of getting consistent answers about efficacy of interventions, within each field he got a scattergram – meaning that their answers were all over the map.<sup>8</sup> If there were true expertise, answers should be quite consistent. Yet, specialists frequently drive formulary decisions on the basis of their opinions.

And many times these opinions will be stated as evidentiary facts. Frequently, reviewers or members will use statements such as, “There is good evidence that...” when, in fact, there is no evidence – they are merely stating their opinion – or they are referencing poor or lethally flawed evidence or misusing the evidence.

The remedy for this is to ensure that a very transparent process is used where the evidence is brought to the table and reviewed. This entails a review of the study type and a validity determination *before* looking at a study’s results. (Some EBM experts actually advocate never looking at the results of invalid studies to

help avoid being influenced by them.) It also entails a clear understanding of the difference between the validity of a study or group of studies and the judgments made about using that evidence in conjunction with other issues, such as cost, in making formulary decisions.

The point is to understand the evidence on its own – separate from all other issues – and to understand that other considerations should only be brought into the equation in light of the evidence *after* the evidence is understood. They should not be mixed at the start. In this way, one doesn't make the evidence seem better than it is and one does not "confuse" why certain decisions are made.

Ultimately formulary decisions may be made which are not entirely consistent with what the best available valid and useful evidence states. However, those decisions should be made with a full understanding of what the evidence tells us. And those decisions should also be made with a full understanding of *why* they are being made (i.e., which of the triangulation issues are weighted more heavily than the evidence), and they should be explicitly documented as such, separating evidence from the "value" consideration that ended up driving the decision.

Belief is a powerful thing. Beliefs will show up in a monograph or in a committee meeting in various ways. We mentioned "rooting for the investigator." This can come in several forms. Imagine a circumstance in which authors of a paper stated that they randomized subjects to two groups, but didn't explain how they randomized. The impulse is to believe that the investigator *had to have* done this correctly – whereas the EBM approach is to downgrade the study because of the missing information. (A good investigator knows that readers need to see these kinds of details to evaluate the quality of the research. This kind of missing information not only makes it impossible to assess the quality of study methodology, but it also suggests that the investigator is not sufficiently experienced in good research techniques and may point to other study flaws as well).

Or the investigators make a grandiose claim. The tendency is to believe in their expertise – rather than take the EBM stance that conclusions are potentially biased and only results of valid studies should be evaluated for conclusions. Or the investigator faces the challenge of trying to answer questions that don't easily "cooperate" with good science as in our earlier example of the highly mobile population that will not refrain from moving around to ensure a good follow-up rate. There is a tendency to "forgive" the investigator for problems beyond his or her control: after all, that investigator can't help it that the population needed isn't going to be easy to work with, right? But an EBM approach recognizes that the laws of science don't bend just because one is trying hard in the face of adversity. The research doesn't get "extra validity points" for being tough to do: the science is only as valid as it is!

Belief also shows up in "rooting for the intervention," as in, "We have no way to cure cancer and so the science on this new drug now looks better than it actually is," or "Drug X is much cheaper than Drug Y so I want to believe the science that suggests that they are equivalent."

Even those who have strong skills in evidence-based medicine can get lost in the evidence-belief-value triangle. Many EBM working groups will apply an actual grade to a study following their critical review. Through our work evaluating monographs for various clinical pharmacy teams, we note a strong overall tendency to "up-grade" studies. We see many studies that are highly flawed getting A- or B-type grades and conclusions about cause and effect being made by reviewers where none should be because the evidence is so uncertain.

Strange but true: even with all the interventions that have been used which have later been shown to harm people – and provide no benefit -- and even considering that most interventions carry a risk of harm, and even adding to that the fact that the high likelihood is that most people will not benefit from an intervention at all (rare is the number-needed-to-treat of 1!) – even given all this, when asked whether they would rather be randomized to a new intervention or to placebo – without even being given a hypothetical condition -- in our experience, the majority of even the most knowledgeable health care professionals state they would hope for assignment to the intervention. This means that most of us are biased in favor of the intervention. It is this kind of blanket hopefulness, favoring the intervention, that can undermine the best attempts at a truly evidence-based process. Couple this inherent bias with clinical hopes in areas where there are true gaps between a clinical problem and a wholesale lack of any effective solution and the pressure to approve interventions increases greatly. Under these circumstances, even some of the most hardy EBM-trained evaluators sometimes break, allowing hope to affect their assessment of the science and render a

judgment that the evidence is better than it actually is. Awareness of this tendency and transparency built into the process are key to help mitigate these influences.

Conducting scientific, clinical and economic drug reviews entails a number of components. There are numerous ways of approaching this work. We describe one method.

### **Scientific, Clinical and Economic Drug Review Processes: Introduction to a Method For Applying an “Explicit” Evidence- and Value-based Approach**

Review processes sometimes need to vary depending upon whether the perspective is a local one or more broad – such as a national one. A committee that represents local concerns may have an easier time doing a cost analysis, for example, than a committee that has to take into account price variability across different locations. And even for those who are similarly situated, different groups have different approaches to conducting their drug reviews. Some groups expend more effort than others by doing a fairly extensive review of the literature. Other groups rely to a greater extent on others’ reviews. Either method can be reasonable provided that the process results in the use of valid and useful, clinically meaningful information to support meaningful analyses and thoughtful recommendations.

A useful approach to evidence-based clinical improvement was originally inspired by David Eddy, MD, who emphasized the need for organizations to be explicit and transparent in the steps for acquiring and appraising information as well as stressing the need for projecting the impacts of change prior to making judgments about what constitutes a clinical improvement.<sup>9</sup> This approach, referred to as the “explicit” evidence-based approach, was developed further under the leadership of Michael Stuart, MD, and others, at Group Health Cooperative in Seattle, Washington, a managed care system that has had a reputation for being of very high quality. We have further refined it into a model and series of sequential tool-based process steps that are being used by some of the best providers of medical care in the country.

The features of the approach we will describe include –

- Validity and usefulness as the informing drivers for the basis of decision-making;
- Patient-centeredness as its heart;
- Rigor, robustness, efficiency and transparency as its hallmarks; and,
- Value as a deciding force, taking into account all important considerations for rendering a judgment.

Our process is framed by what we call our evidence-based value model for clinical quality improvement. All too often we see a division in the perspectives taken by health care professionals who do not take a full system view, but become too narrowly focused on the perspectives of their particular viewpoints, often driven by education, history, occupation and existing system structures in the environments in which they work. We feel it is important to take a full system view, informed by the varying perspectives and talents offered by the different focuses and approaches that each discipline can offer – such as those by medical leaders, health care administrators, practicing physicians, clinical pharmacists, nurses and others. Our experience has led us to believe--and it may be worth emphasizing here that neither of us have a clinical pharmacy background -- that the best solutions for quality and value-based medical care can come from the discipline of clinical pharmacy. Medical leaders and individual physicians lack time and frequently lack the robustness of skills that can be found in clinical pharmacy, which is increasingly called upon to inform meaningful clinical decision-making. For this reason, it is strategically important that clinical pharmacists be afforded a larger view into what is required for quality clinical care. Clinical pharmacists are now being trained in a discipline that can provide many of the solutions to our ailing health care system.

The model we advocate takes into account the net gains and net losses from considerations of health outcomes, the patient perspective, satisfaction of clinicians and patients and savings versus costs, along with the other considerations we have described as other triangulation issues – and drawing from varying health care disciplines. This model can yield thoughtful judgments about clinical value. What clinical quality improvement is about is finding and closing quality, value and uncertainty gaps in the health care system, understanding that the best available valid and useful evidence informs quality care, and that combining that best available evidence with a value-centered approach, along with effective implementation and measurement of clinical change, results in a system that can improve health care outcomes and improve use of resources.

### **Stages and Steps of Evidence- and Value-based Clinical Improvement**

The various stages of evidence-and value-based clinical improvement entail --

- **Phase 1: Organizational Readiness**
- **Phase 2: Clinical Improvement Project & Team Selection**
- **Phase 3: Project Outline**
- **Phase 4: Evidence Review**

- **Phase 5: Clinical Content Development**
- **Phase 6: Impact Assessment**
- **Phase 7: Communication Tools Development**
- **Phase 8: Implementation: Create, Support and Sustain Change**
- **Phase 9: Measure and Report**
- **Phase 10: Update and Improve**

The specific steps in our approach are taken sequentially to increase efficiency by putting first things first. Each step includes pass/fail points in an effort to ensure efficiency by helping terminate clinical quality improvement efforts – which can be very expensive – at the earliest stage possible. This helps redirect resources to other efforts that are more likely to provide value.

The steps in our model are framed by the 5 “A”s of evidence-based medicine<sup>10</sup>:

- Ask the right clinical question
- Acquire information using evidence-based and efficient techniques – meaning know what types of study designs fit your clinical question -- and for questions of therapy such as faced by clinical pharmacists and P&T committees, this entails the use of randomized controlled trials or well-done systematic reviews of randomized controlled trials for establishing cause and effect for efficacy of interventions — and know how to utilize the best sources in the most efficient way to obtain the highest quality information
- Appraise for validity and usefulness
- Apply outcomes of these efforts to clinical care
- And “A”s again – meaning knowing the importance of and methods for going through this cycle of the preceding four “A”s again to continuously improve quality and value.

The steps in our model are these:

<b>Ask &amp; Acquire</b>	1. Identify significant gaps and uncertainties; identify possible projects for consideration → <b>Pass/fail further development of projects</b> 2. Search for the best available project content. Apply systematic strategies to obtain evidence; filtering for strength of the study design and for relevance → <b>Pass/fail projects depending upon lack of content available</b>
<b>Appraise</b>	3. Assess the amount of work needed – adapt content or develop own project from evidence available → <b>Pass/fail depending upon ability to acquire or develop the content</b> 4. Unless the information is from a “trusted” source,” critically appraise content for validity – and ensure the content is up-to-date (consider auditing “trusted” sources to ensure validity and clinical usefulness). → <b>Pass/fail invalid information</b> 5. Examine results of valid content and assess usefulness → <b>Pass/fail information that is not useful or usable</b> 6. Summarize and synthesize the evidence 7. Assess potential impacts of practice or other change <ul style="list-style-type: none"> <li>a. Create evidence-based estimates of local quality and cost outcomes → <b>Pass/fail</b></li> <li>b. Assess potential program change (including implementation and measurement)</li> <li>c. Perform analysis of economic and non-economic changes, including sensitivity analyses</li> <li>d. Summarize and decide → <b>Pass/fail project if you cannot meaningfully narrow or close a significant gap</b></li> </ul>
<b>Apply</b>	8. Create information, decision and action aids – these can be for clinicians, patients, leaders, other health care staff, etc. 9. Implement and measure success of implementation or performance and report findings.
<b>AAAA Again</b> →	10. Cycle back through the first 4 “A”s to update information and continuously improve care

All of these steps require the right work components which include leadership, organizational support, well-thought out and supported work structures and processes, clearly defined staff roles and staff skilled in the concepts and methods of clinical quality improvement. A key component is having a set of tools to assist with performing the work in a rigorous and consistent fashion, creating clear steps for the work and providing for good documentation – which is at the heart of transparency.

### **Practical Tips for Conducting Scientific, Clinical and Economic Drug Review & Suggested Resources**

Here are some practical tips on how to achieve these steps. We also strongly advise meticulous documentation of everything that goes into the review: search strategy, assumptions used, references, sources, background calculations, unit values used, etc. This is important for transparency, decision support, updates, legal reviews, audits, and other needs that may arise. (While it may seem onerous at the time to do, imagine what you would go through if you had to retrace your steps – viewed in that light, it's easier to be meticulous.)

### **How Agents Get Selected for Review**

Most organizations have a process for submitting requests to the P&T committee. Sometimes, the process requires the chief of a clinical department to verify that the clinical specialty wants the new agent considered. At other times the P&T staff pharmacists, through their scanning of the media and medical literature, request that an agent be reviewed or re-reviewed. This raises the need for pharmacists to have a systematic approach to scanning the various media for signals that an agent of value (such as one that is improved, equivalent and less costly, etc.) is or is likely to become available for clinical use.

### **Background Information**

Once it has been determined that an agent will be considered for a formulary determination, a good start is to obtain key background information such as FDA approval status, indication, label, harms (including abuse and dependency issues), interactions, therapeutic equivalents and other alternatives. It is also a good approach to obtain clinical background on the conditions for the specific indications.

Information on many of the above topics may be found on the website of the US Food and Drug Administration (FDA).

- As of this writing, the site is huge and complex to navigate. It requires patience and persistence to find relevant information. Information is not consistently available for all agents.

Especially useful sections are Drugs@FDA (<http://www.fda.gov/search/databases.html>) and the Center for Drug and Evaluation and Research (CDER; <http://www.fda.gov/cder>). CDER is an up-to-date source for new drug applications (NDAs) and useful background information on new drugs. The medical reviews and statistician reviews can be of great value. It is worthwhile to do a search using the generic name of the agents of interest at both of these sections, as well as the brand name.

The British National Health Service supports a health technology assessment program (HTA). The purpose of the HTA program is to ensure that high quality research is available on the effectiveness and cost of health technologies. HTA awards funding for monographs which are produced by various people or groups who apply for their grant funding. Another source to be considered is the Canadian Co-ordinating Office for Health Technology Assessment (CCOHTA). CCOHTA is a source for unbiased, evidence-based information on drugs, devices, health care systems and best practices. CCOHTA is funded by Canadian federal, provincial and territorial governments.

The Canadian Agency for Drugs and Technologies in Health (CADTH). CADTH provides evidence-based information on drugs and health care technologies (<http://www.cadth.ca/index.php/en/hta/reports-publications>).

For information on clinical background and alternatives, the following sources may be of help: Clinical Evidence, Cochrane Collaboration, Agency for Healthcare Research and Quality (AHRQ), DynaMed, Turning Research into Practice (TRIP) are just a few of the medical reference sources that may be of use. However, be aware that many sources can be relied upon **only** for background information and not for drawing conclusions about efficacy because they might not be based on valid research studies. Many sources are available by subscription only; however, you may be able to obtain free access to Clinical Evidence through the United Health Foundation. Many times, well done randomized controlled trials provide very helpful background information in the introduction of the article.

### **Ideal Study Parameters**

After obtaining this background information, we start out framing a clinical question which involves considering the condition and the intervention. We then advise doing some further background work to understand potentially ideal methods for what high quality scientific studies might look like. For example, in the ideal world, what would be the best clinical question to serve our needs, paying particular attention to clinical significance in ways that directly benefit patients? What would the most representative patient population look like considering appropriate inclusion and exclusion criteria? What is the ideal dosing? What might be the optimal comparator against the agent being evaluated? What are the potency equivalents for any active comparators? What would be the ideal length of time for wash-out phases for various competing agents in any pre-trial period or in the case of a cross-over design? What would be the ideal study length? What are ideal ways to measure the outcomes?

The benefits of doing this preliminary background work are several. It provides for a "gold standard" to which actual studies can be compared. It is also an approach which can be more instructive to reviewers, such as the typical pharmacy and therapeutics committee member who, practically speaking, will not have had the time – or often the skills – to be able to make such an assessment to evaluate the quality of the science found.

For example, if we are evaluating a new drug, X, for use in atopic dermatitis, the ideal study question would be directed to patient outcomes of symptom relief and improved skin appearance; it would be an RCT; it would have a duration of six to twelve months; the new agent would be compared to the best-available current care using infant, children and adult study subjects who are representative of our population (i.e., have appropriate inclusion and exclusion criteria such as excluding pregnant women and people taking other immunosuppressive agents); the dosing used would be the "usual" dosing approved by the FDA; and, validated and clinically useful instruments for measuring improvement would be used, such as the Investigator's Global Assessment (IGA) and the Eczema Area and Severity Index (EASI). Potency equivalents of alternative agents would be determined in advance of the review along with information on ideal washout periods. We use specific templates or tools in each step to increase efficiency, rigor and create documentation.

### **Evidence Round-up and Assessment for Validity & Usefulness**

The next step is to round-up the potentially most useful evidence for assessment. The process starts with a focused clinical question to be applied for searching. Key points include using the generic and the brand name in the search since database filing might use only one name. Tip: If you are concerned that you may not have sufficient key words to be comprehensive enough in your search, look through the references of articles that you have found for more clues to broaden your search. Finally, it is important to use medical subject headings (MeSH) terms if available. When using PubMed, it is easy to see if the search has included MeSH terms by clicking on the "Details" button and looking for "MeSH Terms."

Also it is very important to document your search strategy. (Tip: Once you have identified articles you wish to use, recording the PMID number from PubMed that can be found at the bottom of each abstract can speed up getting to that abstract again in PubMed if you or others ever need to go in search of that specific article again. Reference managers are electronic products that assist users locate and create bibliographies and citation lists through automation. In the next chapter, details of using reference managers are reviewed.) Including key elements from the search strategy documentation in the documents that are prepared for drug review contribute to transparency. We provide just a few tips below on effective filtering of information for efficiency.

1. An efficient way to find the best quality information is to start with "trusted" sources you can rely on for valid, useful and usable information. ("Trusted" means that there is general agreement by EBM experts with the methods used, increasing the likelihood that the outcomes are valid. However, sometimes quality of information varies even with trusted sources; therefore, some EBM experts would advocate auditing any trusted source used and critically appraising information from all other sources.) These sources are Clinical Evidence, Cochrane and Database of Abstracts of Reviews of Effects (DARE). Clinical Evidence and Cochrane evaluate and synthesize original research. DARE reviews potential systematic reviews and assesses for methodological quality against a set of inclusion criteria – DARE judgments are subtly worded: when DARE advises "use with caution," that means that the information is likely to be of poor quality and probably should not be used.

#### **"Trusted Sources"**

- **Clinical Evidence** -- [www.clinicalevidence.org](http://www.clinicalevidence.org)  
**Clinical Evidence** provides you with systematic reviews and RCTs published after the systematic reviews. Abstracts at <http://www.informedhealthonline.org/index.2.en.html>
- **The Cochrane Collection** -- [www.cochrane.org](http://www.cochrane.org)  
**Cochrane** focuses on the effects of health care interventions. (Includes DARE below.)

**Database of Abstracts of Reviews of Effects (DARE)** --<http://www.york.ac.uk/inst/crd/crddatabases.htm>

**DARE** identifies potential systematic reviews and assesses for methodological quality against a set of inclusion criteria and summarizes the results.

Note: Several of these sources are available by subscription only. (As of this writing, free access to Clinical Evidence may be obtained through the United Health Foundation). These are just a few of the medical reference sources that may be of value.

Caution: Be aware that while many of these sources can be relied upon for background information, they should not be used for drawing conclusions about efficacy without deeper scrutiny, because they may not be based on valid research studies. We strongly recommend that any secondary sources such as those mentioned above be audited to determine if the individual studies, upon which the conclusions are based, are in fact valid and clinically useful.

2. Information from trusted sources and systematic reviews (which includes meta-analyses) must be updated.
  - a. Choose studies published after your source's **search date** matching study type to your question (i.e., RCTs for questions of therapy, screening and prevention).
  - b. Critically appraise these studies you find for updating. Anything you retrieve through PubMed that isn't from one of the trusted sources needs to be critically appraised – and as we mentioned, some health care professionals would say that everything needs to be critically appraised regardless of the source.
3. If you cannot find information from a trusted source, you may wish to –
  - a. Search PubMed for a systematic review – you must appraise and update the review (updating includes appraising the new studies identified). If you find a review, see if DARE has already critically appraised it.
    - Search PubMed (<http://www.pubmed.org>) for systematic reviews or meta-analyses: Click on the “Limits” button at the top, then under “Type of Article” select “Meta-Analysis” or under “Subsets” and “Topics” select “Systematic Reviews.”
    - To specify type of article, choose “Limits” from the menu bar; then check appropriate box under “Type of Article.”
  - b. Search PubMed for randomized controlled trials.
    - Search PubMed for RCTs: Click on the “Limits” button at the top, then under “Publication Types” select “randomized controlled trial.”
    - Appraise and update articles as described earlier.
    - Check out links within PubMed to comments and related articles for critical appraisal issues or something else of interest.

TIP 1: You can set up tabs for study types -- such as randomized controlled trials -- by signing up for My NCBI on the PubMed Welcome screen which will organize your search output for you by type without your having to use the “Limits” button.

TIP 2: PubMed provides easy links to comments and related articles. Someone may have addressed an important critical appraisal issue or something else of interest to you, so it might be fruitful to check out those links.

### **Searching Tips for Harms**<sup>11, 12, 13</sup>

- Large RCTs should be sought when evaluating safety, but RCT results may be problematic if harms are rare or occur late. Also look for long-term follow-up of RCTs. Systematic reviews of RCTs dealing with harms should be sought, but harms may be described in various ways in different studies. In addition, systematic reviews of randomized, controlled trials have many limitations that may bias the results toward showing no difference between the treatment groups for end points the original trials were not designed to study. If possible, it is therefore advisable to evaluate harms reported in well-done RCTs of longer duration, ideally with prespecified outcome measures for harms.
- Search for case-control and cohort studies

### **Appraisal for Validity and for Results**

For any studies which you critically appraise, we recommend an approach that quickly gets rid of studies with lethal threats to validity.

Lethal threats to validity or usability include, but are not limited, to the following:

- Observational studies for questions of therapy, prevention or screening (standards may be lowered in instances of harms, but advice is to take a net view)
- Case series (including reports using comparisons to historical controls or “natural statistics”) unless all-or-none results (very rare)
- Lack of clinical significance
- For RCTs, study procedures or schemes that result in patients being unrandomized, e.g., exclusions post-randomization
- Loss to follow-up of five percent or more without an appropriate Intention-to-Treat (ITT) analysis. (Key point: Many authors incorrectly use various terms. It is important to understand the concepts and not just accept what they say. Intention-to-treat is a term that is often cited by authors who have not actually performed the analysis correctly. Evaluate whether outcomes are provided for all patients in the groups to which they were randomized and evaluate the method they use for assigning outcomes for missing values.)<sup>14</sup> This issue of loss to follow-up is frequently misunderstood. At times, loss to follow-up is greater than five percent, but the authors present an ITT analysis in which they have assigned outcomes for missing data that put the intervention through a rigorous test such as analyzing by creating a worst case scenario by assigning positive outcomes to missing controls (i.e., assigning an outcome that all missing controls did well) and assigning negative outcomes to missing intervention group subjects (i.e., assigning an outcome that all missing study subjects did poorly.) If they have made an appropriate choice for assigning all missing outcomes, we do not necessarily consider the loss to follow-up to be a lethal threat to validity. (Note: If the author has not performed an ITT analysis, you may be able to perform one yourself by assigning outcome for missing values that put the intervention or element of interest through a rigorous test.)
- Post-hoc analyses such as is done through database research or any research question not determined in advance
- Subgroup analyses where the subgroups were not determined in advance
- Non-significant findings are reported, but the confidence intervals include clinically meaningful differences
- Studies reporting intermediate markers (also known as proxy or surrogate markers, such as biologic factors such as bone density or test results such as blood pressure readings assume the intermediate markers represent a clinically meaningful outcome such as reduction in fracture or reduction in stroke). For this to be a valid assumption there must be an established, solid causal link from the intermediate marker to the clinically meaningful outcome.
- Valid studies with clinically meaningful outcomes but for which the results are too small to be clinically helpful.
- Studies that are otherwise so flawed that the results cannot be trusted.

We recommend you look for these problems first. We also recommend that you document the study reference and a reason why you are excluding the study. The list need not be complete. Anyone of the above reasons can be enough to exclude a study from your review.

For studies included in your analysis, we recommend preparing the review document with a summary of key study elements along with a critical appraisal critique. This method helps provide for transparency and will facilitate the discussion for formulary decision-making.

We also recommend giving each study reviewed and included in the drug review documents a grade. There are many grading systems for evidence review. We have one available on our website as well. We recommend that the system chosen be selected using criteria including simplicity, ease to remember, ease to apply, comprehensibility, meaningfulness and validity – some systems may mix RCTs and cohort studies, for example, and give a grade of level 1 or 2 for such studies, which can mislead about the quality of the evidence and make the evidence appear better than it actually is. Only valid RCTs with usable results should be applied to address questions of therapy

### **Summarize and Synthesize the Evidence**

The goal of evidence synthesis is to take all of the best available valid and useful evidence you have found and summarize it into a conclusion. The evidence synthesis is usually a text statement in which you make claims from the evidence. This step generally entails applying a great deal of judgment. (An example follows.) We recommend avoiding language that is inaccurate, misleading or vague, such as “The evidence suggests...,” or “It is likely to be shown that...,” or “There is some evidence that...”

Just as we recommend applying a grade to individual studies reviewed, so too do we recommend applying a grade to your evidence synthesis. The grade applies to the strength of the evidence you have found. For example, you

may have moderate to weak evidence to summarize. The grade you apply to the synthesis should reflect that. Lastly, we recommend writing a statement of any limitations of your review and subsequent synthesis.

Note: We recommend a conservative approach for the following reasons –

1. Study biases frequently favor the intervention (and all studies have some bias).
2. Long term harms may not show up for an extended period of time – and are infrequently found in the initial research.
3. The results of research within a research setting (efficacy) are usually better than the results we see in clinical practice (effectiveness).

## Conclusions & Wording Suggestions

The table below can be used to construct a concluding statement about the evidence:

Evidence Grade & Concluding Statement	
Choose the applicable grade and strength of evidence statement (examples found in Results Table below).	
<b>Wording Conclusion Sample for Valid and Clinically Useful Studies</b>	
We recommend <b>not</b> completing for Grade U studies for questions of efficacy. We recommend completing selectively for safety when safety outcomes are judged reasonably likely not to be due to chance.	
Consideration	Research Outcomes
	Replace text and complete the consideration below, adding new tables as needed for different outcomes:
Category	Efficacy, safety or other
Intervention	Include details such as dosing
Was found to be	superior, equivalent, non-inferior, other [specify]
When compared to	
In the following clinically significant area(s)	Indication and applicable outcomes measured
As measured by	Measurement instruments used
Within the following time period	Study time period from intervention to measurement
Typical patients studied	Describe using inclusions, exclusions and key baseline characteristics including ages and other meaningful prognostic characteristics such as relevant medical histories
Results: Absolute	[ARR%], (95% CI [CI, CI%])
Results: Number-needed-to Treat	Complete only for statistically significant results
Additional Considerations for Harms	
Study type	Experiment, observational [specify exact type e.g., RCT, cohort, case report]
Harms were	Prespecified, not prespecified, other [specify]
For important differences in harms that were not statistically significant, confidence intervals did not exclude a potentially clinically relevant difference between groups for the following harms	Harms and results including confidence interval
Confirmation in additional studies	Yes, no [include references]
<b>References:</b>	

## Project Potential Impacts of Practice Change

As we stated earlier, a truly evidence- and value-based process considers impacts of practice change, taking the net view into account. In many instances, practice change impacts can be assessed by looking at the current processes of care and related considerations and comparing them to imagined possible resulting changes. This means taking into account impacts on the patient and physician perspective, satisfaction for patients and providers, impacts of utilization, such as effects on facilities, systems, roles and skills needed, methods, procedures, equipment, supplies and other resources, on the other triangulation issues, and, importantly, cost.

For example, when considering the addition of an immunomodulating drug for atopic dermatitis, one would want to consider not only the efficacy, but estimates of change in office visits, use of corticosteroids, referrals to specialists and use of other immunomodulating drugs, patient and clinician satisfaction, and cost.

Cost assessment is an area that is frequently a key responsibility for P&T committees – and, therefore, clinical pharmacist staff supporting those committees. Frequently, those involved in determining methods for doing a cost

review will choose from a wide array of potentially confusing methods. Our advice is to choose a method that is appropriate to the need, but which is the most simple and comprehensible from the appropriate choices. Frequently, for most health care organizations, a simple cost analysis approach, applying the Average Wholesale Price" (AWP), may be adequate. Also, too, sometimes a simple before-and-after comparison is sufficient without trying to make the analysis too laborious. It is often enough to have an estimate of how much you will improve care and reduce costs without necessarily carrying out cost-effectiveness or cost-utility analyses.

Our strong advice for all of this work is to break all your assumptions and costs down into base unit values for transparency and greater flexibility.

An efficient and effective way to compare multiple agents is to use number-needed-to-treat (NNT). A vitally important, and often overlooked, consideration for using NNT is the time period associated with NNT (which is the same as the study time period). Consideration of the time period is just as important as the number of people needed to treat when considering efficacy. For example, an NNT of three that can be expected to benefit patients within 1 year is potentially more effective than an NNT of three that can be expected to benefit patients within 5 years. Average cost effectiveness analysis asks the question: "What am I spending for each outcome gained." Ascertaining the cost-per-benefit can be very helpful. One needs three variables: the NNT, the study time period, and the cost for a single study time period unit, such as one year if the study time period is expressed as years.

Sometimes the answer will be very clear. In the example the example below, drug X emerges as the best choice provided the clinician has examined all other factors, such as validity of studies, usefulness of results, safety considerations, application issues, and other triangulation issues, as described earlier in this chapter.

Agent	NNT	Time Period	Cost for 1 Year of Treatment
Drug X	3	1 year	\$100 per year
Drug Y	3	5 years	\$100 per year

In other instances, the choice may not be immediately clear because of complexities arising from variations within the combination of NNT, time period, and/or cost. For example, which of the following agents in the example below appears to be the better agent?

Agent	NNT	Time Period	Cost for 1 Year of Treatment
Drug X	5	4 years	\$100 per year
Drug Y	4	5 years	\$90 per year

When these kinds of combinations occur, a simple calculation provides useful information. Simply multiply the NNT times the study time period times the cost per study time period unit. Using the example below, the cost-per-benefit of Drug X is \$2,000 and the cost-per-benefit of Drug Y is \$1,800. Assuming that the research behind each agent is valid and clinically useful, and that there are not other critical differences in terms of harms, drug administration, etc., this is a simple way to compute an average cost effectiveness analysis which can yield helpful information to achieve greater value.

Agent	NNT	Time Period	Cost for 1 Year of Treatment	Cost-per-benefit
Drug X	5	4 years	\$100 per year	$5 \times 4 \times 100 = \$2,000$
Drug Y	4	5 years	\$90 per year	$4 \times 5 \times 90 = \$1,800$

Various scenarios might be worthwhile to consider. Some useful ways to view the data would be to do a best and a worst case scenario, to consider confidence intervals and to assess estimates for effectiveness (as compared to efficacy).

We have made available an online calculator at [www.delfini.org](http://www.delfini.org) which can help you compute these comparative calculations.

### About Pharmacoeconomic Studies

Many groups use pharmacoeconomic studies to help them with economic analysis. You may find a helpful article in PubMed. However, all pharmacoeconomic studies, unless from one of the trusted sources (i.e., Cochrane, Clinical Evidence and DARE), need to be critically appraised for validity and usefulness (and even if from a trusted source,

are best audited). Plus there are additional considerations for quality and applicable pharmacoeconomic studies of which you should be aware. We address these briefly below.

Pharmacoeconomic analysis essentially entails combining several elements into an economic model – meaning a construct that is created in an attempt to help predict what may happen in clinical practice. The elements that create the model include health care outcomes, which should be based on valid and useful randomized controlled trials, cost data and assumptions such as the number of patients projected to make an office visit, estimated number of patients who will be prescribed a particular medication or projected number of patients who will experience an adverse event, etc.

First and foremost, look to see if – and by what method – the authors critically appraised studies included in the model. Often, this important step is neglected in pharmacoeconomic studies. Second, note that evidence is usually a global consideration. Cost, however, is a local one and a paper published in a national journal, coming from a national perspective, may not have relevance in cost outcomes for the group using the data. Third, assumptions are assumptions. They are such things as opinions, estimates, conjectures and guesses, even when based on data – and like cost, they are likely to vary locally. Your assumptions, based on local considerations, may be as meaningful or more meaningful than those used in the study. It may be worthwhile to create your own model and use these kinds of studies for ideas or inputs to create and adjust your own model.

Also, if you are going to use any pharmacoeconomic studies, it may be best to obtain and use a tool that is appropriate for evaluating pharmacoeconomic studies. In addition to ensuring they have critically appraised any studies upon which they are basing their effectiveness projections for health care outcomes, other items should be considered such as relevance to your circumstances, appropriateness of the mode of economic analysis, whether the best information or reasonable assumptions were included in the model, whether reasonable alternatives were compared, whether sensitivity analyses conducted to test out various scenarios (such as worst case and efficacy versus effectiveness), limitations and biases, as examples.

Practitioners might want to consider the following criteria, at a minimum, to determine the appropriateness of a study for their practice:

- Did the authors critically appraise any studies on which they based their effectiveness projections for health care outcomes and only utilize valid and clinically useful studies?
- Is the information relevant to the practitioner's circumstances?
- Is the mode of economic analysis appropriate for the local practice?
- Are the best information or reasonable assumptions included in the model?
- Were reasonable alternatives compared?
- Were sensitivity analyses conducted to test various scenarios (e.g., worst case, efficacy versus effectiveness)?
- Do limitations and biases exist?

### **Summarize Drug Review and Make Recommendations**

The final step in conducting the drug review is to create a concluding summary. This summary should be the “roll-up” for all the preceding information that has been reviewed and synthesized. The summary should be very clear and transparent about what is evidence and what is a judgment. It should address findings on evidence and safety, appropriate patient population, value assessment, comparison to alternatives, implications of practice change and recommendations. There should be an attempt to assess the possible physician perspective (e.g., satisfaction, acceptability, likelihood of appropriate application and actionability) and the patient perspective (e.g., benefits, costs, risks, harms, uncertainties and alternatives) along with issues that may affect patient adherence to treatment, dependency or abuse potential, and so on. It should also describe limitations of the overall review and analysis. Lastly, many clinical pharmacists are expected to consult with clinicians and others to make recommendations for committee consideration (including guidance, restrictions and exclusions, giving consideration to substitutions, prior authorizations, and overrides).

### **In Conclusion**

We have provided a detailed approach to creating an effective system that will inform formulary decision-making. This approach includes the details about how to find and critically appraise the best medical evidence, how to determine value, how to perform an economic drug review, and how to effectively – and efficiently – use the results of your work to ensure high quality of the information that is used to support formulary decisions. In essence, this approach considers the weight of the scientific evidence, the net benefits and harms, costs and other triangulation

issues in order to inform decision-makers about a new agent: is its clinical value superior to, equal to or lesser than existing agents?

#### The Bottom Line

The steps to an explicit evidence-based formulary are referred to as the “five A’s” of EBM”:

- Ask where significant gaps within the formulary exist.
- Acquire information using evidence-based techniques which includes a systematic search and appropriate filtering techniques.
- Appraise information for validity, usefulness, and value.
- Apply information by careful crafting of conclusions to create information, decision, and action aids, and implementing new therapy programs, measuring the success of implementation and performance, and reporting key outcomes.
- Again, cycle back through preceding steps to continuously improve clinical care.

Transparency through good documentation of all steps and reporting is critical to good evidence-based practice.

#### Glossary

Term	Definition or description
Class effect	Class effect (i.e., “equipotency,” meaning deciding which agents are to be considered sufficiently similar as to be able to group them into one drug family – or “drug class” as if they are, for all intents and purposes, clinically the same – although some other factors, such as cost, may vary).
Drug utilization review (DUR)	A system for evaluating appropriateness of drug therapy. Prescribing patterns are evaluated to determine if drugs are being misprescribed, resulting in problems with safety or effectiveness.
Equipotency	Which agents are to be considered sufficiently similar as to be able to group them into one drug family – or “drug class.”
First-line therapy	The drugs to be utilized first in treating a patient.
Formulary	A formulary is a list of therapeutic agents available for caring for patients. It is also sometimes referred to as a “preferred drug list.” <ul style="list-style-type: none"> <li>▪ Open formulary may have few or no restrictions.</li> <li>▪ Closed formulary has restrictions.</li> </ul>
Formulary system	A formulary system provides for the processes for establishing and managing the formulary
Generic substitution	Replacement of one agent with a different agent having the same chemical structure. This may be done when the patent on a brand-name drug expires. Bioequivalence is frequently assumed (i.e., it is assumed that the generic agent is equivalent to the brand-name drug). In some cases the effects of other components of the generic preparation (e.g., the vehicle in a dermatological preparation) may vary and result in outcomes that differ from those reported for the brand-name agent
Monograph	Reviews, analyses and recommendations often for a single agent
Narrative review	An article in the medical literature summarizing other studies for a given topic, characterized by a lack of a transparent, scientific and systematic approach, and thus, highly likely to be misleading. Instead, systematic reviews should be sought (and appraised).
Overrides	Setting aside a prescriber’s choice of a medication and usually substituting another in its place.
Pharmacy & Therapeutics Committee	Committee that is charged with making formulary management decisions, along with performing other formulary management functions.
Pharmacy benefit managers (PBMs)	Companies that manage pharmacy benefits and formulary management for health care systems and/or insurance companies.
Prior authorizations	Requirements that a clinician obtains approval before a drug can be dispensed and/or covered.
Rebates	Cost offsets pharmacy systems receive when purchasing large quantities of drugs

	based on volume of use.
Second-line therapies	Therapies for patients failing on drugs established as “first-line” therapies.
Systematic review	An article in the medical literature summarizing other studies for a given topic, using a transparent, scientific and systematic approach to identifying and including valid and useful studies in the review. Meta-analysis is a subset and is characterized by how the results of the studies are combined quantitatively and statistically. Unless retrieved from “trusted” sources, systematic reviews need to be critically appraised for validity and usability. (It is advisable to audit trusted sources for validity and clinical usefulness.)
Therapeutic substitution	Therapeutic substitution (i.e., substituting agents with different chemical structures, but with similar clinical benefits).
Triangulation issues	A euphemism for all the various considerations that need to be made in making a decision.

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