GUIDELINES FOR FORMULARY EVALUATIONS

[PROPOSED]

PROGRAM IN SOCIAL AND ADMINISTRATIVE PHARMACY

COLLEGE OF PHARMACY

UNIVERSITY OF MINNESOTA

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Version 1.0: July 2016

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1. BACKGROUND

1.1 Credibility and Replication

If formulary decisions to admit or retain pharmaceutical products and devices are to be credible they must recognize the standards of modern science. The focus of the Guidelines for Formulary Evaluations (GFE) lies in the recognition that if claims are made to support pharmaceutical products and devices, they must be evaluable and reproducible. Claims must be presented in a testable form that allows feedback to formulary committees as part of ongoing disease area and therapeutic reviews. This evidentiary standard applies equally to claims for comparative clinical effectiveness as well as to claims for cost-effectiveness. If non-evaluable claims are presented by manufacturers then they should either be reformulated or put to one side as lacking credibility for formulary decisions.

This standard for experimentation based on evaluable claims is unexceptional. It has been recognized as the core of the scientific method since the mid-17th century. Unfortunately current standards for formulary submission fail to recognize this standard. Claims are submitted to support formulary decisions that are incapable of falsification and replication. This is true, not only of the Academy of Managed Care Pharmacy (AMCP) Format for Formulary Submissions (Version 4, April 2016) but also of ‘gold standard’ reference case claims mandated by agencies such as the National Institute for Health and Care Excellence (NICE) in the UK, PHARMAC in New Zealand and the Health Information and Quality Authority (HIQA) in Ireland. The same criticism applies to modeled or simulated claims published in journals such as Value in Health, PharmacoEconomics and the Journal of Medical Economics.

If the NICE reference case standards are applied, for example, cost-utility models are submitted to formulary committees which make the comparative case for chronic disease interventions in lifetime discounted cost-per-QALY terms. These claims are, quite clearly, impossible to evaluate; nor were they ever intended to support evaluable outcomes. Yet formulary committees are asked to accept such modeled or simulated claims even though they have no idea whether they are right or even if they are wrong. The argument that because a modeled or simulated claim demonstrates a sufficient correspondence to reality it should necessarily be accepted in the absence of experimentation is not a basis for informed formulary decision making. Such claims are nothing more than thought experiments or imaginary worlds and are not relevant to evidence based formulary decision making. The claims fail the test that demarcates science from pseudoscience.

To base formulary decisions on clinical and cost-effectiveness claims that fail to meet the standards of normal science in both testability and replicability is an untenable situation. With increasing concerns over the ability to replicate claims from Phase 3 trials and output switching...
in reporting phase 3 results, formulary committees have to be aware of the need to establish the credibility of claims 20 21 22.

1.2 Quality-Adjusted-Life Year Claims

Under the GFE proposed guidelines, quality-adjusted-life year (QALY) claims are only acceptable if (i) they are expressed in evaluable terms; (ii) a protocol is presented detailing how the claim is to be evaluated and reported to a formulary committee in a meaningful timeframe and (iii) the submission justifies the use of the particular QALY measure for the disease area. Modeled or simulated claims that track the course of a chronic disease, for example, are of little interest as there is no chance that they could be evaluated. They have no credibility. A similar objection applies to claims expressed in lifetime cost-per-QALY terms that apply notional cost-per-QALY thresholds to justify premium prices or discounting of competitor pricing. Although a QALY endpoint has been proposed as the ‘gold standard’ outcome claim, the fact is that in the US QALYs are never collected as part of health care systems’ administration. Formulary committees have expressed little interest in QALY based claims as a useful input to decision making. Rather, the focus is on value claims comparing products within disease or therapy areas. Claims are presented that are specific to that disease or therapy area. They can then be evaluated in a timeframe relevant to a formulary committee’s decisions for formulary placement and pricing.

1.3 Submission Protocol

The purpose of GFE is to ensure that claims supporting formulary decisions are credible, evaluable and replicable. Manufacturers and others who submit claims are asked to justify the claims made by presenting those claims in an evaluable form, supported by an assessment protocol. The assessment protocol is central to the assessment of claims. It requires manufacturers to stand behind their product. Until an assessment has been made, claims made for products should be treated as provisional. The decision then rests with the formulary committee either to accept provisionally a protocol subject to the claims being evaluated and reported back to the committee or to put a formulary decision to one side until a claims assessment has been presented. If an assessment has already been made then these results can be reported to the committee as part of the submission.

Requiring claims for products to be evaluable is essential if clinical and pricing decisions are to be driven by a credible evidence base. Feedback is essential if the credibility of claims is to be maintained. This does not mean evidence from one or more phase 3 trials, but evidence from assessing those claims in the target patient population. Application of the standards proposed here will provide a more believable and robust evidence base to support not just personalized but precision medicine in matching individuals to products.
1.4 Target Populations
A key element in the claims protocol is the identification of target populations. With the increasing emphasis on personalized or precision medicine, the expectation is that diseases will be defined in terms of their molecular taxonomy or pathology rather than their symptoms, gross pathology or part of the body in which they appear. At the same time, those arguing for a target population need to justify the choice of molecular algorithm as a decision support tool. The choice of a diagnostic test or device to identify the target population must meet regulatory standards. Replication of claims, which will likely become more necessary as manufacturers compete for smaller target populations with high-cost products in the same molecular ‘space’, will have to be able to identify target populations for such assessment.

At the same time, asking target populations to be identified in a protocol will contribute to defining and establishing the boundaries of a disease state for claims evaluation and replication. This, hopefully, will limit the extent to which ‘disease mongering’ occurs.

1.5 Drug Costs in Target Populations
With increasing concern being expressed over the pricing of drugs, particularly in the anticancer area for end-of-life metastatic treatments, a critical input to a formulary decision is the launch price (wholesale acquisition cost) of a product and the current price of comparator therapies for the target indications. The GFE asks manufacturers to indicate what the anticipated launch price of the drug is expected to be (or the current price if it has already been launched). Where a drug has been launched, information should be provided on whether or not there have been price changes since launch. At the same time, for comparison purposes, manufacturers are asked to provide anticipated launch or current prices in other global markets: Canada, the European Union and Australia.

As well as launch price, manufacturers are asked to provide estimates of the costs of an episode of care for their product compared to comparator products. This can be expressed as the cost over an expected survival period for end-of-life therapy or the annual cost in an ongoing chronic disease intervention. The episode of care costs should capture (i) drug costs and (ii) total direct medical costs for patient evaluation, monitoring and administration.

1.6 Options in Claims Evaluation
The credibility of claims to support formulary assessments of pharmaceutical products and devices can be established by:

- A retrospective assessment of established products as inputs to ongoing disease area and therapeutic class reviews
- A prospective or tracking assessment of prospective claims for new products or devices matched to existing products
• A prospective observational assessment of claims in the context of a phase 4 trial or similar

The standards proposed here apply equally to the entry of new products where claims are prospectively matched against existing comparator products as well as to comparisons between existing products. In the latter case, the issue of replication of phase 3 based claims may be important if there is evidence that attempts to replicate these claims elsewhere have failed.

1.7 Comparative Effectiveness Research

The standards for formula submission recommended here are consistent with interventions under, for example the Patient Protection and Affordable Care Act to support quality outcomes and metrics in health care delivery. The standards are designed to provide a robust evidence base for formulary decisions in target patient populations. These populations may be risk stratified to match the proposed indication for the pharmaceutical product. The standards proposed can support targeted interventions to improve clinical outcomes in, for example, at-risk populations.

Implementation of the GFE proposed protocol to support the assessment of comparative clinical and cost-effectiveness claims is, of course, consistent with the objectives of comparative effectiveness research. The principal difference is that the GFE links the assessment to claims made for the product on market entry and not an assessment sometime after market entry. This may involve, not a prospective observational study to track product uptake and response, but a randomized controlled trial. Once the product is listed on formulary there may be less incentive or willingness to evaluate comparative clinical and cost-effectiveness claims. Linking a claims assessment protocol to a product submission for formulary listing, with a commitment to underwrite a comparative evaluation, provides such an incentive.

1.8 Value Claims

Putting on one side claims couched in QALY terms also means that, unless specifically requested by a formulary committee, attempts to construct composite cost-outcomes claims are also unlikely to convince formulary committees. While it might seem paradoxical after some 20 or more years focusing on composite outcome measures such as QALYs that allow, at least in the context of reference case or similar models, gross comparisons across disease areas, the view is now that value claims are best seen as stakeholder specific and within disease areas.

The absence of agreements on disease specific outcome metrics and on metrics that might allow comparisons across disease areas means that it is the responsibility of health systems to establish standards for evaluating comparative drug claims. These might involve health system and disease area specific value frameworks such as those proposed by the American Society of Clinical Oncology or estimates of the impact of a new therapy on resource utilization and health system budgets. Irrespective of the value frame work, the two key elements are that: (i) a value
framework should encompass a range of outcome measures (which a health system may weight to create a composite index) and (ii) the value measures should be credible and evaluable.

The choice of a value framework is at the discretion of stakeholders in the health system. The GFE is not concerned to set value standards but rather to ensure that stakeholders see that value claims are provisional and necessarily subject to evaluation and replication.

1.9 Adherence and Persistence

Claims from models and simulations typically make no allowance for patient adherence and persistence following product launch. This is an unfortunate oversight as medication adherence and persistence is seen as a global health problem. Despite decades of research the patterns of poor adherence and lack of persistence remain essentially unchanged. This is true across all major disease areas and most notably for older patients with chronic disease.

Given the potential impact of poor adherence and the lack of persistence on clinical, cost-effectiveness and other value claims, the GFE proposes that where a submission is prepared it should not only provide a systematic review of adherence and persistence behavior for the target population and comparator therapies within the disease or therapy area but should also detail, if considered relevant, potential interventions to mitigate such behavior.

Evaluable claims for the clinical and cost-effectiveness impact of competing therapies should, therefore, accommodate anticipated adherence and persistence behavior. This is of particular interest for value claims in older target populations with the presence of co-morbid chronic disease and consequent polypharmacy. Claims should factor in the potential (and evaluable) impact of adherence and persistence.

1.10 Systematic Reviews and Evidence Summaries

Where appropriate submissions should meet the PRISMA-P standards for systematic reviews in adults and the pediatric extensions PRISMA-P-C (Protocol for Children) and PRISMA-C (Children)\textsuperscript{27} \textsuperscript{28}. Where a systematic review is undertaken a summary of the search protocol and principal findings should be provided. Reporting of randomized trials should conform to the CONSORT and CONSORT-C standards \textsuperscript{29} \textsuperscript{30}.

Systematic reviews to support modeled or simulated cost-effectiveness claims should be restricted to studies where the claims have been expressed in evaluable terms and an evaluation undertaken.

1.11 Request for Submission

The GFE is not intended to support unsolicited submissions and claims for clinical or cost-effectiveness. If a formulary committee wishes to evaluate a new product or device, or to revisit a product or device already on formulary, then it is at the discretion of the committee as to
whether or not a request would be made. In the latter case submissions may be requested from all manufacturers of the comparator products selected.
2. EVALUATING FORMULARY SUBMISSIONS

2.1 Product and Comparator Descriptions and Pricing

For each product and comparator the respective product inserts should be provided. There should be a brief description of the approved indication(s) for the product and comparators together with any black box warnings. The submission should justify the selection of comparator products.

As well as providing a clinical profile of the product and its comparators, manufacturers should submit the anticipated or launch price (Wholesale Acquisition Cost) of the drug (or current price if the drug has been launched) and the identified comparators, together with the anticipated cost of the drug and its comparators over an episode of treatment (or annual cost if proposed in a chronic indication).

If the product is expected to be launched in other national markets (or has been launched) the anticipated or actual launch price in the following markets (where applicable) should be provided: Canada, major European Union countries and Australia.

2.2 Target Population and Place in Therapy

For each product and comparator the submission should include a description of the target patient population(s), including target sub-populations, and the place of the product(s) in therapy. If there are agreed national treatment guidelines these should be provided indicating where there may be anticipated changes following approval of the new product. The descriptions of the target populations should include a profile of co-morbidities and the prevalence of those co-morbidities.

2.3 Significant Adverse Events and Contraindications

For each of the products and comparators a summary should be provided detailing the significant adverse events (≥ 1%) and contraindications. The adverse event profiles should detail (i) those reported as part of the phase 3 trials and (ii) those reported as part of risk assessments following product approvals.

2.4 Primary and Secondary Outcomes

For each of the products and comparators a summary should be provided detailing for the respective pivotal phase 3 trials the primary and secondary outcomes. This summary should detail if the claims made for the product and comparators are consistent with the primary outcomes identified for the phase 3 trials. If, during the trial process, the primary outcomes were switched and/or secondary outcomes dropped/added this should be documented. A statement is required indicating that this has not occurred in any of the product and comparator trials. If
outcome switching has occurred a statement is also required that the trial was powered to support those claims. Summaries of the pivotal trial protocols should be provided as part of the submission.

2.5 Direct and Indirect Comparisons

If there have been head-to-head comparisons between the product and comparators these should be documented. Similarly, the results of indirect comparisons should also be documented, together with a brief description of the techniques employed. If the claims from indirect comparisons have been evaluated from phase 4 trials or observational studies these should be documented.

2.6 Replication

For each of the products and comparators any attempts to replicate the primary outcomes of the phase 3 trials in successor trials or observational studies these should be documented together with the respective results. If there is a lack of concordance between the original phase 3 outcomes and those reported for any replication this should be reported.

2.7 Adherence and Persistence

For each of the product and comparators evidence is required for adherence and persistence behavior (i) during the pivotal phase 3 trials and (ii) for a period up to 4 years from product launch. In the latter case the evaluation should include evidence for switching between the product and comparators as well as between the comparator products. This review of adherence and persistence should report on descriptive studies as well as those that have attempted to assess the determinants of this behavior in the therapeutic product class. The review should report on the extent to which patterns of adherence and persistence have modified primary clinical claims for the product and comparators in the target population or sub-populations, together with the results of any interventions to impact adherence and persistence behavior.

2.8 Completed Evaluations

If a manufacturer has already completed an evaluation for the clinical and cost-effectiveness claims it proposes to submit for the product or device then this should be included as part of the submission. The manufacturer should provide copies of the protocol that supported this evaluation. The manufacturer should state why this previous evaluation is appropriate for claims made for the target health system population and why replication of this previous study is unnecessary.
2.9 Evidence Summaries

The submission should include, as an Appendix, systematic review and evidence summaries in spreadsheet form for all product and comparator randomized clinical trials. These summaries should conform to the PRISMA and CONSORT standards (see Section 1.8)
3. VALUE AND COST-OUTCOMES CLAIMS

3.1 Scope and Options in Value and Modeled Cost-Outcome Claims

Value and cost-outcomes claims submitted are only considered if:

- The claims submitted are evaluable
- The proposed claims evaluation provides feedback in a meaningful time horizon

There is no restriction on the type of value or cost-outcomes claims that can be submitted. Value claims can be expressed in clinical terms, as patient reported outcomes, as direct medical costs and as cost-outcomes. Where patient reported outcomes are used they should meet accepted standards for their measurement properties with a statement indicating whether or not interval differences are clinically meaningful.

Claims presented should be evaluable within a 2-year time frame. Longer time frames, including those that model the natural course of a chronic disease are not relevant to formulary decision making. The objective should be to present claims that can be evaluated and reported back to decision makers to support effective decision making.

3.2 Claims Evaluation Protocol

The formulary submission should be accompanied by a protocol as detailed in Section 4. From an evaluation perspective, it is important that claims made are capable of being assessed either from existing data sets (e.g., administrative claims linked to EMRs) to capture resource utilization impacts as well as clinical endpoints or from a prospective observational study to capture outcome that are not typically captured in EMRs. Those making the submission have the choice, therefore, of tailoring their claims to available data from third party vendors or underwriting a prospective study.

3.3 Value Claims and Model Structures

It is entirely at the discretion of those making the submission whether the value and cost-outcomes claims are presented as specific clinical endpoints, as outcomes from a simple decision model or as a more complex structure such as a Markov model or a discrete event simulation. It is entirely at the discretion of those submitting claims whether or not to present them as incremental cost outcomes ratios supported by sensitivity analyses.

Again, it is also entirely at the discretion of those making the submission whether they want to support their choice of model and the assumptions driving the model by reference to quality checklists such as CHEERS. The focus on generating testable predictions means that a model is not judged on the correspondence of its input assumptions and core mechanism to some
perception of reality. The issue of the sufficiency of correspondence necessarily entailing the claims made is irrelevant. The merits of a model rest upon its ability to generate testable claims and the results of an assessment of those claims.

3.4 QALYs and Cost-Outcomes Thresholds

GFE advises against claims being presented as utilities or as costs-per-QALY (quality adjusted life years). Apart from the obvious case of lifetime or long-term cost-per-QALY claims which are clearly unevaluable and which should be rejected as reflecting simulated imaginary worlds, GFE would also caution that few health care decision makers in the US, in either public or private domains, have the slightest interest in QALY based claims. In the first place, there is no agreed standard for measuring QALYs, in the second place QALY measures are seldom (if ever) reported as the primary outcome measure in RCTs, and thirdly, they are never captured in electronic medical records or other data bases. In addition, it is not the intention of GFE to support modeled cost-utility claims that are designed to demonstrate that a product or device is ‘cost-effective’ because it generates incremental claims that are below a notional community willingness to pay threshold. If a formulary committee is prepared to base its decision making on willingness to pay thresholds that is their decision and they should inform those making submissions accordingly.

3.5 Adherence and Persistence

Modeled claims submitted should accommodate anticipated adherence and persistence behavior. In many chronic disease states product utilization data point to relatively low rates of adherence and persistence by the end of the first 12 months from the index prescription. Those presenting a submission should make clear what the anticipated adherence and persistence behavior for the product is expected to be and whether or not it offers advantages in these respects over comparator products. Claims should not be based on a possible minority of patients introduced to a new therapy who are assumed to be adherent (e.g., medical possession ratio ≥ 0.8) and persistent over a modeled time horizon of, say, 2 years.

It is, of course, entirely at the discretion of those making the submission to suggest, as part of their claims for the product to propose evaluable intervention strategies that could support longer term adherence and persistence.

3.6 Dispensing with a Modeled Claim

It is not mandatory for those subscribing to the GFE guidelines for a modeled claim to be presented. If those preparing a submission believe they are not in a position to develop a credible, composite cost-outcomes modeled claim then this should be put to one side. The focus of the submission would be, therefore, on evaluable comparative clinical or value claims such as comparative cardiovascular events avoided as well as resource utilization, direct and indirect medical costs for patients and caregivers.
3.7 Concurrent Submissions

In situations where a manufacturer has already submitted a protocol to another health system and is underwriting an evaluation this should be reported as part of the submission. In this case, as long as the formulary committee agrees that the protocol is acceptable, then the manufacturer should commit to reporting to the committee once the other study is complete. There is no requirement for the evaluation to be undertaken in the health system’s patient population.
4. CLAIMS ASSESSMENT PROTOCOL

4.1 Protocol Standards (PROST)

The claims assessment protocol can be applied to clinical claims, modeled cost-outcome and budget impact claims. The assessment checklist recommended by GFE is a revised version of an earlier Protocol Standards (PROST) checklist. The protocol is designed to support prospective studies where patients are tracked from existing data sources as well as prospective observational studies involving reporting from human subjects. The protocol can also support prospective applications of value calculators where, rather than relying on inputs from randomized clinical trials, the elements of the value calculator based on those trial results can be evaluated with potential feedback to support re-calibration of initial value scores.

4.2 Format for Protocol Submission

**Title:** Proposed Assessment Protocol for Evaluating Clinical and Cost-Outcome Claims for [product]

**Abstract:** Structured summary of protocol assessment objectives: (i) claims to be evaluated; (ii) target population; (iii) proposed study design; (iv) data sources; (v) timelines for evaluation; and (vi) reporting format

**Context:** A statement of the context of the study to include: (i) a systematic review of clinical and cost-effectiveness claims for the product and comparators in the relevant time horizon; (ii) a systematic review of adherence and persistence patterns for the product and comparators in the target population; and (iii) a statement of the contribution this study is expected to make in evaluating competing interventions in this disease or therapy area.

**Claims:** A statement of the claims that the proposed study will be evaluating: (i) clinical outcomes; (ii) adverse event and safety outcomes; (iii) resource utilization outcomes; (iv) direct medical costs; and (v) cost-effectiveness.

**Target Population:** Characteristics of target population (age, gender, ethnicity, race) to include sub-groups and clinical markers (presence/exclusion of co-morbidities; stage of disease)

**Data:** Description of proposed data source(s) and any permissions required to access data/target population (e.g., IRB approvals, EMR approvals, access to administrative claims data) and confidentiality requirements

**Study design:** Rationale and description of study design, to include: (i) rationale for choice of study design; (ii) concurrence with good practice guidelines; (iii) treatment comparators; (iv) timeframe; (v) statistical and analysis plan; (vi) data sources; (vii) statistical hypotheses; (viii) description of statistical methods; (ix) sample size; (x) procedures to minimize bias; (xi) quality assurance; (xii) confidentiality; (xiii) data handling; and (xiv) reporting.
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Budget: A detailed budget and a commitment to underwriting the evaluation.

Interim Reporting: Proposed schedule for interim reporting of study implementation and progress.


4.3 Questions a Formulary Committee Should Ask

On receipt of a protocol the formulary committee should consider:

Objectives: Has the protocol provided a summary of the study objectives? Does the protocol abstract provide a summary of (i) population targeted; (ii) comparators; (iii) timeframe; (iv) study design; (v) data sources; (vi) endpoints; and (vii) reporting format.

Context: Has the protocol provided a systematic review to establish the context for the claims to be evaluated and the contribution this evaluation have to an overall assessment of comparative treatment benefits and harms in the population targeted and indication for the product?

Target Population: Has the protocol provided a rationale for the population to be targeted, to include (i) demographic characteristics; (ii) clinical status; (iii) disease stage; (iv) co-morbidites

Claims: Has the protocol provided a summary of the modeled claims for cost-effectiveness to be evaluated? Has the protocol identified claims for (i) clinical benefits; (ii) adverse events and safety; (iii) resource utilization; (iv) direct medical costs; (v) cost-effectiveness and (vi) adherence and persistence?

Study Design: Has the protocol provided a rationale for the study design (e.g., prospective effectiveness trial, cohort/observational study)? Were alternative study designs proposed? Were risks of bias and other limitations described?

Implementation and Reporting: Has the protocol provided a schedule for initial implementation? Has a schedule been provided for interim and final reporting of the claims evaluation?
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