



American Society of Clinical Oncology
Guideline Procedures Manual

Expert Panel Version 3.0

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About This Manual

The ASCO Guideline Procedures Manual is designed to assist ASCO expert guideline panels in the development of ASCO guidelines and technology assessments. The Manual was developed by the ASCO Health Services Committee's Guideline Methodology Subcommittee, and was approved by the Health Services Committee on September 27, 2005. The Manual is considered a living document that will be updated periodically by the Methodology Subcommittee, as needed.

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The Manual is organized around the major steps in the ASCO guideline development process, from topic proposal to the dissemination and implementation process. Comments on the Manual from panel co-chairs are welcomed and encouraged. Direct any comments to Mark Somerfield at 571-483-1615 or guidelines@asco.org. Guideline development is an intensive process; ASCO's goal is to make it as easy and efficient as possible for volunteers.

ASCO is grateful to you for agreeing to develop a guideline or technology assessment. Surveys of the ASCO membership on the value of the wide range of ASCO programs have consistently highlighted the popularity and importance of ASCO guidelines to the membership. Guidelines represent a key component of ASCO's commitment to improving the quality of cancer care.

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I.ASCO Clinical Practice Guidelines: A Brief History and Rationale

A Brief History and Rationale

Clinical practice guidelines are “systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances.” The American Society of Clinical Oncology (ASCO) began its guidelines program in 1993 following an ASCO strategic planning initiative. As part of this initiative, ASCO conducted a membership survey. Guideline development was ranked second among the priority areas for ASCO by the membership. In more recent membership surveys, ASCO guidelines have consistently ranked third behind the Annual Meeting and the *Journal of Clinical Oncology* in terms of member value. The impetus for guideline development is straightforward: Guidelines are thought to improve cancer care by helping to bring practice in line with the state of the art in oncology as defined by empirical evidence.

The guidelines program falls under the auspices of the ASCO Health Services Committee (HSC). The HSC oversees development of guidelines and their panels. Guidelines address the use of generally established practices (use of adjuvant chemotherapy in colon cancer management). They are developed by Expert Panels that comprise individuals drawn largely from outside the HSC membership.

For additional information about the evolution of the ASCO guidelines program, see Somerfield MR, Einhaus K, Hagerty K, et al. American Society of Clinical Oncology Clinical Practice Guidelines: Opportunities and Challenges. *Journal of Clinical Oncology*. Vol 26, 2008: pp. 4022-4026.

II. Guideline Development Steps

Step 1. Nominating a Guideline Topic

ASCO will entertain guideline topic proposals from any ASCO member. The Health Services Committee (HSC) is charged with the responsibility of reviewing and approving topics on behalf of the ASCO Board of Directors.

The guideline topic proposal process is guided by the Topic Selection Algorithm that can be found behind **Appendix 1-A**. ASCO members who submit topic proposals are required to submit a narrative proposal that is organized around the series of questions or “nodes” within the Topic Selection Algorithm. The nodes address the burden or importance of the condition or intervention, the degree of uncertainty or controversy about the relative effectiveness of existing clinical options, the perceived or documented variation in practice in the management of the condition or the use of the intervention, the availability of evidence to inform practice recommendations, and the existence of high-quality guidelines or technology assessments on the topic in question.

The HSC will review guideline topic proposals at HSC meetings, which occur three times a year in fall, winter and spring or summer. ASCO staff can provide specific HSC meeting dates upon request. In rare cases, the HSC may review proposals via teleconference or electronic mail.

A sample narrative guideline topic proposal can be found behind **Appendix 1-B**.

Of note, the last node of identifying existing guidelines is often addressed incompletely. ASCO staff can assist with this step by searching relevant databases, including Medline and the Agency for Healthcare Research and Quality’s National Guideline Clearinghouse. It is critical that the HSC be aware of existing guidelines on the same topic to avoid duplication of effort. Other groups’ guidelines, if judged to be methodologically sound by the HSC’s Methods Subcommittee, can be submitted for ASCO endorsement consideration (**Appendix 1-C**).

LESSONS LEARNED – Those who propose topics should limit the number of clinical questions to be addressed by the guideline to 2 or 3. Scope creep is endemic to guideline development and impedes the ability to create a focused work product in a timely fashion that is useful to clinicians.

Step 2. The Summary of Roles and Responsibilities, the ASCO Confidentiality Policy and the Guideline Conflict of Interest Disclosure Policy

A. Summary of Roles and Responsibilities of ASCO Staff and of Volunteers who Serve as Panel Co-Chairs or Panel Members

This document can be found behind **Appendix 2-A**. It is intended to clarify the expectations of participation in an ASCO guideline panel. It describes what resources and support panel members can expect from ASCO and what is expected of panel members.

B. ASCO's Confidentiality Policy and Prepublication Access Policy

The Policies can be found behind **Appendix 2-B**. The ASCO prepublication access policy strictly prohibits access to guideline documents to anyone outside of the panel membership, the ASCO staff, the HSC, and the Board of Directors.

C. The ASCO Conflict of Interest Disclosure Policy for Guideline Panel Members

The ASCO Conflict of Interest Disclosure Policy Can be found behind **Appendix 2-C**. Panel members are required to disclose, in writing and verbally, potential conflicts at the start of each guideline panel meeting

Step 3. Completing the Clinical Practice Guideline Development Protocol Worksheet

- A. A key step in the conduct of ASCO guidelines is completion of the Clinical Practice Guideline Development Protocol Worksheet (the “Worksheet”). The Worksheet specifies the purpose of the guideline, the target patient population and clinical outcomes of interest, key features of the systematic literature review, and a proposed timeline for guideline completion.

The Panel Co-Chairs are ultimately responsible for completing the Worksheet for their guideline. However, ASCO staff, following an initial conference call with the Panel Co-Chairs and possibly others selected by the Co-Chairs (the Panel Steering Committee), will typically complete a first draft of as many sections as possible before sending it to the Co-Chairs for revision.

A template for the Worksheet can be found behind **Appendix 3-A**. For some of the Worksheet items, a brief explanation has been provided to provide directions for completing the item. Although most of the Worksheet items are self-explanatory, two items merit special attention here.

1. **“Proposed Expert Panel Membership.”** ASCO guideline panels are, by design, multidisciplinary, and can include—as appropriate—content experts from medical, surgical, radiation, and pediatric oncology, as well as experts from other disciplines such as biostatistics, pharmacology, oncology nursing, and psychology. At least one representative from the patient community is also included on the panel. Panel membership will also include a liaison from the Health Services Committee.
 2. **“Specify Clinical Questions to be addressed by the Guideline.”** The clinical questions flow from the broad guideline topic that is nominated and help focus the evidence review. The questions should include three major components: the intervention, the population, and the outcomes of interest. As an example, the adjuvant chemotherapy for stage II colon cancer guideline asked, “Should all medically fit patients with curatively resected stage II colon cancer routinely receive adjuvant chemotherapy [to improve overall survival]?”
- B. Once the Co-Chairs have completed a first draft of the Worksheet, ASCO staff will submit the Worksheet on behalf of the Panel to the Health Services Committee’s Methodology Subcommittee for review and approval. Usually, Subcommittee reviewers make suggestions for revision that are intended to clarify aspects of the plan for developing the guideline. These suggestions are sent along to the Co-Chairs. Work on the systematic literature review can proceed upon approval of the Worksheet by the Methodology Subcommittee.

A sample Worksheet from the ASCO guideline on adjuvant chemotherapy for stage II colon cancer can be found behind **Appendix 3-B**.

Step 4. The Systematic Literature Review

- A. Upon approval of the Clinical Practice Guideline Development Protocol Worksheet, ASCO staff and the Expert Panel can begin work on the systematic review. The systematic review has become the sine qua non of ASCO clinical practice guidelines.
1. What is a systematic review? There are various definitions and descriptions. We like this one: “A systematic review is an integrative review of the literature on a specific clinical question or set of questions, characterized by explicit methods of data searching, selection, and review. Inclusion and exclusion criteria for the review are stated up front and the goal is to reduce bias in identifying, selecting, and summarizing the evidence.”
 2. Systematic reviews are often contrasted with narrative reviews, which are selective and often biased summaries of research evidence. The major difference between the systematic review and the narrative review relates to the transparency and formality of the processes used in each: Systematic reviews are guided by explicit statements about literature search strategies and study selection criteria; narrative reviews are not guided by explicit methods or are much less so.
- B. How does one conduct a systematic review? A systematic review checklist can be found behind **Appendix 4-A**. Below, we elaborate on particular features of the process.
1. The initial steps of defining the clinical questions, specifying inclusion and exclusion criteria for studies that will qualify, and suggesting relevant literature search terms or phrases, and the range of study dates are completed in the course of filling in the Worksheet.
 2. ASCO staff or subcontracting groups experienced in systematic reviews then launch into the literature searches of selected databases, including The Cochrane Library, Medline (via PubMed), and EMBASE. Initial searches are done to identify systematic reviews, practice guidelines, and technology assessments on the topic in question.
 3. More targeted searches on the condition or intervention are done in collaboration with the panel co-chairs using the search terms and inclusion and exclusion criteria specified in the Worksheet. (Based on recent HSC policy and procedures changes, the literature search should include search terms to address health disparities as relevant to the clinical questions considered by the particular guideline.) ASCO staff complete a first-level screening of the abstracts from these searches to eliminate obvious “false positives.”

*After this first-level screening, and depending mostly on the volume of abstracts yielded to review, the Systematic Review System, or SRS, may be employed to facilitate completion of the systematic review. SRS is a web-based system that is designed to accelerate the process of conducting systematic reviews. SRS is used to coordinate the review of abstracts by pairs of panel members; to direct the data extraction phase of the review; to create evidence tables that summarize the studies selected as eligible for the systematic review; and to download data for meta-analysis, if indicated. Behind **Appendix 4-B** you will find directions for the use of SRS. ASCO staff can guide you through this process from beginning to end.*

Step 5. To meta-analyze or not to meta-analyze...

The Use of Meta-Analysis: A Guide for Guideline Panel Chairs

In putting together a practice guideline for a specific intervention or set of interventions, an ASCO expert panel may be faced with either interpreting existing meta-analyses or initiating a meta-analysis of its own. It is important to emphasize that not all systematic reviews will justify or require a formal meta-analysis. It is also important to understand that a meta-analysis will only be as good as the systematic review upon which it is based. This briefing note is intended to assist ASCO guideline panels in dealing with the questions surrounding meta-analyses, including their appropriate use and interpretation.

Oncologists will most commonly come across published meta-analyses in relation to specific therapeutic interventions. In the usual case, the panel will want to know how effective a particular intervention is, compared with an alternative, to achieve the desired, specified outcomes of interest (e.g., survival).

A. Most meta-analyses are premised on a systematic review of a topic based on a comprehensive search of the literature and selection of appropriate studies using predefined criteria. When properly conducted, such reviews are considered more complete and less biased than traditional narrative reviews, whether or not a formal meta-analysis is performed. Results of studies identified in some but not all systematic reviews may be summarized and evaluated in a meta-analysis. *A meta-analysis is a formal statistical (i.e., quantitative) procedure for combining events (e.g., deaths in a survival analysis, or recurrence in an analysis of disease free survival) across comparable studies that address the same, or a similar clinical question.* A meta-analysis attempts to derive both:

1. the overall direction of effect across all studies, and
2. a more precise estimate of the intervention's average magnitude of effect, compared with its alternative(s).
 - The statistical approach seeks to base these estimates (direction and magnitude) on a total body of evidence, rather than focusing on one or several selected trials. Furthermore, the statistical methodology is designed to minimize bias in combining the results across studies. The key feature of a meta-analysis is that it weights trials according to size, such that larger trials contribute relatively more information to the final estimate.
 - The statistical method used to obtain the best estimate of effect makes assumptions about how the individual trials are distributed within the total theoretical population of trials. For example, if all of the trials can be considered to come from the same theoretical

population of studies, statistical analysis can use a *fixed-effects* model. In such a situation, the individual trial results when plotted (effect size versus trial size) will conform to a normal distribution (i.e., bell-shaped curve). However, it is possible that different trials, although they seem to be addressing the same or similar question, are actually drawn from different *theoretical* populations of studies. In such a case, tests for heterogeneity will tell you that the assumption of a single theoretical population for all studies is not valid, in which case the best statistical procedure to estimate overall average effect is a *random-effects* model.

- Note that the statistical test for ‘heterogeneity’ has relatively low power to detect this problem. For example, studies of a particular intervention in older patients may produce systematically different results for the same interventions in younger patients, the interventions may be administered in subtly different ways that affect the results, or the control groups may differ.

B. What are the implications of the above for either interpreting or initiating a meta-analysis?

Because the intention is to obtain an unbiased estimate of the comparative effects of two or more interventions in relation to one another for a complete body of evidence:

- The trials included in a meta-analysis should be chosen from among **the whole body of available evidence**,
- The validity of a meta-analysis is affected by the **internal validity** of the studies it includes; therefore, it is most reliably applied to estimates from randomized controlled trials;
- Although **statistical heterogeneity** is a clue that perhaps studies are not drawn from the same population of studies, it is important to determine the potential sources of heterogeneity. Use of the random effects model does not resolve the problem of statistical heterogeneity because trials may be so unlike that combining them doesn’t even make clinical sense;
- **The decision of whether or not to combine different studies in a meta-analysis is initially a clinical one, not a statistical one.** The panel should determine, before deciding on the statistical approach, whether or not it makes sense to include within the same analysis patients who are different (e.g., stage II and stage III colorectal cancer for adjuvant therapy); or treatments that are different (e.g., platinum-based versus non-platinum based treatments for estimating effects of erythropoietin);
- The **quality of individual studies** included in a meta-analysis may matter – for example, blinded, or placebo-controlled trials may produce systematically different results from open-label comparative studies.

Issues such as those in bullet 5 can be explored in either subgroup analyses (a separate meta-analysis on each of the subgroups) or sensitivity analyses (where certain suspicious trials, say of poor quality, are removed from the analysis to see if this changes the overall estimate for the remaining sample of trials). A relatively new technique called ‘meta-regression’ also can be used to investigate how different variables contribute to heterogeneity in meta-analyses. This technique can also be used to test whether certain variables contribute more (or less) to the intervention’s overall estimate of effect that may depend on baseline risk for the event of interest (e.g., contribution of nodal status to overall effect of systemic adjuvant therapy in breast cancer). Subgroup differences identified by any of these means should be considered hypothesis-generating, but may provide very useful information to better understand variation in study results as well as planning future studies.

C. There are fundamentally two different approaches to combining the events across different studies, depending on the data sources available.

- *Individual patient data meta-analysis (IPD)*-If original data on trial participants are available, these can be combined as if all patients were entered into the same trial, thus yielding an overall estimate that also generates a survival curve for the whole population (if recurrence or death is the event of interest).
- *Aggregate data (literature-based) meta-analysis*-If the only data available are group results from the published literature, then estimates of event rates at selected periods of follow-up need to be gleaned from the published papers and combined.

In general, IPD meta-analyses are preferred as less biased and more informative, but are much more time consuming, labor-intensive, and costly since reviewers must collect the data from various investigators. If the original data are unavailable, a literature-based meta-analysis is still far better than citing or choosing selected studies.

D. There are different software packages available to combine and express results of a meta-analysis, using various summary statistics, e.g.:

- Odds ratio (the odds of an event occurring in one group relative to the odds in another, with odds calculated as the group’s ratio of events to non-events);
- Relative risk (risk in one group relative to risk in another, with risk calculated as the group’s ratio of events to sample size);
- Absolute risk difference (risk in one group minus risk in another)
- Hazard ratio (if event rates are assumed to be constant over time, this is preferred because it summarizes the whole survival experience, rather than using point estimates at a fixed time).

These summary statistics will produce different values from the same data set, and panel members should understand how this happens.

E. Interpreting a published meta-analysis

If the panel has access to a meta-analysis to address a clinical question that is relevant to a guideline they are preparing, then members should watch for the following:

- Was the clinical question driving the meta-analysis clear?
- Was there due diligence in identifying as many relevant studies as possible – i.e., a systematic, comprehensive literature search?
- Were all included studies truly eligible, and were there studies excluded for reasons that are not credible; or were rules for study inclusion/exclusion not provided?
- Did it make clinical sense to pool the different studies (i.e., was there clinical heterogeneity)?
- Were potential sources of heterogeneity explored credibly?
- Was the appropriate statistical test used (fixed or random effects model)?
- Was the quality of all individual studies included in the meta-analysis reasonable? (An extreme example of unreasonable quality would be combining results from randomized trials and trials using historical controls).

There are validated tools available to assess the quality of individual trials (e.g., Jadad scale¹) and to assess the quality of a meta-analysis (e.g., the QUORUM statement²).

F. Considering initiating your own meta-analysis

- Is a meta-analysis really required? – if all studies are of high quality and show an important and similar directional effect, then the effort needed might not be worthwhile; or, will deriving a more precise estimate of the overall average effect make a difference to decision making or to recommendations?
- The following rules will help in doing a good quality meta-analysis:
 - Be very precise in formulating the clinical/research question;
 - Make the effort to prepare a formal protocol for the process. This should have been done anyway for the systematic review that precedes the meta-analysis. As noted above, all quantitative analyses should accompany a formal systematic review; but, not all systematic reviews require a meta-analysis;

- In a meta-analysis, each study should be treated in the same way that one would treat a patient potentially eligible for a randomized clinical trial (formal ‘research’ question, formal eligibility criteria, document reasons for exclusion, specify interventions to be compared and primary outcome of interest);
- Include key quality criteria as part of your eligibility criteria;
- Decide ahead of time the criteria for pooling or not pooling studies and specify this in the protocol;
- Explore potential sources of heterogeneity, if it exists;
- Include a statistician early in the process, and use technical help.

G. Avoid nihilism; be transparent

In the same way that there is no such thing as a perfect original study, so too there is no such thing as a perfect meta-analysis. We have a responsibility to do the best we can with the data we have available.

For example, it is now well established that the language of publication is associated with bias, with studies showing that trials published in English are more likely to report positive results than trials published in other languages. We also know that positive trials are more likely to get published than trials with a negative result, and that negative trials take longer to get published. We also know that industry sponsored trials are more likely to be positive.

All these reasons can be used to make the excuse that a systematic review and meta-analysis should not be done, especially if resources aren’t available to hand search all journals of all languages, etc.

The solution is not to avoid doing a systematic review or meta-analysis, but to reveal to the reader what short cuts were taken (e.g., we included only peer reviewed published studies, or restricted our eligibility to studies published in English). This shows transparency, and then the readers can decide how important this problem is in applying the results of your meta-analysis to their situation.

H. Other issues

Meta-analysis (i.e., pooling results across different studies that address like questions) can be used also in other situations. For example, one could combine results across diagnostic interventions to get average estimates of sensitivity, specificity and predictive values that define the performance of diagnostic, prognostic or predictive tests. An important consideration for pooling in these circumstances is consistent use across included studies of a reliable, valid “gold standard” to discriminate correct from incorrect test results as the basis for calculating sensitivity and specificity. Note that single-

arm studies can be used for this type of pooled analysis, provided all enrolled patients are evaluated with both the test of interest and the “gold standard.”

For therapeutic interventions, one can also pool results across case control or comparative cohort studies. However, because the individual studies are methodologically limited, the pooled results are not as reliable or convincing as those obtained with randomized trials.

This briefing note is intended to address mainly the commonest situation where panels will be faced with meta-analyses, in the context of treatment interventions.

I. Myths about meta-analyses

- A literature-based meta-analysis is not worth doing
- Using a random-effects model in the analysis will correct for biases associated with statistical heterogeneity
- A statistical test of non-significance for heterogeneity ($P > 0.05$) rules out important heterogeneity

References:

1. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJM, Gavaghan DJ, McQuay HJ: Assessing the quality of randomized clinical trials: is blinding necessary? *Control Clin Trials* 17: 1-12, 1996
2. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF et al.: Improving the quality of reports of meta-analyses of randomised controlled trials: the Quorum Statement. *The Lancet* 354: 1896-900, 1999

Step 6. Formulating Guideline Recommendations

The aim of this chapter is to help panel members move from the empirical evidence, as summarized in the systematic review of the literature (with or without meta-analysis), to the actual guideline recommendations for clinical practice, or adoption of a new technology.. The chapter summarizes some key features of the evidence-based consensus approach used by ASCO in developing recommendations; discusses the role of expert opinion in this process; summarizes the why and how of the narrative approach to characterizing the status of the evidence and to crafting recommendations, with concrete examples drawn from existing guidelines; and concludes with a discussion of the utility of evidence classification schemes for informing discussions about recommendations.

A. The Evidence-Based Consensus Approach to Guideline Development

ASCO uses an evidence-based consensus approach to developing guideline recommendations. This approach requires explicitness (i.e., clarity of presentation) in describing the methods used for making practice recommendations. The entire process of developing guidelines should be transparent to the guideline user. Transparency is intended to achieve clarity about how various underlying factors were considered by the expert panel in informing clinical recommendations.

1. At the core of the evidence-based consensus approach is the systematic review. The systematic review is conducted as specified by the guideline development protocol that you completed in your role as panel co-chairs. *The eventual guideline recommendations are informed by the results of the systematic review, blended with expert interpretation of evidence, and considered together with a range of other factors.*
2. The opinions of clinical or disease experts, those of clinical researchers, and those of methodological experts are combined in interpreting available evidence on the guideline questions. As noted in the American College of Cardiology/American Hospital Association guideline development manual, expert interpretation will always be necessary, and serves “as a funnel through which evidence on multiple questions is combined, condensed, and formulated into recommendations.”

B. The Narrative Approach to Describing the Status of the Evidence

The ASCO Subcommittee on Methodology recommends a narrative approach to describing the status of the evidence support for recommendations. This approach can be contrasted with approaches that rely heavily on “levels of evidence” rating systems. These latter approaches attempt to rate the quality of evidence using an ordinal scale with Level I evidence, for instance, being

stronger than Level II, and so on. To many, using levels of evidence was equivalent to an evidence-based approach, when in reality it was simply a shorthand way of ordering different studies as to their threats to validity. However, even within study types, there are degrees of rigor and it is virtually impossible to account for these differences using a simplistic classification scheme. As a result, the systems have frequently been modified, almost always resulting in a more complicated scheme, which eroded the apparent simplicity of the original scheme.

Over 100 systems for evaluating the quality of evidence or the strength of recommendations based on the evidence have been reported. These systems vary considerably with no one validated system universally employed. Historically, ASCO Panels adopted classification schemes from other sources and employed them to assess the level of evidence and strengths of the guideline recommendations. More recently, ASCO Panels have chosen not to use these classification schemes to assign levels and grades to recommendations. Evidence rating schemes may, nevertheless, have utility as a framework for informing internal discussions about the state of the evidence. We will return to this point in the last section of the chapter.

In place of evidence rating schemes for describing the status of the evidence, the ASCO Methods Subcommittee encourages panels to describe, in conventional language, the type and quality of the research that bears on the recommendation. In the old ASCO approach of levels and grades, where panels might characterize a recommendation as “Level II/Grade B,” the narrative approach might specify that the recommendation was based on *“Three small and one larger (N=375) placebo controlled randomized trials, and non-blinded trials with generally consistent results favoring the intervention.”* A Level II/Grade C recommendation might specify that the recommendation was based on *“Seven small (N < 100), randomized and non-randomized, mostly non-blinded studies consistently favoring the intervention but with inconsistent statistical significance for reported outcomes across the studies.”* And so on.

C. The Narrative Approach to Formulating and Writing Guideline Recommendations

The narrative approach to formulating and writing recommendations requires that panels explain how the evidence was considered and applied in deriving the recommendations. This approach promotes the more explicit use of language to clarify the logic of recommendations. The recommendations should be based on thoughtful analysis of all of the factors considered, and should reflect panel discussions around the nature of the evidence and the link between the evidence and the statements contained in the recommendations.

In terms of the guideline manuscript, the recommendation is included in a section entitled Evidence Summary and Recommendations. (See Step 7 of this Manual.) This section should provide a synopsis and interpretation of the evidence and other factors considered by the panel, followed by a concise recommendation that should flow logically from the Evidence Summary.

D. Some Examples of the Narrative Approach in Action

So, how does all of this work in practice? We have excerpted language from existing ASCO guidelines to try to illustrate how the narrative approach plays out. We present two Evidence Summary and Recommendations sections. We then offer some comments on the examples by way of underscoring some key points to consider.

1. Example 1: from the ASCO technology assessment on chemotherapy sensitivity and resistance assays.

Evidence Summary and Recommendations: The Working Group's review of the literature found that little had changed since the review published by Cortazar and Johnson in 1999. The concept underlying CSRAs remains a compelling one. Unfortunately, there does not appear to be a single assay that is ready for routine integration into the clinical setting. The absence of a suitable CSRA for routine clinical use reflects problems in the technical success and yield of the assays, the lack of adequate prospective evaluation of CSRAs in clinical trials, and the tendency of CSRAs to "recommend" treatments that would be given empirically.

The single study of a resistance assay that met the Working Group's inclusion criteria deserves special mention. The Loizzi et al study was designed to compare response rates to chemotherapy for recurrent ovarian cancer among patients receiving either assay-guided therapy or empiric treatment. This was a prospective, but not randomized, clinical trial including 100 consecutive patients (50 treated by assay-guided regimen; 50 empirically). A subset analysis looking at secondary endpoints among the platinum-sensitive group revealed a survival difference; no survival difference was seen in the platinum-resistant group. Because standard treatment for recurrent ovarian cancer includes platinum therapy, and owing to the lack of a randomized design and the small number of patients, this study has not made an impact on current treatment recommendations. In addition, the chemotherapy regimens selected under assay-guidance are nearly identical to those selected by empiric treatment. This makes it hard to understand the dramatic difference in survival. It is a provocative finding, which may justify large, randomized, prospective clinical trials with similar treatment elements.

Thus, based on the evidence from studies that compared outcomes for patients treated with empiric chemotherapy to those treated using assay-guided chemotherapy, the use of chemotherapy sensitivity and resistance assays to select chemotherapeutic agents for individual patients is not recommended outside of the clinical trial setting. Oncologists should make chemotherapy treatment recommendations on the basis of published reports of clinical trials and a patient's health status and treatment preferences. Selection of chemotherapeutic agents on the basis of results of chemotherapy sensitivity and resistance assays is not warranted based on the current body of evidence.

2. Example 2: from the ASCO-CCO guideline on adjuvant chemotherapy for stage II colon cancer.

Summary and Recommendations: The recommendations that follow are based on the Panel's review of the evidence on prognostic and predictive factors in colon cancer, and Panel consensus. The evidence base considered includes the final reports of early Stage II and III adjuvant chemotherapy trials that include risk factor data, large-scale National Cancer Data Base (NCDB) analyses of nodal status and prognosis, a secondary analysis of data from a large Intergroup randomized trial to determine the association between number of nodes recovered and overall survival, a recent pooled analysis of prognostic and predictive factors in colon cancer, a College of American Pathologists consensus statement on prognostic factors in colorectal cancer, and selected studies on emerging molecular markers.

Patients for whom the number of sampled lymph nodes was very small can be considered inadequately staged and at greater risk of having microscopic residual disease. As a result, patients with inadequately sampled nodes, could be offered adjuvant chemotherapy. In general, the greater the number of lymph nodes examined, the easier it is to have confidence that the patient truly lacks micro-metastatic disease. The NCDB analyses suggest that when 13 or more lymph nodes are analyzed, the probability that the patient has residual disease is lower than when fewer nodes are analyzed. Although there is no absolute number of lymph nodes analyzed that should be considered adequate or inadequate, clinicians should weigh adjuvant treatment recommendations and decision-making in the context of the number of nodes analyzed.

Other patients with any of a number of poor prognostic features such as T4 lesion (defined as adherence to or invasion of local organs), perforation, or poorly differentiated histology, might also be considered as candidates for adjuvant chemotherapy. It should be emphasized that, although these tumor characteristics may be prognostic markers, there are no data to suggest that they serve as predictive markers (i.e., tumor

characteristics that predict response to adjuvant chemotherapy). Finally, it should be noted that the magnitude of risk conferred by these characteristics, relative to nodal status, cannot be reliably estimated from available data.

The question of whether or not to offer adjuvant chemotherapy to Stage II patients at high risk or with inadequately sampled nodes should be considered in light of the available evidence. *Direct* evidence from randomized controlled trials, and from meta-analyses of such trials, does not yet demonstrate a survival benefit for adjuvant chemotherapy in high-risk Stage II disease, and, as previously reviewed, there are toxic effects of treatment; it is thus reasonable to recommend against the use of such therapy to a well-informed patient. However, because of the limited numbers of patients with high-risk disease evaluated in trials, the potential benefits of adjuvant therapy have not been adequately tested.

On the other hand, given this uncertainty, it is reasonable in the setting of high-risk disease for oncologists and patients to invoke *indirect* evidence of benefit by generalizing from the positive results of adjuvant chemotherapy in patients with Stage III disease. Those who would generalize are prepared to take the risk that the toxicity of treatment is worth the potential--but as yet unproven--benefits of therapy, based on the beneficial results obtained in the Stage III population and the assumption of biological equivalence of Stage II and Stage III colon cancers.

In summary, *direct* evidence from randomized controlled trials does not support the use of adjuvant chemotherapy, even for patients with high-risk Stage II colon cancer. Patients and oncologists might reasonably be reluctant to choose adjuvant therapy because of this lack of direct evidence of benefit. However, patients and oncologists who are prepared to take the risk of accepting the results from Stage III disease as adequate *indirect* evidence of benefit are justified in considering the use of adjuvant chemotherapy in Stage II disease, provided that they understand that the magnitude of benefit as measured in absolute improvement in survival, is small. Patients who have had a complete resection can be reassured that adjuvant treatment for typical stage II disease does not improve 5-year survival by more than an absolute 5%. Whether smaller incremental improvements in survival can be derived from treatment remains open to question.

In either case, the clinical decision should be based on a discussion with the patient about the nature of the direct evidence supporting treatment, the assumptions inherent in accepting indirect evidence of benefit, the anticipated morbidity of treatment, the presence of high-risk prognostic features, and patient preferences. A subsequent section on “talking points” advises oncologists about how to approach such a discussion. The

optimal approach remains to encourage patients with Stage II disease who are facing this decision to participate in randomized trials.

Comments on the Examples: These two examples illustrate the complexity of formulating guideline recommendations. The stage II colon cancer recommendation, in particular, highlights the need to simultaneously consider a host of factors—biological and clinical plausibility, absent or weak data on predictive factors in colon cancer therapy, direct evidence versus extrapolation from indirect evidence, and physician and patient preferences and comfort with ambiguity--through a seldom-straightforward and sometimes-painful process of mental calculus. The evidence evaluated by guideline panels is infrequently abundant and/or consistent, and panels need to acknowledge and summarize the status of the evidence and relate in detail the deliberative process, including the compromises, through which it nonetheless arrived at its recommendation (or lack thereof in some cases). The Evidence Summary and Recommendations section should tell a story that takes the readers from the evidence to the recommendation.

E. Using Classification Schemes for Guiding Discussions About the State of the Evidence

As mentioned above, despite the complexity and limitations of existing evidence rating classification systems, they might serve as useful frameworks for guiding discussions about the state of evidence and how it ought to be handled in making recommendations. These frameworks typically include a hierarchy of study designs reflecting the strength of the evidence yielded, as follows.

For intervention studies, in general their strength is ordered as follows:

- Well-powered single, multicenter randomized controlled trials;
- Rigorous systematic review that includes well powered randomized trials (individual patient data-based)
- Rigorous systematic reviews of mainly under-powered individual RCTs
- Prospective cohort studies with parallel, concurrent controls
- Cohort studies with non-concurrent controls
- Uncontrolled studies

Within this scheme there are various factors that can influence further the confidence that the panel has in the study results. These include:

- For RCTs- whether allocation to treatment was blinded, whether placebo-controlled or outcome assessments were blinded, whether follow-up time was adequate to provide clinically meaningful inferences;

- For systematic reviews- the extent to which publication bias was accounted for (e.g., comprehensiveness of literature search strategy, use of unpublished trials, search for studies in various languages), rating of study quality and sensitivity analysis based on study quality, use of appropriate statistical approach.

The above is only a framework for considering how to incorporate evidence into recommendations. Some panels may choose to address other issues.

F. Special Topics

1. Cost Considerations in ASCO Guideline Development

The inclusion of a section in the guideline where costs and/or commentary about published cost-effectiveness analyses relative to the clinical question should be considered optional.

When guidelines address a narrow clinical question, for instance, one where one or a few drugs are the focus (e.g anti-emetics), then it is highly encouraged that a table be prepared listing drug costs of the available therapies at the time a draft is finalized.

Upcoming guidelines on various new ‘biologic’ therapies or predictive assays for patient-specific target therapies should include a table similar to the example below.

Example

Anti-emetic	Manufacturer	Usual dose, delivery and Schedule	“Cost”, Internet Data Source
Zofran	Glaxo Smith Kline	24 mg, p.o. 1 hour before chemotherapy	4 mg (10 each), \$223, drugstore.com
Zofran	Same	8 mg, p.o. 3X per day on day of radiation therapy	8 mg (10 each), \$365, drugstore.com

Other examples of where a cost table should be considered are for comparisons of alternative diagnostic procedures where there are commonly available billing codes used for reimbursement.

For complex multi-faceted procedures (i.e., sentinel lymph node biopsy, laparoscopic colectomy) there are many dimensions that must be evaluated and a cost section should be considered carefully before inclusion in a guideline.

Cost-effectiveness Analysis:

The broad subject area of what represents ‘value’ among new cancer interventions reflects an individual or group making an implicit cost-effectiveness judgment or analysis.

While cost-effectiveness issues are a major cancer policy question, the methodology-working group recognizes that this issue can distract from the prior focus of the guideline process, which is the scientific evidence. However, economic analyses (cost-effectiveness, cost-utility, cost-benefit) are important elements of technology assessments.

If there are published cost-effectiveness analyses addressing the subject, then a review with or without a commentary on the strength of the analyses should be included as a distinct commentary section of the guideline. No endorsement or rejection of the relative value of this work should be made.

Expanding the role of cost-effectiveness analysis in the guideline process will require a clear mandate from the ASCO Board.

2. Health Disparities

The HSC recently approved a proposal to address health disparities in all ASCO guidelines. Disparities will be addressed in the systematic review and specific studies should be referenced in the guidelines. Additionally, the following text and references will be inserted into the manuscript:

Since ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Cancer patients from racial/ethnic minority groups suffer disproportionately from co-morbidities, they experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.¹⁻⁴ Many other patients lack access to care because of their geography and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

1. Mead H, Cartwright-Smith L, Jones K, et al. Racial and ethnic disparities in U.S. health care: a chartbook. The Commonwealth Fund. March 2008.
2. U.S. Cancer Statistics Working Group. [United States Cancer Statistics: 1999–2002 Incidence and Mortality Web-based Report](#). Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; 2005.
3. Ries LAG, Eisner MP, Kossary CL, Hankey BF, Miller BA, Edwards BK, editors. SEER cancer statistics review, 1973-1997. Bethesda, MD: National Cancer Institute; 2000. http://seer.cancer.gov/csr/1975_2003/results_merged/topic_race_ethnicity.pdf
4. American Cancer Society. Cancer facts and figures for African Americans 2005-2006. Atlanta, GA: American Cancer Society; 2005.

3. Patient Communication

ASCO has incorporated a patient communication section into each guideline. This section presents possible options on how oncologists can communicate with their patients. In many cases, the patient representative assists in drafting this section. (see 5-alpha reductase inhibitors guideline [www.asco.org/guidelines/5ARI]) .

Step 7. Drafting the Guideline Manuscript: The ASCO Guideline Template

ASCO guideline manuscripts should conform to a standardized format. The sections are listed below with annotation, as needed. ASCO staff will provide Co-Chairs with a template for the ASCO guideline format. The templates for original guidelines and updates differ slightly.

INTRODUCTION

Introduction: This section outlines in 1-2 manuscript pages the rationale for the guideline in terms of the questions addressed in the original topic proposal, (i.e., burden of the condition or importance of the health care intervention, controversy or uncertainty concerning appropriate management or use, perceived or documented variation in practice, and need for guidelines to facilitate decision-making in clinical practice).

Clinical Questions: Lists the clinical questions addressed by the guideline. ASCO staff can draft this section based on the Worksheet.

Practice Guidelines: This section is largely boilerplate material that defines practice guidelines and outlines attributes of good guidelines. The section concludes with legal boilerplate material that underscores the voluntary nature of adherence to the guideline and the critical role of individual physician judgment. The language of this section was crafted years ago by legal counsel and should not be edited. ASCO staff will draft this section.

METHODS

Panel Composition: Reviews the members of the panel and the process used for selecting panel members: “A steering committee under the auspices of the Health Services Committee chose Panel participants...” ASCO staff can draft this section.

Literature Review and Analysis: Describes the methodology of the systematic review from beginning to end and includes databases searched, search terms used, the inclusion and exclusion criteria employed, the abstract review processes, the data extraction methods, and so on. ASCO staff will typically draft this section for review by the Panel Co-Chairs.

Consensus Development Based on Evidence: Describes the process used by the Panel to develop recommendations. ASCO staff can draft this section.

Guidelines and Conflict of Interest: A largely boilerplate section that ASCO staff will draft.

Revision Dates: Boilerplate section that ASCO staff will draft.

Definition of Terms: This section includes definition of key terms used in the guideline. For example, “Stage II colon cancer was defined according to the TNM system classification of the....”

Summary of Outcomes Assessed: Describes the outcomes considered in the guideline and can be drawn from the Worksheet.

RESULTS

Literature Search Results: This is a narrative summary of the results of the literature search in terms of number of eligible studies and systematic reviews and meta-analyses identified. This section should note if the panel performed meta-analysis and, if not, the reasons why not (e.g., studies judged to be too heterogeneous for meaningful quantitative synthesis). Results of the meta-analysis can be briefly summarized here. This section also gives reasons for exclusion of studies.

Clinical Question 1 (list first clinical question here)

Evidence Summary and Recommendations: This section should provide a synopsis of the supporting evidence. Subsequent topically organized subsections can be used to review specific study results in detail. Pertinent data in support of the recommendation should be presented in tabular form wherever possible. The succinct recommendations should immediately follow the Evidence Summary. After reading these two sections, the guideline user should be able to delineate the bases for the practice recommendations.

Status of the Evidence: As discussed in Step 6, panels for this section should describe, in conventional language, the type and quality of the research that bears on the recommendation. An example is: “*The recommendation is based on three small and one larger (N=375) placebo controlled randomized trials, and non-blinded trials with generally consistent results favoring the intervention.*”

Clinical Question 2 (list second clinical question here)

Evidence Summary and Recommendations: See above for guidance.

Status of the Evidence: See above for guidance.

Limitations of the Literature: This section should describe methodological limitations of the data reviewed for the guideline.

Ongoing and Future Studies: This section should review studies in progress, of which panel members are aware, that may help answer the clinical question more definitively and discuss what additional research is needed. This section could reasonably be combined with the Limitations of the Literature section.

Interpretive Summary: This section provides the panel's broad perspectives on the issues raised in the course of reviewing the data on the clinical questions. It could also include minority opinions among panel members and how consensus was achieved.

Acknowledgment: Self-explanatory.

References: Self-explanatory.

Step 8. The ASCO Guideline Review and Approval Process

Process for JCO/HSC Review of Draft ASCO Guideline Documents

Step 1: Expert Guideline Panel reviews and approves first complete draft of the guideline.

Step 2: ASCO staff makes request of JCO Editor-in-Chief (or his designated Associate Editor) and HSC Chair (or his or her designated HSC member/liaison) for peer review of the draft Guideline. [Note. External review of ASCO guidelines will be completed using the JCO peer review data base by 1-2 reviewers selected by the JCO Associate Editor and the HSC Chair or his/her designee. The reviewer pool should include content experts, patient advocates, community oncologists, and others as appropriate to the topic (e.g., radiologists, surgeons). Reviewers should disclose any financial interests in companies affected by the Guideline, in accordance with the ASCO Conflict of Interest Policy. It will concurrently be sent for external review (outside the JCO system) to appropriate parties, ie patient advocates.]

Step 3. Draft Guideline is sent to the external reviewers with instructions to use the ASCO guideline external reviewer form. [Note. Reviewers are given two weeks to complete the review. Strategies for dealing with delinquent reviewers need to be resolved. Reviews will not be accepted after three weeks.]

Step 4. JCO Associate Editor and HSC Chair/designee send the reviewers' comments and suggested revisions and a letter to the Panel Co-Chairs that provides a deadline for submission of a revised manuscript.

Step 5. Panel Co-Chairs address external reviewers' suggested revisions and resubmit the guideline manuscript to the JCO Associate Editor and the HSC Chair/ designee. [This process should parallel that used for any response to reviewers in that the Panel can make the case for not making selected suggested changes.]

Step 6. JCO Associate Editor and HSC Chair/designee review revised Guideline manuscript and make joint editorial decision to approve for submission to the HSC for review and approval, or to request additional revisions. [Note. A procedure for handling differences between the JCO Associate Editor and the HSC Chair/designee on the editorial decision is needed. For example, if the HSC Chair/designee approves but the JCO Associate Editor disapproves, one proposal is to allow the Guideline to go forward to the HSC for review and approval, but with a letter from JCO Associate Editor that summarizes his/her reason for disapproval. This letter would be included with the Guideline manuscript when it is submitted to the Board, assuming HSC approval.]

Step 7. Expert Guideline Panel submits Guideline for HSC review and adoption. [Note. HSC Chair provides the full HSC membership with the joint JCO/HSC Chair/designee decision letter and Panel's response to the external reviews; or with the HSC Chair/designee letter and a separate letter of dissent from the JCO Associate Editor.]

Step 8. ASCO HSC Reviews/Approves Guideline. [This process should follow the present process wherein two HSC reviewers are assigned to review the guideline on behalf of the HSC; one of these should be the HSC Chair/designee. The Panel would be required to resubmit the Guideline to the two HSC reviewers for final HSC sign-off if substantive revisions are requested by the HSC.]

Step 9. HSC Submits Guideline for ASCO Board of Directors Review and Adoption. [Note. The Guideline and the joint JCO Associate Editor-HSC Chair/designee letter to the Panel Co-Chairs is submitted with the Guideline manuscript to the Board of Directors. If applicable, the JCO Associate Editor's letter of dissent is sent to the Board with the Guideline manuscript. If the Board adopts the Guideline, the Board may direct that the Guideline be submitted to the JCO. If the Guideline is not accepted for publication by the JCO, the decision will be communicated to the Chair of the Health Services Committee.]

Step 9. Guideline Dissemination and Implementation: The Guideline Clinical Tools and Resources

As outlined in the materials in **Appendix 2-B** (Part I, Role of ASCO Guideline Panel Co-Chairs and Expert Panel Members), Panel Co-Chairs will be asked to assist in the review of a number of potential guideline derivative products. The Co-Chairs are not expected to draft these documents necessarily, but are expected to critically review them to ensure that the content is accurate and clear. The purpose of these derivative products is to more widely disseminate, in a practical and user-friendly form, the recommendations contained in the guidelines.

The HSC has identified a series of templates to be included in the tool box. These companion documents/tools will be developed as the first full draft of the guideline document is assembled and circulated for review at the same time as the draft, aiming for joint approval and release. Specific proposed products are listed below. Items a-c should be done for each guideline; items d. and e. are discretionary but should be formally considered.

- a. Summary for Health Professionals – A table or executive summary no longer than two pages containing headings similar to those used in publications like *Annals of Internal Medicine* (e.g., context, content, and recommendations). The primary target audience for this summary is the busy clinician looking for a synopsis of the guideline recommendations, for example, in the setting of an active clinic. Although patients may also access this summary, it is written at the health professional level.
- b. Patient Material – A one page summary containing sections like: What is the problem and what is known, Why did ASCO decided to release this guideline/tech assessment, What evidence was reviewed, How was the study done, What did the panel find, What are the limitations of this review, What are the implications, etc ...
NOTE: Both summaries to be available for printing in PDF format in the ASCO guidelines website (both) and plwc.org (patient summary).
- c. Power Point Slide Set – Slides containing sections like Problem, Question, Background, Methodology, Evidence, Recommendations, and Implications. Lecturers currently create their own slides, which is time consuming and may ultimately not reflect the intended message from ASCO about the topic in question. These slides are designed to be used during Tumor Boards, Grand Rounds, and similar lectures.
- d. If appropriate (e.g., colony stimulating factors, bisphosphonates) create a Flow Sheet for Patient Care that could be used by clinical practices in their daily activities and affixed to patients' charts. The intent is to create a practical product that will facilitate guideline adherence in day-to-day situations for the practicing clinician. Early interaction with QOPI members necessary (see below).

- e. Consider the creation of a Flow Chart or Algorithm, perhaps similar to the NCCN model – Busy clinicians seeing patients frequently go to the NCCN web site on the fly to review the flow diagrams, but will rarely download a 13-page JCO document for a quick “what do you do now” consultation. The intent is to provide the clinician with a quickly accessible and understandable tool which facilitates rapid comprehension of the core guideline recommendations. Available either for download as PDF (if simple) or online use (if more complex) with hot links to relevant websites and PubMed references. This could serve as the basis for the PDA tool below.

III. Recent Procedural Changes or Additions

A. Update Processes

1. Guideline Updates Schedule

- Schedule for Updating Literature Searches and Reviews
 - Some ideas: (a) panel steering committee receives letter annually from ASCO HQ asking about the need for update that year, (b) every two or three years panels must do formal updated literature searches, (c) need provision for ad hoc updates as key evidence is published.
- Review and approval options
 - Scenario 1: No new evidence. Publish an “e-update” with notice in JCO and JOP. Insert box at top of guideline that summarizes literature search including dates and number of abstracts reviewed, and indicates no new evidence identified and thus no changes to recommendations. Approval by co-chairs and HSC leadership group. To Executive Committee of ASCO Board of Directors for final approval.
 - Scenario 2: New evidence/no change to recommendations. Same “e-update” approach with summary of search and review, plus include a list of relevant references identified. Approval by co-chairs and panel and HSC leadership group. To Executive Committee of ASCO Board of Directors for final approval.
 - Scenario 3: New evidence/recommendations change. Current review and approval process for substantive updates and publication in print and online versions of JCO with summaries and derivative products in the JOP.
 - Scenario 4: Ad hoc, rapid update. New evidence/change to recommendations. Publish an “e-update” with notice in JCO and JOP with summary of key new evidence. Would allow for more rapid change to a guideline without a formal, comprehensive literature search and review. Change would be made to selected recommendations based on relevant published high-impact evidence or regulatory decisions. Example: ASCO’s 2003 NSCLC guideline update includes a recommendation for gefitinib. FDA label change in June 2005 limits gefitinib indication. Guideline has not been updated to reflect this.

2. Guide to “Signals” Updating¹ of Clinical Practice Guidelines for Panel Co-Chairs

Overview

To ensure that ASCO guidelines remain as current as possible, ASCO requires an annual assessment of the literature for each of the ASCO guidelines to determine the need for an update of each guideline. The purpose of the annual assessment is to identify new, practice-changing data that might warrant an update of the guideline. This document outlines formal criteria for identifying these new, practice-changing data.

Preliminary Steps in the Signals Approach

To begin this process, ASCO staff will provide panel co-chairs with an updated literature search on the guideline questions. ASCO staff will complete an initial screening of the search yield in accordance with the inclusion and exclusion criteria of the systematic review conducted for the original version of the guideline, or for the latest substantive update thereof. Based on this screen, ASCO staff will provide co-chairs with a set of the relevant abstracts or, if available, the full text articles for review. The co-chair review is guided by a short series of questions that reflect the criteria, or “signals,” for identifying new and potentially practice-changing evidence.

The signals for a substantive guideline represent two major categories of changes in the available evidence: (a) a potentially invalidating change in evidence, and (b) a major change in evidence. “Evidence” and “findings” as used here refers to the following:

1. At least one new high-quality RCT with a population at least twice/three times the size of the largest RCT currently cited in the recommendation
2. At least one new meta-analysis with one new trial not considered in the existing recommendations

[Note. The above section may need to be adjusted depending on the original evidence considered for the guideline. For example, some guidelines (RFA, Fertility) were based on cohort studies, case-control studies, etc., as no RCTs were available at the time of the original systematic review. So, evidence that fits parameters for signals for those guidelines might include: the first RCT; a cohort study double the largest

¹ Adapted from Shojania et al, Ann Intern Med 2007;147:224-233.

in the existing guideline; a large new series from a group cited in the existing guideline, etc.]

Specific Instructions to Co-Chairs with Guideline-Relevant Illustrative Examples

For each of the articles you have received, consider whether any of the following apply (a, b, or c from either #1 or #2). If any of the following do apply, it is very likely that a full guideline update would be warranted.²

1. Potentially invalidating change in evidence: Clinicians should no longer follow at least one of the current recommendations, because there exists:
 - a. Opposing Findings: New evidence suggests conclusions opposite to those underlying current recommendation(s). *EXAMPLE*: Gefitinib was recommended for third-line treatment in advanced lung cancer based on surrogate endpoints. Subsequent studies and longer follow up clarified a lack of efficacy on overall survival (except in a small subset of patients) and real potential harm.
 - b. Substantial Harm: New evidence suggests that the intervention would no longer be recommended due to substantial harm. *EXAMPLE*: Recommended six cycles of platinum-based chemotherapy found to produce unacceptable levels of toxicity compared with two cycles.
 - c. Superior New Treatment: New evidence suggests that another intervention is significantly superior, based on efficacy or harm, such that it would be preferred in most settings. *EXAMPLE*: New biological therapy with superior efficacy and side effect profile is approved by the FDA.

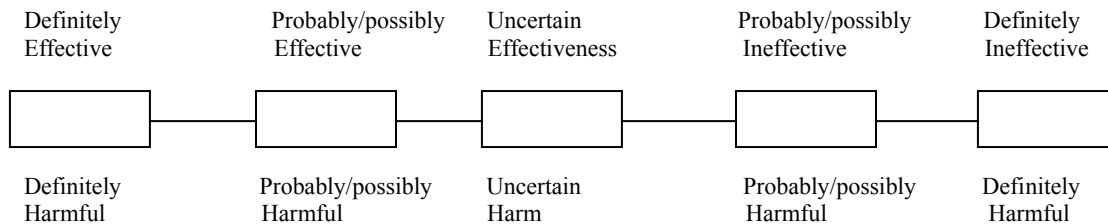
2. Major change in evidence: Recommendation is still essentially valid, but new evidence clearly has the potential to affect clinical decision making:

² *Important Note*: This document is intended as a tool to help guide the decision-making process surrounding the need to undertake a full update of the guideline. While it is hoped that this document will cover most changes to clinical evidence necessitating an update, there may exist other situations, not described in this document, that in the opinion of the co-chairs warrant an update. For example, there may exist a scenario where a specific type of imaging study has come into common use since the publication of the guideline. The imaging study was not addressed in the original guideline, and there currently exists very little to no data addressing use of the imaging study directly. In this situation, the co-chairs may feel that a more substantive update to the guideline is necessary, in order to inform readers that the imaging study has not been proven in well-designed studies.

- a. Important Changes in Effectiveness, but not Opposing Findings: New evidence suggests that the benefit is greater or less than reflected in the current recommendations (e.g., the recommendation could be changed from “consider use” to “routinely use”). *EXAMPLE:* Benefit of second-line chemotherapy demonstrated in large RCT to be greater than benefit observed in prior trials.
- b. Expansion of Treatment: New evidence suggests efficacy in new populations. *EXAMPLE:* Clear benefit from recent adequately powered (statistically reliable), planned subset analysis of combination chemotherapy in performance status 2 stage IIIb NSCLC patients.
- c. Important Caveat: New evidence suggests an important caveat about the patient population who may benefit, way in which treatment has to be delivered, sustainability of benefit, or increases in harm not sufficient to undermine use altogether but that would affect the decision to recommend the intervention for at least some patient populations. *EXAMPLE:* A recent RCT shows that the elderly with co-morbidities are several times more likely than other patients to experience life-threatening cytopenias with a new chemotherapy regimen.

“Potentially Invalidating” vs. “Major Change” in Evidence

Due to the qualitative nature of many of the judgments being made, it may be difficult to tell if a change in evidence constitutes a “major change” or is “potentially invalidating.” It may be helpful to consider the graphic, below. Conceptually, a potentially invalidating change (opposing conclusions) involves movement of at least two positions on the scale below. A major change in evidence (important changes in effectiveness short of opposing findings) involves movement of one position on the scale.



3. Response to Requests for Revising Guidelines or Adding New Material

Any individual or organization may submit comments or new suitable evidence to the ASCO Health Services Committee (HSC) at any time regarding existing guidelines. These data will be considered in the standard guideline review process at the time of the next scheduled update, as per HSC policy. If these data include new randomized clinical trial (RCT) data published in peer-review literature, these data will be reviewed by co-chairs or steering group of the applicable ASCO panel or the HSC to determine if the data meet the established criteria for an ad hoc update. Any conflicts of interest of individuals soliciting the HSC, should be disclosed, as per ASCO policy.

4. Provisional Clinical Opinions (PCO)

Policy and Procedures:

Background and Overview

The leadership of the ASCO Health Services Committee (HSC) is proposing a rigorous, evidence-based approach--the provisional clinical opinion, or PCO—to offer a rapid response to emerging data in clinical oncology. The PCO is intended to offer timely clinical direction to the ASCO membership following the publication or presentation of potentially practice-changing data from major studies (e.g., k-ras and cetuximab data from 2008 ASCO Annual Meeting). The PCO may serve in some cases as interim direction to the membership pending the development or updating of an ASCO clinical practice guideline. Heretofore, there has not been a mechanism within ASCO for providing a rapid response to key data from clinical cancer research. The PCO offers such a mechanism.

Procedures

Provisional Clinical Opinion Topic Selection

The HSC leadership (Chair, Immediate Past-Chair, Chair-Elect, HSC Board liaison) will generally be responsible for accepting, reviewing and approving proposed PCO topics on behalf of the ASCO Board of Directors. The topic selection process will be guided by the Topic Selection Algorithm that is used by the HSC to guide selection of topics for ASCO clinical practice guidelines. The algorithm is organized around a series of questions or “nodes.” The nodes address the burden or importance of the condition or intervention, the degree of uncertainty or

controversy about the relative effectiveness of existing clinical options, the perceived or documented variation in practice management of the condition or the use of the intervention, the availability of evidence to inform practice recommendations, and the existence of high-quality guidelines.

Evidentiary Basis for the PCO

Provisional clinical opinions would be informed by substantive and expeditious methodological assessments of the data in question. To this end, ASCO has established a relationship with the National Cancer Institute's Physician Data Query (PDQ) Editorial Boards. The PDQ's Editorial Boards are comprised of content experts in oncology and related specialties. Upon request from ASCO, the relevant PDQ Editorial Board will provide a written assessment of the new data.

Ad Hoc PCO Panel

The PDQ assessment will be forwarded to an ad hoc panel that has been selected and charged by the HSC to draft the PCO. The panel will include 4-6 content experts in the topic area. If the new data relate to an existing ASCO guideline topic, the HSC leadership will work with the guideline panel Chairs and Co-Chairs to appoint the ad hoc panel. The ad hoc panel will be drawn from members of the guideline panel with a provision for additional content experts as needed. Otherwise, members of the ad hoc PCO panel will be recruited in consultation with acknowledged content experts in the topic area.

The membership of the ad hoc panel will be chosen in accordance with the panel composition requirements of ASCO's Conflict of Interest Management Procedures for Clinical Practice Guidelines ("COI Procedures"). The COI Procedures call for the majority of panel members to have no relationships with companies potentially affected by the PCO, and generally require panel Chairs and Co-Chairs to be free from relationships with affected companies as well.

PCO Manuscript Format

The ad hoc panel will produce a PCO based on the PDQ assessment and on their own review and consideration of the PDQ report. The PCO document will include a general introduction that will: define the concept of a provisional clinical opinion, and provide an overview of the issue at hand; include a brief methodological section and a legal disclaimer section akin to the standard section in ASCO practice guidelines; provide a summary of the PDQ assessment and the ad hoc

panel's deliberations; and, finally, it will summarize the provisional clinical opinion.

Review and Approval of the PCO

The PCO will need to be approved by a unanimous vote of (1) the ad hoc panel members; (2) the HSC leadership (Past-Chair, Chair, Chair-Elect, and Board Liaison) and selected content experts drawn from the HSC membership; and (3) a subset of the ASCO Board (Past-President, President, President-Elect) and selected content experts drawn from the Board membership and appointed at the discretion of the President.

Publication of the PCO

The PCO would be posted online at asco.org soon after approval of the manuscript by the appointed Board subgroup. Publication in the next issue of the *Journal of Oncology Practice* would follow, space permitting, and pending review of the manuscript and acceptance thereof by the Editor-in-Chief of the *Journal*.

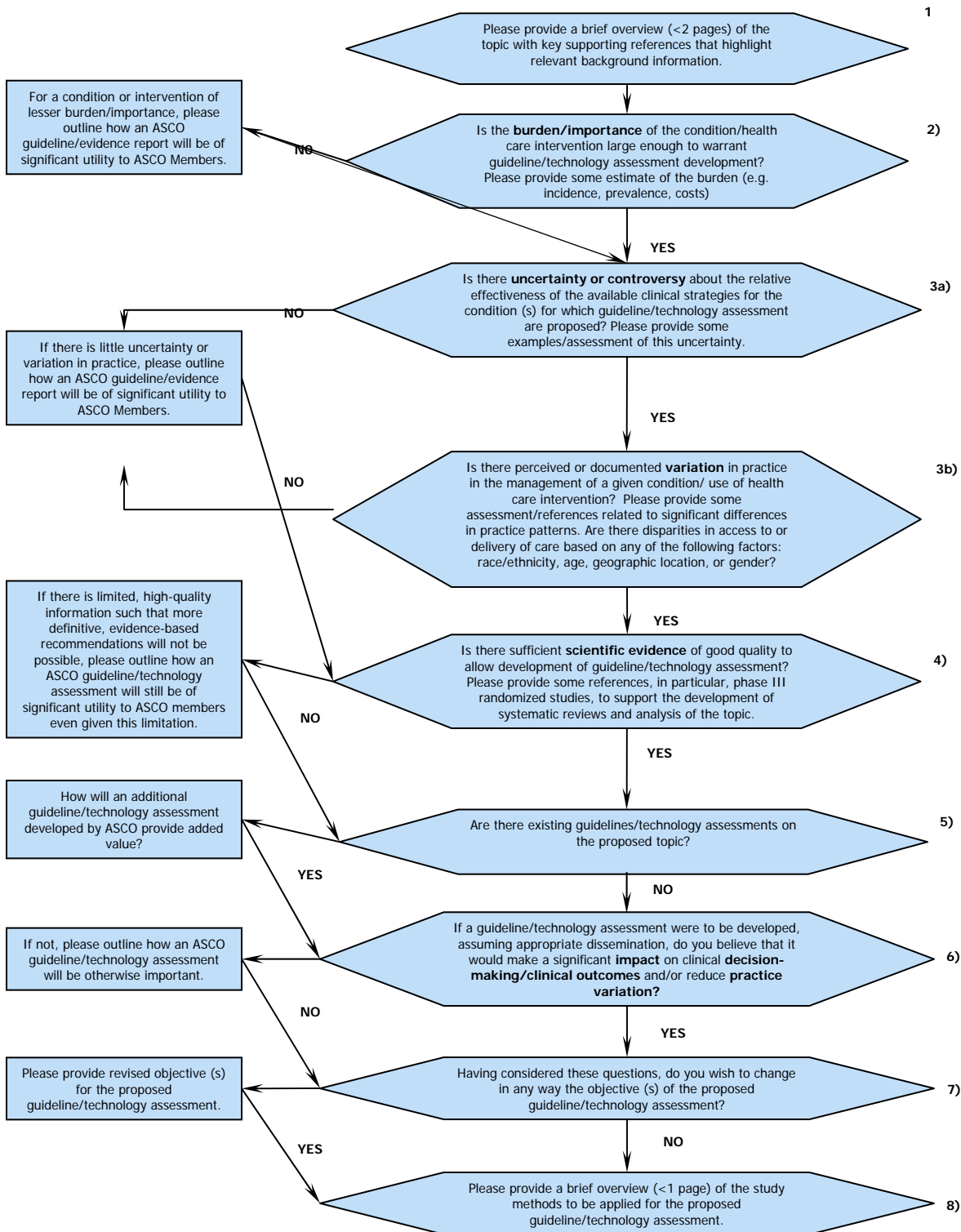
Exceptions

ASCO's goal is to assemble a diverse and well-qualified group of experts to develop and approve provisional clinical opinions. If required to achieve this goal, these procedures may be adapted by the Health Services Committee, the President, or the Chief Executive Officer on a case-by-case basis to the extent necessary.

IV. Appendices

Appendix 1-A: ASCO Call for Evidence-Based Clinical Practice Guideline Topics

Please enter a short title and the specific objective (s) for the proposed guideline/technology assessment topic



Thank you for your time. Your proposal will be reviewed by the ASCO Health Services Committee (HSC). You will be contacted after this review is complete.

Appendix 1-B

Sample Topic Proposal

ASCO Call for Evidence-Based Clinical Practice Guideline and Technology Assessment Topics

Please enter a short title and the specific objective (s) for the proposed guideline/technology assessment topic

Prevention of venous thromboembolism in cancer patients

Please provide a brief overview (<2 pages) of the topic with key supporting references that highlight relevant background information.

The risk of venous thromboembolism (VTE) is known to be increased in cancer patients, especially in those receiving chemotherapy¹. The annual incidence of VTE in the cancer population was estimated to be 0.5%². Current incidence rates are believed to be much greater. Newer anti-cancer therapies, in particular anti-angiogenic agents, are associated with very high rates of VTE³⁻⁵. A study of cancer patients treated at three medical centers reported an incidence of 7.8% over a median follow-up of only 26 months (0.3%/month)⁶. A recent analysis of over 66,000 hospitalized cancer patients on chemotherapy reported a 5.4% incidence of VTE per hospitalization. In this study, the rate of VTE increased by 36% from 1995 to 2002 (P for trend<0.0001)⁷.

The diagnosis of VTE has important clinical implications as well. Thromboembolism is reportedly the second leading cause of death in cancer patients⁸. Cancer diagnosed at the same time as or within one year of an episode of VTE is associated with an advanced stage and a 3-fold lower survival at one year⁹. Hospitalized patients with VTE have a greater in-hospital mortality rate (odds ratio 2.01, 95% CI 1.83-2.22, p<0.0001), and this is true even of patients without metastatic disease⁷. In addition to its clinical impact, VTE has economic consequences related to cost of hospitalization¹⁰.

Known risk factors for VTE in cancer patients include the stage and site of disease, use of chemotherapy, use of hormonal therapy, use of surgical procedures and the presence of a central venous catheter. Cancer patients undergoing surgery have twice the risk of postoperative venous thrombosis and more than three times the risk of fatal pulmonary embolism than patients without cancer undergoing similar surgery¹¹.

It is important to reduce the burden of VTE in cancer patients, because the treatment of VTE is less effective when associated with cancer, and leads to more bleeding complications than in the non-cancer population¹². In a clinical trial of VTE prophylaxis during chemotherapy, patients with metastatic breast cancer who received very-low-dose warfarin had a reduced incidence of VTE compared to placebo¹³. Two

trials have shown that prolonged (3 week postoperative) low-molecular-weight heparin prophylaxis significantly reduces risk of venographic deep venous thrombosis (DVT)^{14,15}. Specific guidelines for prevention of VTE in cancer patients are not available from any of the major professional oncologic or other societies. The American College of Chest Physicians issues guidelines on prevention of VTE, which includes a section on cancer¹⁶. These recommend prophylaxis for surgery patients or acutely ill hospitalized medical patients. According to a recent survey, however, less than 5% of medical oncology patients are routinely given thromboprophylaxis¹⁷.

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*Is the **burden/importance** of the condition/health care intervention large enough to warrant guideline/technology assessment development? Please provide some estimate of the burden (e.g. incidence, prevalence, costs)*

Yes.

Patients with cancer have a sixfold increased risk of developing VTE. Cancer patients account for nearly one-fifth of all new VTE events. The incidence of VTE in hospitalized cancer patients on active therapy is 5.4% per hospitalization. The incidence of VTE in cancer outpatients ranges from 0.3%-0.8%/month. Patients with certain cancers are at much higher risk e.g., patients with pancreatic cancer have reported incidence rates of VTE ranging from 17-57%. VTE is reported to be the second leading cause of death in cancer patients. The occurrence of VTE in cancer patients is associated with an increase in both in-hospital and 1-year outpatient mortality. The management of VTE consumes considerable resources. The mean length of DVT-attributable hospitalization is 11 days, and the average cost of hospitalization for the index DVT episode is \$20,065 (in 2002 US dollars).

*Is there **uncertainty or controversy** about the relative effectiveness of the available clinical strategies for the condition (s) for which guideline/technology assessment are proposed? Please provide some examples/assessment of this uncertainty.*

Yes.

Several studies have assessed the role of anticoagulants in the primary prevention of VTE in cancer patients. Low-dose warfarin therapy did reduce the risk of VTE in one study when compared to placebo; however, rates of VTE were not significantly different in a randomized study of a low-molecular-weight heparin, dalteparin, versus placebo. Similarly, in patients with central venous catheters, one study with low-dose warfarin showed a reduction in catheter-associated thrombosis, but two did not; one study with low-molecular-weight heparin showed a benefit, but one did not. The role of thromboprophylaxis in ambulatory cancer patients is also controversial.

*Is there perceived or documented **variation** in practice in the management of a given condition/ use of health care intervention? Please provide some assessment/references related to significant differences in practice patterns.*

Yes.

Despite published clinical trials demonstrating reduced rates of VTE using thromboprophylaxis in both acutely ill medical and surgical inpatients, considerable variation in practice exists in implementation of prophylaxis. In a global survey of over 3,800 physicians, respondents reported considering thromboprophylaxis routinely in less than 5% of their medical oncology patients, as compared to 52% of surgical patients. Respondents would continue thromboprophylaxis for the duration of hospitalization in only 39% of surgical patients and 45% of medical patients.

*Is there sufficient **scientific evidence** of good quality to allow development of guideline/technology assessment? Please provide some references, in particular, phase III randomized studies, to support the development of systematic reviews and analysis of the topic.*

Yes.

Clinical trials evidence exists to show that unfractionated heparin reduces the risk of DVT and fatal PE following cancer surgery, and low-molecular-weight heparins have been shown to be at least as efficacious. Randomized studies in cancer patients undergoing surgery have shown that increasing the duration of prophylaxis for 3 weeks after hospital discharge reduces the risk of late venographic DVT by 60%. A recent systematic review identified 19 studies of thromboprophylaxis using heparins and mechanical methods in colorectal surgery, although it included non-cancer surgery. Randomized studies have shown the efficacy of low-dose warfarin in primary prevention of VTE in breast cancer patients and the superiority of low-molecular-weight heparins over warfarin in secondary prevention of VTE in cancer patients. Five randomized trials evaluating the benefit of low-dose warfarin or low-molecular-weight heparin therapy for primary prevention of central venous catheter-associated thrombosis have been reported, with conflicting results.

*Are there existing guidelines/technology assessments on the proposed topic? If a guideline/technology assessment were to be developed, assuming appropriate dissemination, do you believe that it would make a significant **impact** on clinical **decision-making/clinical outcomes** and/or reduce **practice variation**?*

Yes.

There are no existing guidelines specifically on the proposed topic. The American College of Chest Physicians issues guidelines on prevention of venous thromboembolism, which includes a section on cancer. However, these guidelines are not intended for an audience of oncologists, and receive little dissemination in the oncology community. Development of guidelines specifically for the prevention of VTE in cancer by ASCO would increase the awareness of VTE as a significant complication of cancer, leading to an increased use of thromboprophylaxis in cancer patients. This would hopefully reduce the significant practice variation in prophylaxis strategies described above, and help in reducing the burden and costs of cancer-associated VTE.

Having considered these questions, do you wish to change in any way the objective (s) of the proposed guideline/technology assessment?

No.

Please provide a brief overview (<1 page) of the study methods to be applied for the proposed guideline/technology assessment.

1. A panel of experts including surgical oncologists, medical oncologists, hematologists and methodologists should be convened.
2. An initial meeting of this group should compile a list of the major questions/issues related to prevention of VTE in cancer including:
 - Mechanical methods of thromboprophylaxis
 - Primary prevention of VTE in the post-operative setting, including duration of thromboprophylaxis
 - Primary prevention of VTE in hospitalized patients
 - Primary prevention of central-venous-catheter-associated VTE
 - Warfarin versus low-molecular-weight heparin therapy for secondary prevention of cancer-associated VTE
 - Complications of VTE therapy in cancer patients, including recurrent VTE and bleeding
 - Best methods to measure efficacy, HRQOL and cost
 - A comprehensive list of outcome variables and covariates should be compiled for any future systematic review
3. An independent, exhaustive literature search should be undertaken of the world's literature utilizing existing systematic reviews, electronic searches and reference searches along with direct contacts with institutions known to be involved in research with this technique
4. The working group should review the data compiled for the systematic review and agree to the following:
 - Eligibility criteria including exclusion and inclusion.
 - Methods of searching to be utilized.
 - Whether a formal meta-analysis will be conducted.
 - How the results will be presented.
 - How issues of HRQOL and cost will be addressed.
 - Whether clinical practice guidelines will be offered or only an evidence summary provided.
 - Membership of the writing committee and authorship.

Appendix 1-C

Guideline Endorsement Policy

ASCO will consider review of clinical practice guidelines initiated by other professional organizations when relevant and appropriate to the mission and interests of ASCO and its membership. Endorsement of guidelines will be considered in selected circumstances either upon request from peer professional organizations, or when ASCO seeks to endorse another organization's guideline in lieu of undertaking its own guideline on the same topic.

Criteria for Endorsement of Guidelines:

Endorsement of selected guidelines developed by other peer professional organizations without ASCO participation or co-sponsorship will be considered under special circumstances as outlined above. The following criteria will be applied to requests for ASCO endorsement of clinical practice guidelines:

1. Endorsement of clinical practice guidelines from peer professional organizations will be considered upon formal request to ASCO.
2. Such guidelines should be relevant and appropriate to the mission and interests of ASCO and its membership and not be duplicative of existing ASCO guidelines.
3. Guidelines considered for endorsement should be based on a systematic review of the available evidence
4. There should be an explicit statement of the purpose, methodology utilized and recommendations made.
5. Guidelines proposed for endorsement should be reviewed and approved by the Methodology Subcommittee and the Health Services Committee before submission to the ASCO Board of Directors for approval.
6. An appropriate ASCO member will be identified as liaison for the endorsed guideline.
7. A brief summary of endorsed guidelines will be prepared by ASCO staff including a synopsis of the following:
 - a. Guideline title and the group responsible for development of the guideline
 - b. Purpose and rationale
 - c. Target population

- d. Major recommendations
 - e. ASCO Commentary summarizing the ASCO perspective on the guidelines including any additions or modifications specific for the ASCO membership
 - f. Selected references
8. The summary and links to the endorsed guideline will be provided to members on the ASCO website.
 9. Such endorsements should be reviewed annually and updated when appropriate

American Society of Clinical Oncology
Practice Guideline Endorsement Content Review Form*

Guideline Title: _____

Organization: _____

Reviewer Name: _____

Background and Instructions. ASCO considers clinical practice guidelines developed by other professional organizations for endorsement. This is done most often in lieu of undertaking its own guideline on the same topic. You have been asked to provide a content review of a guideline that is under consideration for endorsement by ASCO. Please check the box that best applies for each of the following items.

	Strongly Agree	Neither Agree or Disagree	Strongly Disagree	Unsure
The results of the studies described in this guideline are interpreted according to my understanding of the data.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The recommendations in this report are clear.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
I agree with the recommendations as stated in the guideline.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The recommendations are suitable for the patients for whom they are intended.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The recommendations are too rigid to apply to individual patients.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
When applied, the recommendations will produce more benefits for patients than harms.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The guideline presents option that will be acceptable to patients.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The guideline should be endorsed by ASCO.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

* This form was adapted from the Cancer Care Ontario Program in Evidence-Based Care Practitioner Feedback instrument.

Appendix 2-A

Summary of Roles and Responsibilities of ASCO Staff and of Volunteers who Serve as Panel Co-Chairs or Panel Members

This document is intended to clarify the expectations of participation in an ASCO guideline panel. It describes what resources and support panel members can expect from ASCO and what is expected of panel members. Guideline development is time-consuming, but the end-products are especially valued by members. Panel members have found the experience especially rewarding. Increased ASCO staff support has recently been implemented to make the processes run more smoothly. We recognize that participation in development in an ASCO guideline involves significant commitment of time and energy. Therefore, before you make a commitment, we hope that the material that follows provides some clarification regarding the expectations and scope of the undertaking. Please contact the panel chairs and/or Mark Somerfield, Director of Clinical Affairs, with further questions.

Part I: Role of ASCO Guideline Panel Co-Chairs and Expert Panel Members

Role in the Conduct of the Systematic Review of the Literature

- Panel Co-Chairs collaborate with the ASCO Clinical Affairs Division to develop a systematic review. The systematic review is what grounds ASCO guidelines and ensures that they are “evidenced based.”
- Panel Co-Chairs work with ASCO staff in development of a strategy, a “guideline Development Protocol,” including specific inclusion and exclusion criteria for the systematic review. This may involve utilization of an existing systematic review performed by an outside or contract organization, or may involving directing the conduct of a systematic review by ASCO staff.
- Panel Co-Chairs plan a strategy for the Panel to review the results of the systematic review. They assume responsibility for deciding what components of the work can be done face to face and what can be done via electronic communication or conference calls
- All panel members are expected to substantively contribute to interpretation of the evidence in formulating guideline recommendations.

Meeting Attendance and General Responsibilities

- All panel members attend typically one face-to-face meeting (usually at ASCO headquarters) to synthesize the results of the systematic review, discuss the structure of the guideline, and to formulate consensus recommendations. Depending on the scope of the systematic review, Panel co-chairs occasionally attend one earlier meeting with ASCO staff (prior to the full Panel meeting) in order to more fully characterize the evidence and plan for a full Panel meeting.

- Panel members are asked to meet deadlines for literature review, manuscript drafting, and manuscript editing within a reasonable time frame.
- Panel members who are unable for whatever reason to adhere to the project timeline/work schedule are asked to notify ASCO staff and Panel Chairs. They may be asked to resign so as to ensure timely development of guidelines and so as to facilitate recruitment of an alternate to prevent an unusually heavy burden from falling on the shoulders of other panel members.

Manuscript Development and Guideline Authorship Policies

- Panel Co-Chairs assume primary responsibility for drafting the manuscript, but may divide the work by having specific panel members draft some sections. It is recommended that no more than three to four people assume responsibility for initially drafting the manuscript.
- Panel Co-Chairs typically serve as first and last authors of the finished product, although there can be exceptions to this at the discretion of the Co-Chairs.
- All Panel members are expected to critically edit and review drafts of the document.
- Panel members who have attended meetings, participated in the review of evidence and helped draft and edit the guideline are expected to serve as authors. There is no reason that all panel members cannot serve as authors.
- The order of middle authorship is determined at the discretion of the Panel Co-Chairs.

Confidentiality Policy and Disclosure of Potential Conflicts of Interest

- Panel members are required to observe a strict policy of confidentiality of guideline documents, draft and final, pending guideline publication; and are required to keep content of panel deliberations confidential.
- Panel members are required to disclose any potential conflicts of interest, including commitments that might be perceived as conflicts prior to initiating work on the guideline; and are asked to apprise ASCO staff of any changes that arise over the course of the project.

Role in Guideline-Related Media Relations and the Development of Clinical Tools & Resources for Physicians and Patients

- Panel members are expected to interface with the media at the time of publication and to assist ASCO in the development of press releases, and of materials suitable for use with patients and for publication on the Cancer.net website. Panel members are not expected to draft these documents, but to critically review them to ensure that the content is accurate and clear.
- Panel members may be asked to provide feedback regarding or input into the development of “clinical tools and resources” such as summary tables, charts or medical records forms that are designed to facilitate adherence to the guideline.

- Panel members may be asked to review “indicator statements” developed from the guideline recommendations. These statements are considered by the Quality of Care Committee for use as quality indicators. ASCO staff will work with Panel co-chairs to develop these statements.

Role in Guideline Updates

- Panel Co-Chairs, with ASCO Headquarters Staff assistance, decide when to reconvene the panel and have ultimate responsibility for updating the guideline recommendations and for developing the manuscript that results from any changes to these recommendations.
- Panel members continue to serve on the guideline panel after publication of the guideline. Periodically (typically every one to two years), the Panel reconvenes in person or by conference call to discuss whether the guideline should be updated. Panel members are expected to participate in the meetings and to volunteer literature that may expedite the update process.

Part II: ASCO Headquarters Staff Guideline Infrastructural Support

This section outlines the kinds of assistance that Panel Chairs and Panel Members can expect from ASCO staff.

Administrative Support

- Coordinate meetings and conference calls for Panel members.
- Coordinate mailing both traditional and electronic of documents/manuscripts that require review
- Coordinate adherence to a timeline by helping with scheduling and reminders.
- Manage reference database (ENDNOTE), confirm guideline references through electronic databases for accuracy and completeness, and obtain articles via electronic library service then compile and distribute as appropriate
- Field inquiries regarding ASCO clinical practice guidelines, and other related information from members
- Special project management, including contract and vendor negotiations when necessary
- Assist the Panel Chair with meeting organization, the development and preparation of meeting agendas and reports, maintenance of calendar-based responsibilities, and evaluation of materials submitted to the committee.

Systematic Review/Methodological Support

- Coordinate the conduct of literature searches, systematic literature reviews, and meta-analyses as needed to support guideline development
- Monitor published literature and coordinate guideline update schedule

- Facilitate adherence to ASCO policy and procedure on Guideline Development as formulated by the Health Services Committee's Subcommittee on Methodology

Editorial Support

- Contribute to the editing of practice guideline documents
- Maintain standardized format for guidelines
- Collate and assemble revisions to the guidelines that are submitted by Panel members as directed by the Panel Chairs
- Coordinate communication with ASCO media affairs
- Coordinate communication with ASCO staff in the development of patient materials, office practice tools and web-based versions, power point summaries of the guidelines

General HSC and Subcommittee Support

- Provide status reports to Health Services Committee leadership and the Board as needed
- Attend Expert Panel and Working Group meetings and serve as primary staff liaison to Expert Panels and Working Group
- Assist Health Services Committee in developing a program of guideline implementation and evaluation strategy
- Ensure proper legal review of guidelines
- Monitor all conflict of interest statements for Committee and Panel members

APPENDIX 2-B

AMERICAN SOCIETY OF CLINICAL ONCOLOGY

CONFIDENTIALIALITY AND PREPUBLICATION ACCESS POLICIES

Our work as a Committee is confidential. The materials that are sent, our discussions, and the decisions made by this group shouldn't be shared with anyone outside the ASCO leadership and staff.

Non-authors, including but not limited to third parties, with a direct or indirect financial interest, are not permitted prepublication access to ASCO Board of Directors-approved clinical practice guidelines, technology assessments, and related materials developed for ASCO publication and public dissemination. An exception to this policy is individuals solicited by the corresponding author of the ASCO document, or staff acting in his or her behalf, for the purposes of invited and confidential peer review." (Approved by Board of Directors November 3, 2000)

Appendix 2-C

Implementation of ASCO's Conflict of Interest Policy To Clinical Practice Guideline Co-Chairs and Expert Panel Members

(Approved by the ASCO Board of Directors on November 18, 2005)

Background and Rationale

As the leading medical society for physicians involved in cancer treatment and research, the American Society of Clinical Oncology (ASCO) has a special responsibility to support the efforts of its members to provide quality cancer care. One of the primary ways in which ASCO fulfills this responsibility is through the development of clinical practice guidelines. Public confidence in these guidelines depends on the involvement of experts who make determinations based on the best available evidence and who are free from actual and perceived conflicts of interest.

In reviewing qualifications for prospective chairs or co-chairs, the Health Services Committee will not appoint chairs and co-chairs who have certain financial interests or relationships, as outlined below. In appointing other members of the panel, the Health Services Committee will conduct advanced review of the financial interests of prospective panel members. Appointment of panel members will take into consideration the nature and intensity of the reported financial interest. When ASCO publishes the guideline in the *Journal of Clinical Oncology*, all disclosures of panel members will be published as a part of the guideline.

Panel Chairs or Co-Chairs

The ASCO conflicts policy (see attached) includes certain restrictions on principal investigators of clinical trials that are published in ASCO journals or presented at ASCO meetings. The ASCO Board of Directors determined that these same restrictions should apply to the chairs or co-chairs of a guideline panel. Therefore, the chair or co-chair of a guideline panel should not be an individual with any financial ties to a commercial entity with a product affected by the guideline under review, except they may be in receipt of payments intended to cover the costs of any clinical trials they may be conducting (including travel expenses associated directly with the trial). Prohibited financial interests for panel chairs/co-chairs include:

1. Stock or equity interest in the commercial entity (except in a diversified fund)
2. Royalties or licensing fees from the product under consideration
3. Patents for the product under consideration
4. Serving as an officer, board of directors member or employee of the relevant commercial entity
5. Reimbursement from the commercial entity for travel or trips to attend scientific or educational meetings (not including,
 - a. widely attended and independently sponsored scientific meetings in which the co-chair's primary aim was to present trial data, or
 - b. investigator meetings related to a trial in which the individual serves as a principal investigator)

6. Research-related payments from the relevant commercial entity that substantially exceed actual research costs
7. All honoraria, gifts or other payments from the relevant commercial entity, including payment for service on speakers bureaus or advisory committees. The chair and co-chair may receive research payments from the relevant commercial entity, so long as the payments are based on the actual time and efforts of research staff in conducting a clinical trial.

To the extent that a prospective chair or co-chair is aware that the affected commercial entity has provided substantial financial support to the division, department or other institutional unit within which the individual conducts clinical research and care, the prospective chair or co-chair should disclose that fact to the Health Services Committee. The existence of such substantial support does not necessarily disqualify the individual from service as a chair or co-chair, but can be taken into account by the Health Services Committee in making its decision.

These restrictions apply to the activities and interests of prospective chairs and co-chairs of guideline panels for a period of one year prior to the commencement of the guideline process. Thus, no panel or co-chair of a guideline panel should have the prohibited financial interests for the year preceding his or her selection by the Health Services Committee. In addition, panel chairs and co-chairs must provide a written commitment not to become involved in prohibited financial interests for a period of one year after publication of the guideline.

To the extent that the above restrictions are perceived by the Health Services Committee as inhibiting development of a guideline, the Committee may petition the Ethics Committee for an exception. However, exceptions will be considered only in rare circumstances and only with a convincing demonstration of need.

Because the guidelines are subject to periodic revision or updating, panel chairs or co-chairs must maintain their freedom from restricted financial interests following initial guideline publication if they expect to remain in the chair or co-chair positions. If current financial interests preclude their continuing in those roles, these individuals may be considered by the Health Services Committee for service as members of the panel for the update (with full disclosure of their current financial interests).

Panel Members

While panel members not serving as chair or co-chair are not subject to the above restrictions, they are required to make full disclosure of financial interests in a commercial entity with a product affected by the guideline under review, as well as entities with financial interests in directly competing products. Disclosures should conform to the requirements set forth in the ASCO conflicts policy (see attached). The Health Services Committee will review disclosures of prospective panel members to ensure that they are qualified for service. This review will consider the nature and intensity of the reported financial interest and take into account whether the existence of such interest might undermine public confidence in the guideline process.

These considerations will be balanced against the necessity of securing qualified individuals for participation in guideline development. In situations where the number of qualified experts is limited, panel members may inevitably have financial interests.

ASCO will address this situation through full disclosure of panel members' financial interests with publication of the guideline. In addition, the Health Services Committee may require that financially interested panel members recuse themselves from specific discussions or votes. In addition, the concerns raised by panel members' financial interests may be alleviated somewhat, depending on the breadth or specificity of the issues under consideration; that is, a financial interest may be of less concern where the matter under review is more general and less product-specific in nature.

CONFLICT OF INTEREST MANAGEMENT PROCEDURES for CLINICAL PRACTICE GUIDELINES

As the leading medical society for physicians involved in cancer treatment and research, the American Society of Clinical Oncology (ASCO) has an important role in helping physicians deliver quality oncology care. One of the primary ways in which ASCO fulfills this responsibility is through the development of clinical practice guidelines, technology assessments, and clinical evidence reviews. Public confidence in these guidelines depends on the cultivation of expert opinions based on the best available evidence and in a manner designed to minimize actual and perceived conflicts of interest.

For ASCO, guideline development is a multi-step process. Once drafted by a diverse panel of experts, guidelines must be approved by the Health Services Committee, adopted by the Board of Directors, and peer-reviewed in accordance with rigorous standards set by the *Journal of Clinical Oncology (JCO)*. The following procedures provide strategies for managing potential conflicts of interest through each phase of guideline development.

I. Identifying Affected Companies

Commercial entities with products affected by a guideline are considered “affected companies” for purposes of conflict of interest review of ASCO guidelines.³ A commercial entity is an affected company if there is a reasonable likelihood of direct regulatory or commercial impact (positive or negative) on the entity as a result of care delivered in accordance with guideline recommendations. To facilitate identification of potential conflicts of interest, affected companies will generally be identified at the time of development of the guideline protocol, prior to selection of panel members, chairs or co-chairs. For guidelines already under development, affected companies will be identified before the guideline is reviewed by the Health Services Committee.

Affected companies will generally be identified by an independent party who will not serve as a panel member or guideline reviewer. In some cases where identification is straightforward, an ASCO staff member from the Cancer Policy and Clinical Affairs Department may identify affected companies using criteria approved by the independent party. The list of affected companies should remain consistent throughout guideline development and adoption. If changes in the marketplace or in the focus of the guideline make revisions necessary, a modified list may be developed or reviewed by the independent party. The list of companies affected by a guideline will be made available to prospective guideline panel chairs and panel members, the Health Services Committee, and the Board by the Cancer Policy and Clinical Affairs Department.

³ Implementation of ASCO’s Conflict of Interest Implementation to Clinical Practice Guideline Panel Co-Chairs and Expert Panel Members, approved by the ASCO Board of Directors, December 19, 2005

II. Panels

a. Disclosure

All prospective panel members, including prospective panel chairs and co-chairs, disclose financial interests and other relationships with entities that have an investment, licensing, or other commercial interest in the subject matter under consideration in the guideline under review. Disclosures include employment, paid consulting or advisory roles, stock ownership, honoraria, research funding, gifts, and other payments from affected companies received by panel members themselves and their immediate family members.⁴

Prospective panel members will be asked to disclose at the time of nomination by the Health Services Committee. Generally, the list of affected companies will be provided at the time of disclosure. Prospective panel members will be asked to identify any financial interests in affected companies already listed, as well as any other relationships that are relevant to the guideline under review. It does not matter whether a financial relationship relates to the subject matter of the guideline.

Occasionally, a panel member may have a relevant financial interest or relationship that is not covered by ASCO's formal disclosure process, such as a patent in a product referenced in the guideline. In these situations, the panel member should disclose this interest to the panel chair or co-chair, or appropriate ASCO staff member.

Panel disclosure reports identifying relationships with affected companies will be available to panel members throughout the guideline development process. In addition, panel disclosure reports will be made available to the Health Services Committee and the ASCO Board of Directors before they vote to approve or adopt a guideline.

b. Selection of Panel Chairs and Co-Chairs

Generally, the Health Services Committee will not appoint chairs and co-chairs who have financial interests in or relationships with affected companies or products. This includes all relationships described in Section II.a. However, the Committee may name a panel chair who receives research funding from an affected company if doing so would ultimately help the panel develop a better quality guideline. In this case, the Health Services Committee must appoint a co-chair who has no ties to affected companies, including research funding.

These restrictions apply to the activities and interests of panel chairs and co-chairs for a period of one year prior to the commencement of panel deliberations through one year after the guideline is published.

If a panel chair or co-chair wants to continue to serve as chair for future guideline updates, he or she must remain in compliance with these restrictions. If, at the time of

⁴ American Society of Clinical Oncology: Revised Conflict of Interest Policy. J Clin Oncol 24:10.1200/JCO.2005.04.8926. Also available at www.asco.org/conflictinterest

update, an individual is no longer eligible to serve as a chair because of financial relationships, he or she will be eligible to serve as a panel member at the discretion of the Health Services Committee.

c. Selection of Panel Members

At least 51% of those selected to serve on a panel will have no relationships with affected companies from the start of panel deliberations through publication of the guideline. For the remaining 49%, such financial relationships do not preclude panel membership. All relationships with affected companies must be disclosed. In rare circumstances the Health Services Committee may determine that an individual is not eligible to serve as part of the 49% of the panel because of the nature and extent of his or her financial relationship with an affected company.

d. Voting

At in-person meetings, panel recommendations must be adopted by a 75% majority of panel members in attendance at a meeting where a simple majority of panel members are present. When the panel votes electronically, recommendations must be adopted by a 75% majority of the entire panel.

Because of the supermajority voting standard, panel members who have financial relationships with affected companies do not need to recuse themselves from discussing and voting on guideline recommendations on these grounds. Rarely, relationships may be disclosed that, though not financial in nature, could undermine public confidence in the guideline process. If there is a question as to whether a particular relationship warrants recusal, a determination will be made by the panel chair, with the assistance of an appropriate ASCO staff member.

e. Publication of Disclosure Information

When ASCO publishes a guideline in one of its journals, all disclosures of panel members will generally be published concurrently.

III. Health Services Committee

a. Disclosure

Health Services Committee members disclose financial interests and other relationships with entities that have an investment, licensing, or other commercial interest in the science or practice of oncology. Disclosures include employment, paid consulting or advisory roles, stock ownership, honoraria, research funding, gifts, and other payments received by panel members themselves and their immediate family members. These disclosures will be compared with the list of affected companies before a guideline is reviewed by the Health Services Committee.

Occasionally, a Health Services Committee member may have a relevant financial interest or relationship that is not covered by ASCO's formal disclosure process, such as a patent in a product referenced in the guideline. In these situations, the Health Services Committee member should disclose this interest to the Committee Chair or appropriate ASCO staff member prior to discussion of the guideline.

Committee disclosure reports identifying relationships with affected companies will be available to Health Services Committee members prior to Committee discussion of a guideline. The Health Services Committee's disclosure report may also be made available to the ASCO Board of Directors before the Board votes to adopt a guideline.

b. Health Services Committee Reviewers

From time to time the Health Services Committee Chair appoints Committee members to serve as reviewers of a guideline. Generally, the Committee Chair will select Committee members who have no financial relationships with affected companies or products to serve as guideline reviewers.

c. Recusal

To underscore the independence and integrity of the guideline adoption process, guidelines will be approved only by Health Services Committee members who do not have financial relationships with affected companies or products. Therefore, disclosure of any financial relationship with an affected company or product as described in Section III.a. should be cause for recusal.

Rarely, relationships may be disclosed that, though not financial in nature, could undermine public confidence in the guideline process. If there is a question as to whether a particular relationship warrants recusal, a determination will be made by the Health Services Committee Chair, with the assistance of an appropriate ASCO staff member. Whether a financial relationship relates to the subject matter of the guideline is not a relevant consideration for purposes of determining recusal.

Any Committee member who discloses a financial interest in a company or product affected by a guideline should recuse him or herself from the Committee's decision on approval of a guideline. Such a Committee member may take part in initial Committee discussion of the guideline manuscript, recognizing that there may be additional discussion by remaining Committee members after recusal and before the vote.

d. Voting

Generally, guidelines will be reviewed and approved by a vote of the Health Services Committee at a meeting where a quorum is present.

However, the Committee has delegated its authority to one or more subgroups of the Committee to act when the Committee lacks a quorum to approve a guideline due to

recusal. The Committee will authorize the Committee Chair to appoint, from time to time, an ad hoc subgroup to discuss a guideline and vote on approval of the guideline. The subgroup for a guideline should be comprised of Committee members who do not have financial relationships with affected companies or products.

A subgroup may convene at a Committee meeting where a guideline is scheduled for review, or any time before or after, in person or by teleconference. A majority vote of the subgroup is required to approve a guideline. Approval by the subgroup will be considered approval by the Health Services Committee, and full Committee review will not be needed.

IV. Board of Directors

a. Disclosure

ASCO Board members already disclose financial interests and other relationships with entities that have an investment, licensing, or other commercial interest in the science or practice of oncology.⁵ Disclosures include employment, paid consulting or advisory roles, stock ownership, honoraria, research funding, gifts, and other payments received by panel members themselves and their immediate family members. These disclosures will be compared with the list of affected companies before a guideline is reviewed by the Board.

Occasionally, a Board member may have a relevant financial interest or relationship that is not covered by ASCO's formal disclosure process, such as a patent in a product referenced in the guideline. In these situations, the Board member should disclose this interest to the President or Ethics counsel prior to discussion of the guideline. Board disclosure reports identifying affected companies will be available to the Board members considering adoption of a guideline.

b. Board Reviewers

From time to time the President appoints Board reviewers of a guideline. Generally, the President will select Board members who have no financial relationships with affected companies or products to serve as guideline reviewers.

c. Recusal

To underscore the independence and integrity of the guideline adoption process, guidelines will be adopted only by Board members who do not have financial relationships with affected companies or products. Therefore, disclosure of any financial relationship with an affected company or product as described in Section IV.a. should be cause for recusal.

⁵ Implementation of ASCO's Conflict of Interest Policy for ASCO Leadership, approved by the ASCO Board of Directors, June 8, 2006

Rarely, relationships may be disclosed that, though not financial in nature, could undermine public confidence in the guideline process. If there is a question as to whether a particular relationship warrants recusal, a determination will be made by the Vice President and General Counsel. Whether a financial relationship relates to the subject matter of the guideline is not a relevant consideration for purposes of determining recusal.

Any Board member who discloses a financial interest in a company or product affected by a guideline should recuse him or herself from the Board's decision on adoption of a guideline. Such a Board member may take part in initial Board discussion of the guideline manuscript, recognizing that there may be additional discussion by remaining Board members after recusal and before the vote.

d. Voting

Generally, guidelines will be reviewed and adopted by a vote of the ASCO Board of Directors or Board Executive Committee at a meeting where a quorum is present.

However, the Board has delegated its authority to one or more subgroups of the Board to act when the Board or Executive Committee lacks a quorum to adopt a guideline due to recusal. The Board will authorize the President to appoint, from time to time, an ad hoc subgroup to vote on adoption of the guideline. The subgroup for a guideline should be comprised of Board members who do not have financial relationships with affected companies or products.

A subgroup may convene at a Board meeting where a guideline is scheduled for review, or any time before or after, in person or by teleconference. A majority vote of the subgroup is required to adopt a guideline. Adoption by the subgroup will be considered adoption by ASCO, and full Board review will not be needed.

V. JCO Peer Review

JCO Editors and reviewers disclose financial interests and other relationships in a manner that is consistent with the ASCO Conflict of Interest Policy and the practices and procedures set by the *Journal*. Disclosures include employment, paid consulting or advisory roles, stock ownership, honoraria, research funding, gifts, and other payments from affected companies. The disclosures of all *JCO* Editors are published annually on the *JCO* website (www.jco.org).

JCO Editors and reviewers may decline to review a guideline due to potential conflicts of interest.

VI. Exceptions

ASCO's goal is to assemble a diverse and well-qualified group of experts to develop, approve, and adopt guideline recommendations. If required to achieve this goal, these procedures may be adapted by the Health Services Committee, the President, or the Executive Vice President and Chief Executive Officer on a case-by-case basis to the extent necessary.

APPENDIX 3-A

ASCO CLINICAL PRACTICE GUIDELINE DEVELOPMENT PROTOCOL WORKSHEET

Title of Guideline:

Expert Panel Co-Chairs:

Proposed Expert Panel Membership: Define variety of necessary expertise, constituencies that need to be represented, and estimate optimal size of Expert Panel/Working Group

The proposed panel should include experts in clinical medicine, clinical research, health services, and related disciplines (biostatistics, medical decision making, patient-physician communication), a career development committee representative, as well as a patient representative. The following experts have been selected as qualified members of this panel:

Define the Overall Purpose of Guideline: Specify clinical problem(s) to be addressed.

Specify Population(s) of Interest: Include, as relevant, subgroups defined by characteristics such as age, sex, race, and disease stage.

Identify Relevant Practice Setting(s): (e.g. hospitals; primary care or specialty care office-based practices; freestanding surgical centers; free-standing imaging centers; etc.)

Specify Intervention(s) or Exposure(s):

Specify Comparison(s): As relevant, note types of control groups to be compared.

Identify Relevant Primary and Secondary Outcome(s): (e.g. disease-free survival, overall survival, treatment toxicity, cost-effectiveness, quality of life)

Specify Clinical Questions to be Addressed by the Guideline: Questions should address the population(s) of interest, the intervention, and the outcomes.

Define the Parameters of the Systematic Review

Range of Research Study Dates:

Specify Inclusion and Exclusion Criteria for Literature Review: Delineate study types (e.g., RCTs), patient characteristics (e.g., stage II disease undergoing primary therapy), and publication types (e.g., exclude letters, meeting abstracts) that are included or excluded.

Suggest Relevant Search Terms or Phrases: Include abbreviations and acronyms, as appropriate.

Disease/Topic/Intervention Terms:

Design or Publication Type Terms:

Based upon information provided on this Protocol Worksheet, ASCO staff will identify relevant evidence via systematic searches of appropriate databases. Typically this will include searches of The Cochrane Library, MEDLINE, and EMBASE. Of note, based on recent HSC policy and procedures changes, the literature search should include search terms to address health disparities as relevant to the clinical questions considered by the particular guideline

Proposed Timeline: In collaboration with ASCO staff, assign target completion dates for guideline development milestones as follows.

1. Hold Guideline Panel Steering Group Teleconference to Define or Refine Clinical Questions and Suggest Panel Members [INSERT DATE]
2. Complete Guideline Protocol Worksheet and Submit it to the Methods Subcommittee [INSERT DATE]

3. ASCO Staff Conduct Initial Literature Searches [INSERT DATE]
4. ASCO Staff Send Abstracts to Appropriate Panel/Working Group Members [INSERT DATE]
5. Panel Members Review Abstracts and Select Those That Likely Meet Review Inclusion Criteria
6. ASCO Staff Gets Full-Text Articles and Distribute to Panel Members
7. Panel Members Review Full-Text Articles and Make Final Inclusion/Exclusion Decisions
8. ASCO Staff Create Evidence Tables and, with Co-Chairs and Methods Subcommittee, Decide on Quantitative Versus Qualitative Syntheses
9. Panel Members Draft Narrative Guideline Sections as Assigned [INSERT DATE]
10. Panel/Working Group Meets and Drafts Recommendations (discretionary) [INSERT DATE]
11. Panel/Working Group Reviews and Approves First Complete Draft of Guideline [INSERT DATE]
12. ASCO Staff Send Draft Document for External Peer Review [INSERT DATE]
13. Panel/Working Group Submit Guideline for HSC Review and Approval [INSERT DATE]
14. HSC Submits Guideline for ASCO Board of Directors Review and Approval [INSERT DATE]
15. ASCO Staff Coordinates Development of Patient Guide, Clinical Tools, as Appropriate, and Other Derivative Print and Electronic Products [INSERT DATE]
16. Submit Guideline to JCO for Publication [INSERT DATE]

APPENDIX 3-B

TEMPLATE WITH EXAMPLE FROM STAGE II GUIDELINE

ASCO CLINICAL PRACTICE GUIDELINE DEVELOPMENT PROTOCOL WORKSHEET

Title of Guideline: *Adjuvant Chemotherapy for Stage II Colon Cancer*

Expert Panel Co-Chairs: *Drs. Al. B. Benson III and Daniel G. Haller*

Proposed Expert Panel Membership: Define constituencies that need to be represented and estimate optimal size of Expert Panel/Working Group

The proposed expert panel should consist of experts in clinical medicine, clinical research, health services, and related disciplines (biostatistics, medical decision making, patient-physician communication) with a focus on expertise in colon cancer, as well as a patient representative. The following experts have been selected as qualified members of this panel:

Alfred M. Cohen, MD
Alvaro Tell Figueredo, MD
Patrick J. Flynn, MD
Monika K. Krzyanowska, MD
Jean Maroun, MD

Pamela McAllister, PhD
Deborah Schrag, MD
Eric Van Cutsem, MD, PhD
Melissa Bouwers, PhD, Ex-Officio
Manya Charette, Ex-Officio

Define the Overall Purpose of Guideline: Specify clinical problem to be addressed.

To address whether all medically fit patients with curatively resected stage II colon cancer should be offered adjuvant chemotherapy as part of routine clinical practice, to identify patients with poor prognostic characteristics, and to describe strategies for oncologists to use to discuss adjuvant chemotherapy in practice.

Specify Population of Interest: Include, as relevant, characteristics such as age, sex, race, and disease stage.

Patients with curatively resected stage II colon cancer

Specify Intervention(s) or Exposure(s):

Adjuvant chemotherapy

Specify Comparison(s): As relevant, note types of control groups to be compared.

5-FU-containing regimen versus surgery alone and observation
Exclusion: portal vein infusion

Identify Relevant Outcome(s): (e.g. disease-free survival, overall survival, treatment toxicity, cost-effectiveness, quality of life)

Overall survival benefit, disease-free survival, and treatment toxicity of adjuvant chemotherapy in patients with curatively resected stage II colon cancer

Specify Clinical Questions to be Addressed by the Guideline: Questions should address the population of interest, the intervention, and the outcomes.

- *Should all medically-fit patients with curatively resected Stage II colon cancer be offered adjuvant chemotherapy as part of routine practice?*
- *Should patients with curatively-resected Stage II colon cancer and with identifiable characteristics that predict for a poor prognosis (i.e., high-risk patients) be offered adjuvant chemotherapy?*
- *What strategies can medical and surgical oncologists use to discuss the issue of adjuvant chemotherapy with their patients in clinical practice?*

Define the Parameters of the Systematic Review

Range of Research Study Dates:

1987 to 2003

Specify Inclusion and Exclusion Criteria for Literature Review: Delineate study types (e.g., RCTs) and publication types (e.g., exclude letters, meeting abstracts) of interest.

Articles were selected for inclusion in this systematic review of the evidence if they met the following criteria: Randomized controlled trials (RCTs) or meta-analyses of RCTs involving patients with stage II colon cancer who had undergone surgery with curative intent that compared adjuvant therapy with observation or another systemic therapy. The main outcome of primary interest was survival but disease-free survival was also considered. Due to the inconsistent reporting of treatment toxicities and quality of life, these data were not considered.

Suggest Relevant Search Terms or Phrases: Include abbreviations and acronyms, as appropriate.

Disease/Topic Terms

Colonic neoplasms

Colorectal neoplasms
Rectal neoplasms
Immunotherapy
Adjuvant chemotherapy
Fluorouracil
FU-based chemotherapy

Design or Publication Type Terms

Practice guidelines
Systematic reviews or meta-analyses
Randomized controlled trials

Based upon information provided on this Protocol Worksheet, ASCO staff will identify relevant evidence via systematic searches of appropriate databases. Typically this will include searches of The Cochrane Library, MEDLINE, and EMBASE.

Proposed Timeline: In collaboration with ASCO staff, assign target completion dates for guideline development milestones as follows.

1. Hold Guideline Panel Steering Group Teleconference to Define or Refine Clinical Questions and Suggest Panel Members [INSERT DATE]
2. Complete Guideline Protocol Worksheet Completed and Submit it to the Methods Subcommittee [INSERT DATE]
3. ASCO Staff Conduct Initial Literature Searches [INSERT DATE]
4. ASCO Staff Send Abstracts to Appropriate Panel/Working Group Members [INSERT DATE]
5. Panel Members Review Abstracts and Select Those That Meet Review Inclusion Criteria
6. ASCO Staff Gets Full-Text Articles and Distribute to Panel Members
7. ASCO Staff Create Evidence Tables and, with Co-Chairs and Methods Subcommittee, Decide on Quantitative Versus Qualitative Syntheses
8. Panel Members Draft Narrative Guideline Sections as Assigned [INSERT DATE]
9. Panel/Working Group Meets and Drafts Recommendations (discretionary) [INSERT DATE]
10. Panel/Working Group Reviews and Approves First Complete Draft of Guideline [INSERT DATE]

11. ASCO Staff Send Draft Document for External Peer Review [INSERT DATE]
12. Panel/Working Group Submit Guideline for HSC Review and Approval [INSERT DATE]
13. HSC Submit Guideline for ASCO Board of Directors Review and Approval [INSERT DATE]
14. ASCO Staff Coordinates Development of Patient Guide, Clinical Tools, as Appropriate, and Other Derivative Print and Electronic Products [INSERT DATE]
15. Submit Guideline to JCO for Publication [INSERT DATE]

Appendix 4-A

Systematic Review Checklist: The Basics

1. Hold Guideline Panel Steering Group Teleconference to Define or Refine Clinical Questions
2. Complete Guideline Protocol Worksheet Completed and Submit it to the Methods Subcommittee
3. ASCO Staff Conduct Initial Literature Searches
4. ASCO Staff Send Abstracts to Appropriate Panel/Working Group Members
5. Panel Members Review Abstracts and Select Those That Meet Review Inclusion Criteria
6. ASCO Staff Gets Full-Text Articles and Distribute to Panel Members
7. ASCO Staff Create Evidence Tables and, with Co-Chairs and Methods Subcommittee, Decide on Quantitative Versus Qualitative Syntheses

Appendix 4-B

Reviewing References Using Systematic Review Software (SRS)

This document is intended as an overview and “how to” guide for use of the Systematic Review Software (SRS). If, after reading the directions, you still have questions or are unsure of any of the procedures, please contact Karen Hagerty (karen.hagerty@asco.org) for assistance.

Process Description/Overview

First Level of Review (Panel Abstract Review):

This first level of review is intended to identify those citations for which panel members would like to see the full text. The form for reviewing at this level contains a sole “yes/no” response choice.

- 1) Each abstract needs to be reviewed by 2 different panel members.
- 2) If both say “yes,” the abstract is “promoted” to Level 2 review and the full text is obtained by ASCO staff (see next section for details on Level 2 review).
- 3) If both say “no,” the abstract is excluded from further consideration and does not show up again in the review process.
- 4) If there is a disagreement (one says “yes,” one says “no”) the abstract will be tagged as “disagreement.” ASCO staff will alert panel members of disagreements via e-mail so that a consensus may be reached.

Second Level of Review (Panel Full Text Review):

- 1) Each full text article needs to be reviewed by X panel members. ASCO staff will attempt to locate as many articles as possible in an electronic format; articles in electronic format will be linked directly into the SRS system so that they may be reviewed online or printed out directly from the system. Articles available only in hardcopy will either be scanned into the SRS system or mailed to panel members.
- 2) The panel member reviewing the article will respond to a series of questions presented in a form.
- 3) Please note that this form is dynamic, so depending on your responses to specific questions, you may or may not see subsequent questions. Also, the question numbering may seem odd due to the dynamic nature of the form – please do not worry about this.

Accessing and Using the System

You will receive an automated e-mail from SRS with your username and password and a link to access the SRS system. After you have entered your username and password, there may be a dropdown menu underneath. If so, please choose "Systematic Reviews" and then continue.

(Please note that the e-mails containing usernames and passwords are generated by ASCO staff, but come from the SRS system. ASCO staff do not know or have access to your usernames and passwords. If you forget your user information or misplace the e-mail with that information, please notify Karen Hagerty and they will generate another e-mail to you from SRS containing your username and password.)

Level 1 Review (Panel Abstract Review)

- 1) Click on "Review" on the left hand menu, which will expand the menu, then choose "Panel Abstract Review."
- 2) You should see a list of citations, which you should be able to review individually by clicking the link "Review this article." This will open a new window with the abstract and one yes/no question for you to complete.
- 3) Choose "yes" or "no" and then click the "Submit data" button.
- 4) Please note that if you choose to review abstracts in this manner, once you have submitted data, the next abstract in the list automatically shows up in this second window. Depending on whether or not you want to review the abstract, you have several options:
 - a. Go ahead and review the abstract; again, once you click "Submit data," the next abstract on the list will show up in your second window.
 - b. If you wish to skip the abstract, use the red arrow at the top right-hand corner of the screen to skip to the next abstract.
 - c. Close out the second window to be returned to the original list of abstracts, and click on the "Review this article" link for any abstract you wish to review.
- 5) If you prefer to do a **rapid screening** looking only at the **titles**, click on the red checkmark at the top of the screen. A new window will open with a list of 15 titles and yes/no response buttons next to them. If you decide you want to view an abstract, simply rest your mouse over the title and the abstract will appear.
- 6) Choose "yes" or "no" for each title on the page, then click the "Submit data" button. Once you have submitted your data, a new list of 15 titles will appear in this window.
- 7) If you wish to return to reviewing abstracts one at a time, simply close this window to return to the original list of citations. You can go back and forth between these two views, please use whichever works best for you.

Level 2 Review (Panel Full Text Review)

As soon as two reviewers say "yes" to retrieving full text during the Level 1 Review, the citation is automatically "promoted" to Level 2 (Panel Full Text Review). As reviewers go through the Level 1 process, ASCO staff will monitor the SRS system for citations

promoted to Level 2, and will attempt to locate electronic copies of the full text for upload to the system. If the full text has been loaded into the system, reviewers will see a small PDF/Adobe icon next to the title of the citation.

- 1) Click on “Review” on the left-hand menu, which will expand the menu, then choose “Panel Full Text Review.”
- 2) You should see a list of citations, some of which have a PDF/Adobe icon next to them. Click on this icon to open the full text article in a new window.
- 3) In order to review the article, click on the “Review this article” link. Answer all of the questions in the form, then click the “Submit data” button.
- 4) If you want to view the full text article at the same time you are answering the questions, simply click on the yellow icon at the very top right-hand corner of the review form and the full text will appear at the left of your screen, with the questions on the right side of your screen. Simply answer the questions and click the “Submit data” button as above.

Using Views

At the top of the screen you will see a dropdown menu which allows you to look at citations at different levels in the review process. Dummy data has been entered for some of these already so that you can see what it will look like when you start your real review. The different options and what you will see are detailed below.

“Show All” – shows all references that **you** have already reviewed *and* articles available to be reviewed by you. In this view, you cannot see abstracts that have already been reviewed by 2 other panel members.

“Unreviewed” – shows only those references that have not yet been reviewed by 2 people. **This is the view you will want to use when you are reviewing citations.**

“Reviewed” – shows references that **you** have already reviewed. They may or may not have been reviewed by a second person.

“Excluded” – shows those abstracts for which both reviewers said “no” to full text retrieval.

“Disagreements” – shows those abstracts for which one reviewer said “yes” to full text retrieval and one reviewer said “no.”

“Unreviewed Uploaded” – shows only articles where the full text is available in SRS and where you have not yet reviewed it. This view is useful in the **Level 2 Review** in order to identify and review only citations which have an associated full text article available online.

About the Level 2 Review Form

The Level 2 Review Form was designed by ASCO staff with Dr. Stephanie Lee. ASCO staff used information contained in the protocol document and their review of abstracts retrieved from the MEDLINE search to capture outcomes of interest and other data of use in preparing the guideline (e.g., specific intervention, number of patients, study design, etc.).

We would appreciate feedback on this form from all Panel members. Please let us know if there are other relevant questions that you would like to see on the form, and we can add them prior to beginning the “real” review.