A. Cover Page: Pfizer Extension Grant Request for original program titled *Expert Guidance in Advanced NSCLC: Selection of First-line and Maintenance Therapy (*grant ID number: 038898). Completed online at www.pfizer.com/independentsupport

B. Table of Contents

C. Main Section of the Proposal (**Not To Exceed 15 Pages**)

1. ***Overall Goal & Objectives***: The overall goal of this initiative, which will be jointly sponsored by USF Health and Clinical Care Options (CCO), is to continue to close professional practice gaps associated with the first-line treatment of non-small-cell lung cancer (NSCLC) among clinicians *outside of* the United States and to provide guidance on standards of optimal individualized treatment of the disease in the first-line setting. The primary objectives the joint sponsors will use to accomplish this goal are: 1) expand upon a current continuing education program designed to address these practice gaps, 2) provide an online tool that is easy to access and use that promotes the application of the latest developments in optimal care of NSCLC, 3) measure the educational outcomes associated with this effort, and 4) publish this data for a wider audience.

2. ***Technical Approach***: To meet the stated goal, the current program developed in joint sponsorship by USF Health and CCO will be updated based on recent therapeutic approvals and new biomarkers that guide treatment decisions for patients with NSCLC in the first-line setting. The current program, which includes a CME-certified interactive activity combined with an *Expert Insight Interactive Decision Support Tool*, has been used by 3365 clinicians. Of these, 2228 were non-US physicians (see page 10 for more detail on non-US participants). Moreover, 1391 clinicians used the tool, and the slideset associated with the program was downloaded 4318 times. Changes in standards of care require an update of the previous tool and an additional update will be planned to address further changes to the standard of care within the 12 months following the

publication of version 2.

Specific efforts involved in this activity expansion include the following:

- Update the online CME-certified activity
- Update the online Interactive Decision Support Tool. An analysis will be conducted during the 12-month life span of the tool, to determine if any additional updates are needed
- Expand reporting capability of the tool to capture reasons users do not agree or apply the expert's recommendations
- Expand awareness of the availability of the tool with additional promotion, including emails, to the CCO international membership
- Provide an analysis by major geographical regions outside of the United States (that includes captured barriers), with data to be published or presented at a major oncology conference such as European Society of Medical Oncology (ESMO) or International Association for the Study of Lung Cancer (IASLC)

a. Current Assessment of Need in Target Area: Data from the CME-certified activity that was launched in 2012 demonstrated that 20% of physicians incorrectly identified the most useful biomarkers for guiding therapy selection in NSCLC. In addition, 40% chose an inappropriate therapy based on tumor histology.[1] Data from the *Expert Insight Interactive Decision Support Tool* associated with the program provide strong insight into current practice gaps. The tool allowed participants to input specific characteristics based on 6 clinical variables for a total of 96 patient case variations. Then the participants were asked to identify their recommended treatment for that specific patient scenario, after which they were shown the treatment choices of 5 experts based on the same scenario and given the same treatment options. The participants were then asked if the expert choices affected their treatment choice. In an analysis of the tool, international physicians entered 330 cases. Of these, physicians changed their treatment choices for 22% of these based on the expert guidance provided by the tool. This group was also able to confirm their treatment choices for 52% of the entered cases with the use of the tool. Note that the new tool will be designed to explore reasons *why* physicians *did not* align their treatment choice with expert recommendations.

These findings indicate that expert guidance through the use of online treatment selection tools can change clinicians' treatment decisions to optimal recommendations, reinforce current optimal practice, and potentially improve patient care. Data showing the results, clear educational impact, and value of the tool was presented as a poster at the 20th Chicago Multidisciplinary Symposium in Thoracic Oncology, September 6-8, 2012, in Chicago, Illinois.[2]

Based on the data from the original tool, physician-specific outcomes and a comparison of expert and participant therapy selection in different patient case

scenarios that demonstrate a divergence in expert recommendations and physician application will be reported in a manuscript that is currently in preparation for submission to a peer-reviewed journal.

The expert faculty involved in the development of the original tool unanimously insisted that the mutation status of the tumor be included for the mutations that were considered to drive oncogenesis when present and for which there were drugs that targeted those specific mutations. These mutations have become known as “actionable mutations” to differentiate from the many mutations that are present in tumors but have no associated treatment. The current actionable mutations in NSCLC are EGFR mutations and ALK fusion mutations. The experts insisted that the tool provide mutation status as positive or negative but not “unknown.” This was because, in their opinion, these mutations had to be assessed in order to select first-line treatment for NSCLC.

For example, Figure 1 shows the comparative choice of targeted therapy by the experts and the participants for a newly diagnosed patient with an identified EGFR mutation. In this situation, all 5 experts recommend erlotinib as a standard of care. In the case of EGFR mutations and ALK mutations as well, all the experts selected the only therapeutic option that specifically targeted the actionable mutation (at the time this tool was developed). This is based on the superior efficacy and toxicity profiles of targeted agents compared with chemotherapy containing regimens that had been the previous standard of care. As can be seen in the tables below, participants using the tool prior to seeing the recommendations had not yet adopted this approach. Compared with 100% of experts in the EGFR mutation case, just 49% of the participants selected erlotinib. Notably, 37% of the participants either recommended no targeted agent or were unsure of which targeted agent to use in this clinical scenario.

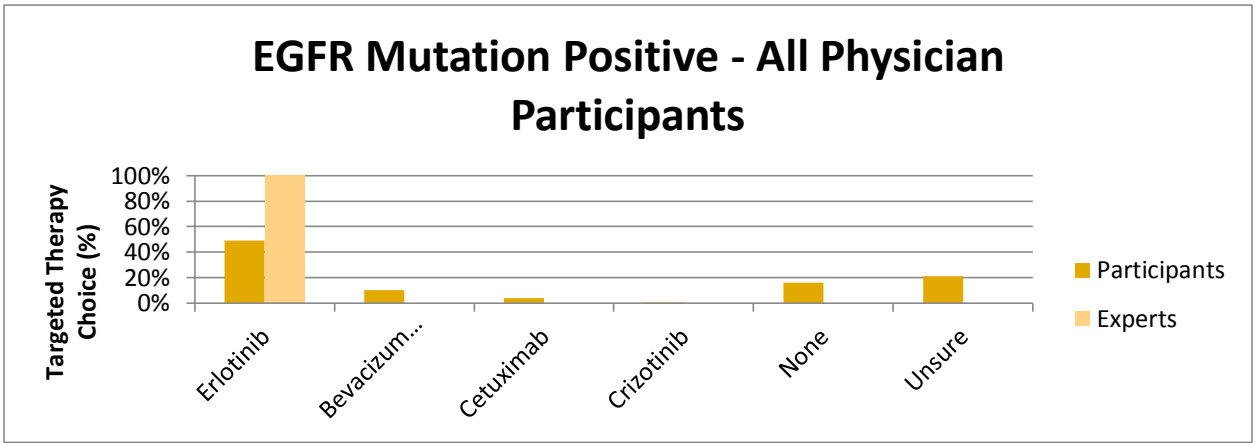


Figure 1. Physician (US and International) choice of targeted agent for advanced NSCLC with a detected EGFR mutation (N = 189 cases).[2]

Similar results were seen in the case of patients with an identified ALK fusion in

which all of the 5 experts recommended crizotinib therapy, again as a standard of care in this subset of patients with advanced NSCLC compared with just 35% of the online participants (Figure 2). At the time of the tool release, 46% of the participants either recommended no targeted agent or were unsure of which targeted agent to use in this type of patient.

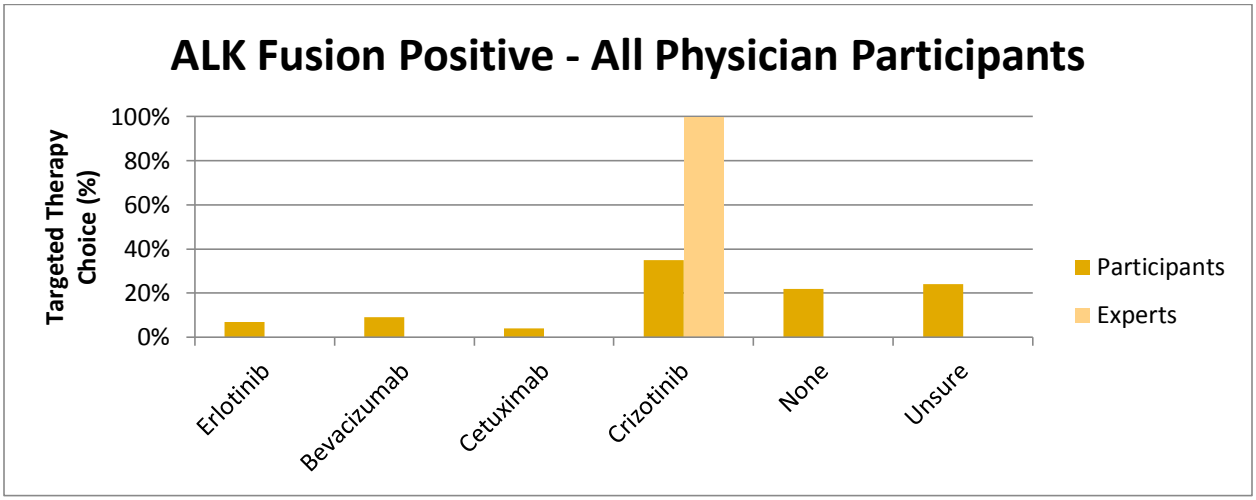


Figure 2. Physician (US and international) choice of targeted agent for advanced NSCLC with a detected ALK fusion (N = 55 cases).

In the absence of either EGFR or ALK actionable driver mutations, there was greater divergence in the choice of therapy with tumor histology playing a significant role. For patients with nonsquamous tumors, 80% of the experts did not use targeted therapy and showed a large preference for chemotherapy with pemetrexed (94%) and carboplatin (88%) (Figure 3). By contrast, carboplatin or cisplatin were used approximately equally by participants who more frequently used paclitaxel and gemcitabine as part of doublet chemotherapy.

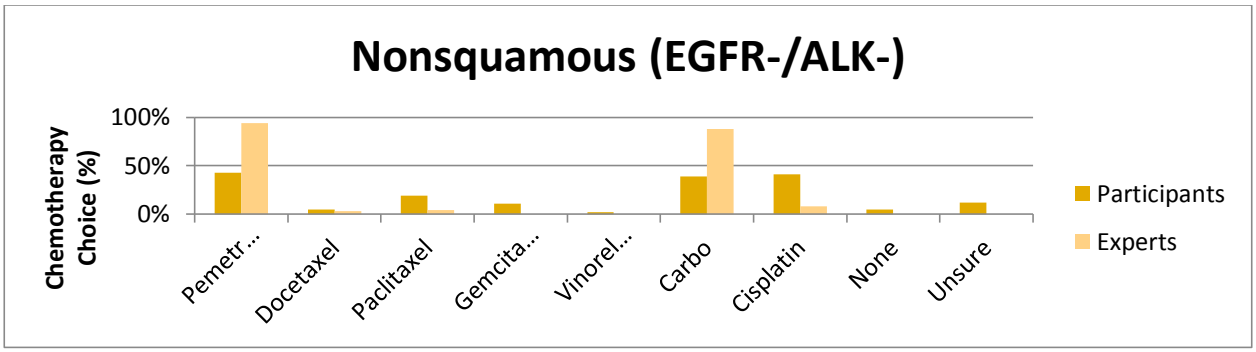


Figure 3. Physician choice of chemotherapy for advanced nonsquamous histology NSCLC without detected EGFR mutation or ALK fusion (N = 244 cases).

For patients with squamous cell tumors, there was also a diversity of first-line targeted therapy and chemotherapy selected by the participating physicians with

19% and 8% being unsure about the choice of targeted therapy and chemotherapy, respectively. Notably, participants rarely selected contraindicated agents for squamous histology (such as bevacizumab [7%] or pemetrexed [3%]) with a predilection to use a cisplatin-based regimen (Figure 4).

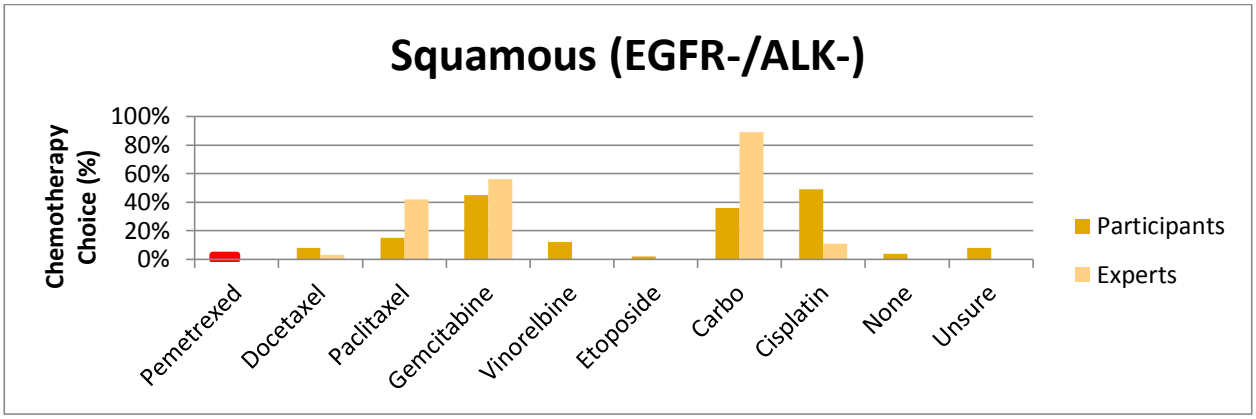


Figure 4. Physician choice of chemotherapy for advanced squamous cell histology NSCLC without detected EGFR mutation or ALK fusion (N = 121 cases).

These results highlight broad clinical practice gaps between experts and participants that were present during the time of the online tool's implementation and therefore, the unique value of this tool in identifying specific areas of focus for continuing medical education and quality improvement initiatives.

References

1. Data on file. CCO NSCLC IVP 2013.
2. Gandara D, Edelman MJ, Giaccone G, et al. Development and utilization of an online tool to guide choice of first-line and maintenance therapy for patients with advanced non-small-cell lung cancer. Program and abstracts of the 20th Chicago Multidisciplinary Symposium in Thoracic Oncology held September 6-8, 2012, in Chicago, Illinois. Abstract 260.

b. Intervention Design and Methods: Following on the success of the 2012 program and to extend and maintain the demonstrated utility of this CME activity and the associated tool, it will be necessary to update both the CME education and the tool in response to new practice-changing evidence such as the approval of new therapeutic agents or the validation of new clinically applicable biomarkers. For the CME activity, expert faculty will provide clinical perspectives on the most important patient and tumor characteristics (eg, histology and biomarkers) to consider in selecting therapy for advanced NSCLC, clinical evidence for best therapy in particular situations (chemotherapy, targeted therapy, maintenance therapy), and examples of best practice. This portion of the educational intervention will be an Interactive Virtual

Presentation (IVP), which consists of a PowerPoint slide presentation enhanced with streaming expert audio narration and "ARS-like" audience polling questions. In a typical IVP, a renowned clinical expert provides audio narration of didactic slides in English that are interspersed with polling questions. Online participants are polled on potential management approaches for a particular scenario. Immediately after the polling, the user is presented with a bar chart that dynamically illustrates how other online participants responded to date. The expert faculty narrator then reinforces this applied learning by discussing the relative advantages and disadvantages of each answer option. The slide presentation then continues until the next question is presented. Therefore, the IVP provides a "virtual classroom" that emulates the environment of a live educational setting in which participants are actively engaged in the educational content. The IVP is posted on the CCO Web site and made available for educational credit to CCO's clinician membership. If updates to the tool are needed during the time the related online CME-activity is active (1 year), this process will be followed: 1) potential updates will be vetted with the faculty, 2) the survey will be repeated with the new variable added, and 3) the new variable and associated faculty selections for treatment will be incorporated into the tool.

To support and augment this education, the *Expert Insight Interactive Decision Support Tool* will allow participants to:

- Enter specific patient and tumor details
- Indicate the anticipated treatment choice for that patient
- View treatment selections of 5 NSCLC experts for that patient

The *Expert Insight Interactive Decision Support Tool* in comparison to typical guidelines are represented in the following table:

	Guidelines	***Expert Insight Independent Decision Support Tool***
Input (ie, how the user interacts)	None	User inputs specific patient and disease characteristics that are important deciding factors in treatment
Output (ie, what the user gets in return)	Static list of options	Customized, dynamically generated report providing treatment recommendations for the patient and disease characteristics input by the user
Discussion of rationale	Relegated to end of document	Integrated into the tool
Granularity: disease characteristics	Good	Good
Granularity: patient characteristics	Poor	Good
Captures participant's	No	Yes

choice of treatment prior to expert advice		
Captures data on whether the new information affects treatment decisions	No	Yes
Optimal use/purpose	1-way guidance when standards of care are clear or consistent	Customized insights in selecting treatment from a longer list of recommended options in patient-specific situations where both tumor and patient characteristics can be important determinants of care

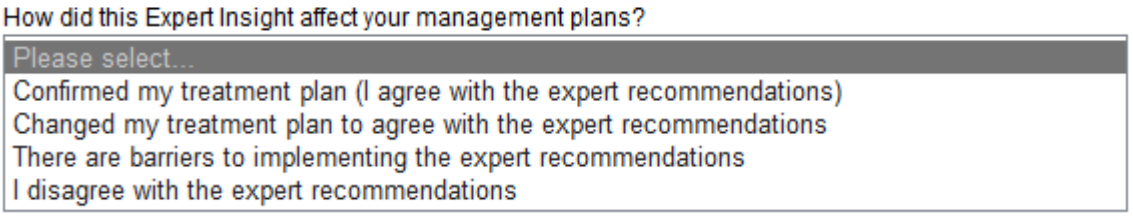
c. Evaluation Design: This program includes an Interactive Decision Support Tool (IDST), designed to facilitate the implementation of current guidelines and best practices. Learners are offered an opportunity to enter specific patient characteristics through a series of drop-down menus and their proposed treatment scheme. In effect, this serves to collect the learners planned treatment at baseline. Once submitted, the learner is then able to review specific treatment recommendations from 5 experts, and is offered an opportunity to reconsider their treatment choice. CCO will analyze the impact of the use of this tool on targeted learners' intent to treat from data gathered during their use of the IDST. All selections made by learners will be collected by CCO for analysis.

Approximately 3 months after the use of the IDST, the learner will be invited by email to participate in a follow-up online survey to subjectively assess change in their performance and its effect on patient health. Question formats may include:

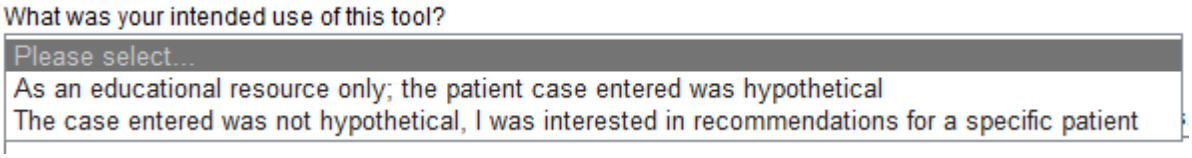
1. Practice change items, typically open-ended or on a 7-point semantic differential scale, tailored to assess learners' change, or degree of change, in their clinical practice
2. Patient health items, typically open-ended or on a 7-point semantic differential scale, tailored to assess changes, or degree of changes, in the health status of their patients

All healthcare professionals who use the IDST and indicate that its use has impacted their treatment choice by selecting any option except "Confirmed my treatment plan (I agree with the expert recommendations)" will be encouraged to take part in the survey. Approximately 5 survey International respondents will also be asked to participate in a follow-up phone interview to obtain a deeper understanding of their practice changes, the barriers that stand in the way of implementation or their disagreement with the expert recommendations. Incentives will be offered for participation in follow-up surveys and phone interviews.

Impact



In addition, the tool will be expanded to capture data on a second question item focused on assessing the real-world impact of the tool, shown below. The completion of these 2 impact questions will constitute the basis for measuring completion of the tool.



Data on the demographics of participants and the results of the educational outcomes gathered using the online survey and phone interviews will also be collected. A report of the findings will be shared with commercial supporters, after sufficient time for data collection, significance analysis, and report writing.

The original program that included the Expert Insight Tool was composed of 3 assets, a CME-certified Virtual Presentation, a noncertified slideset download, and the noncertified Expert Insight Tool referenced above. The Expert Insight Tool did not have a postactivity evaluation, as those are only included on certified activities. A postactivity evaluation that was presented to users of the CME-certified Virtual Presentation and was completed by 139 users out of a possible 2192 physicians for whom credit was available, revealed the following data: **Evaluation Responses:**	
96%	of participants answered "Excellent" or "Good" to "The overall goal was appropriate for the target audience"
96%	of participants answered "Excellent" or "Good" to "The content was evidence based"
96%	of participants answered "Excellent" or "Good" to "The content provided useful information for my clinical practice"
96%	of participants answered "Excellent" or "Good" to "The type and source of evidence was identified"
96%	of participants answered "Excellent" or "Good" to "The activity provided appropriate and effective opportunities for active learning (eg, case studies, discussion, questions and answers, etc)"

94%	of participants answered "Excellent" or "Good" to "The opportunities provided to assess my own learning were appropriate (eg, questions before, during, or after the activity)"
100%	of participants answered "Yes" to "Was this activity fair, balanced, objective, and free of commercial bias?"
96%	of participants answered “Yes, I will implement changes in my practice based on the information presented” or “No, my current practice is already consistent with the information presented” to “Based on this activity, do you intend to change your practice behavior?”
88%	of participants answered "Very confident" or "Somewhat confident" to "How confident are you that you will be able to make your intended changes?"

Regarding data from the Expert Insight Tool itself, a total of 1391 clinicians accessed and used the tool. Of those, 1055 (939 physicians) were based outside of the United States. The table below offers a breakdown of the physician users for the top 15 countries represented within the tool.

Physician Users Based Outside of the United States (Top 15 Countries)	
China (including Taiwan)	107
India	72
Italy	65
Spain	62
Brazil	46
Turkey	45
Germany	30
Argentina	28
Egypt	27
Canada	24
Australia	23
Japan	22
Philippines	22
Mexico	20
France	17

USF Health and CCO are unable to comment on the resource constraints of various countries in the initial version of the tool, but the addition of the second impact question outlined in the Evaluation Design portion should provide valuable insight into those potential barriers.

Previously published data regarding the Expert Insight Tools in NSCLC, breast cancer, and chronic myeloid leukemia have shown that approximately 20% of

users change their planned treatment choice, with another ~45% confirming their planned treatment choice. USF Health and CCO expects to find similar data to that with this NSCLC tool, with the caveat that it may be higher owing to rapidly changing best practices.

i. **Describe how you plan for the project outcomes to be broadly disseminated.**
At a minimum, the results of the tool evaluation will be disseminated through submission as an abstract to a major oncology society meeting such as IASLC, ESMO, and/or the American Society of Clinical Oncology annual meeting. Previous submissions have resulted in poster presentations at these types of meeting. In addition if the data merits publication in a peer reviewed journal, that will also be pursued.

3. ***Detailed Workplan and Deliverables Schedule****:*
In collaboration with USF Health, CCO will work with expert faculty concurrently on the development of the CME-certified IVP and Expert Insight Interactive Decision Support Tool to enable the release of these deliverables at the same time. These activities build upon each other to reinforce guidance on standards of optimal individualized treatment of the disease in the first-line setting. These activities would release within 20-weeks of executed letter of agreement.

After release, participant responses to outcomes and evaluation questions associated with the IVP will be analyzed. In addition, participant responses to the tool and reasons users do not agree or apply the expert's recommendations will be analyzed. The latter information will be submitted as an abstract for presentation at a major medical conference.

To expand awareness of the online deliverables, USF Health and CCO will use an ***online publicity package*** comprising a homepage feature for at least 1 week, site banner rotation for 4 months, 3 email announcements to the entire CCO oncology membership, related links integration, and search optimization on the CCO Web site.

Timeline assumes approval and executed letter of agreement before January 7, 2014.

Deliverable	**Start Date**	**Completion or Delivery date**
Improve and update tool (may be repeated if significant changes are needed within 12 months of publication)		
Invite and confirm expert faculty	10-Jan	27-Jan
Discuss changes with expert faculty	27-Jan	10-Feb
Create survey for the expert faculty	10-Feb	5-Mar

Survey expert faculty	5-Mar	17-Mar
Compile data from expert faculty into tool database and review initial results with faculty as needed	17-Mar	17-Apr
Redesign tool to capture reasons	17-Apr	23-May
Produce tool and prep for online production	23-May	28-May
Publish and host tool	28-May	30-May
Review and evaluate tool		Late Sep
Develop an Interactive Virtual Presentation		
Recruit and confirm expert faculty	27-Jan	10-Feb
Faculty create slides	10-Feb	11-Mar
Record Narration by		14-Apr
Produce online format	13-May	28-May
Publish and Host IVP and downloadable slides on CCO website	28-May	30-May
Analysis and publication of outcomes		
Analyze polling and evaluation data from IVP	July	September
Report polling and evaluation data (1st of 4 quarters)		October
Analyze participant responses to the tool	Mid June	Late January
Submit abstract to major oncology meeting		Early February
Presentation or publication		Late May/early June (ASCO 2015)
Publicize availability of the program		
Email about IVP		July
Email 1 about tool		Mid June
Email 2 about tool		September
Banner ad and other online connectivity		Late May/early June

D. Organizational Detail (Not to Exceed 3 pages)

1. *Leadership and Organizational Capability:*

USF Health (Accredited Provider)

The University of South Florida (USF) created **USF Health** as an enterprise dedicated to making life better by improving health in the wider environment, in communities and for individuals. USF Health has, as its core, the colleges of Medicine, Nursing, Pharmacy, and Public Health, including a School of Physical Therapy. Originally founded as *USF College of Medicine* in 1965, its name was changed to USF Health to reflect its collaborative focus on the full continuum of health. USF Health is *fully accredited by the Liaison Committee for Medical Education.* USF Health collaborates with five affiliate hospitals: Tampa General Hospital, All Children's Hospital, Moffitt Cancer Center, James A. Haley VA Medical Center, and the Bay Pines VA Medical Center. USF Health's most recent partnership with Florida Hospital, combines the Adventist Health System's innovative approach to patient-centered care with USF Health's leading research, to deliver cutting-edge medical therapies in hospital and outpatient settings. Focusing on innovative clinical education, USF Health has partnered with Lehigh Valley Health Network of Allentown, PA to create the Scholarly Excellence, Leadership Experiences, Collaborative Training (SELECT) program. SELECT integrates a dual-campus approach guaranteeing a value-added learning experience. Moreover, USF Health has global outreach through its training agreements with facilities in Panama, Brazil, the Dominican Republic, India, Mexico, Egypt, and Africa.

Continuing education and lifelong learning have always been an integral part of USF Health's educational mission. In 2009, USF Health was awarded Accreditation with Commendation for a second consecutive time by the ACCME for a 6-year term and was recently awarded full accreditation by the ACS as a Level 1 Comprehensive Education Institute. USF Health maintains multiple accreditations by other organizations, such as ANCC, ACPE, APA, ACHE, CHES, and ADA. USF Health is recognized as a leader in research and innovation. The US-Israeli Binational Industrial Research and Development (BIRD) Foundation, which promotes technological research and development collaborations between companies and organizations from the 2 countries, has awarded USF Health and Simbionix™ a grant to develop a simulation module for laparoscopic hysterectomy. In addition, the USF Health Simulation Consortium has recently received accreditation by the Society for Simulation in Healthcare (SSH) for its Assessment, Teaching/Education and Systems Integration. The Consortium earned praise in several areas including the collaborative bond provided to the multiple simulation entities across colleges, and strong educational and training aspects of both the Consortium and of its clinical skills learning center for students.

To fulfill the intent of the conflict of interest standards and guidelines as defined by

the Accreditation Council for Continuing Medical Education (ACCME), Accreditation Council for Pharmacy Education (ACPE), American Nurses Credentialing Center (ANCC) and all accrediting organizations, requests for sponsoring and/or providing of a CME/CE activity submitted to the OCPD, Lead Nurse Planner (as applicable) and USF Health's CPD advisory committee for review must include all completed disclosure forms. Potential conflicts must be identified and resolved prior to convening members of a planning committee or inviting a speaker/author to participate in a CME/CE activity. An individual who refuses to disclose relevant financial relationships will be disqualified from being an activity director, planning committee member, speaker or author for a CME/CE activity and cannot have control of or responsibility for the development, management, presentation, or evaluation of the CME/CE activity. The content or format of a CME/CE activity and its related materials must promote improvements or quality in healthcare and not a specific proprietary commercial interest. Educational materials that are part of a CME/CE activity such as slides, abstracts, and handouts cannot contain any advertising, trade names without generic names or product-group advertising. Presentations must give a balanced view of therapeutic options. Use of generic names will contribute to this impartiality. If the CME/CE educational material or content includes trade names, trade names from several companies should be used and not just trade names from a single company.

Clinical Care Options (Joint Sponsor)

Acting as the joint sponsor for certified continuing education for physicians, nurses and other healthcare professionals, CCO envisions and produces the highest-quality interactive activities and distributes them under its premier brand, Clinical Care Options. CCO is the leader in the development of innovative interactive medical education programs for hematology/oncology clinicians. By providing content in multiple formats, CCO programs meet the readers at their own level of technology adoption, including print, the Internet, Webcasts, and live meetings, to enable them to access the latest data and expert analysis. In addition to a sophisticated editorial staff and medical writers, Clinical Care Options has its own unique models, proprietary technology, and Web sites for the distribution of important state-of-the-art information needed by healthcare professionals. The online program uses CCO's Oncology portal with its already established readership, thereby maximizing the reach and distribution of educational activities.