1. Overall Goal and Objectives:

As part of our mission to transform the future of health by turning science into practical benefit, City of Hope is seeking support for a longitudinal regional project designed to improve the management of patients with metastatic renal cell carcinoma (mRCC) at our hospital and in surrounding communities. The goal of this initiative is to enhance the health outcomes of patients with mRCC by improving physician knowledge of targeted therapies and patient enrollment into clinical trials.

Based on our experience with referrals from community oncologists and urologists managing renal cancer patients and low clinical trial enrollment figures, there is a clear need to educate physicians on dosing guidelines and treatment options for patients with mRCC. Lack of knowledge on new guidelines and the availability of clinical trials may be impacting treatment choices and hindering the provision of optimal care. City of Hope and The France Foundation have designed an educational initiative to address these gaps in clinical practice with feedback provided by our target audience. With funding from the Pfizer, we propose to use a combination of traditional educational mediums such as lectures in combination with innovative strategies that build upon technologies such as mobile phones and web-based e-learning.

The two main objectives of this initiative are to:

- Increase physician adherence to NCCN dosing recommendations for mRCC patients treated in the community
    - As optimal dosing can significantly impact patient outcomes, oncologists and urologists' lack of knowledge regarding recommended guidelines on dosing may reduce treatment efficacy (see section 2a)
    - Introduction of newer, more efficacious and well-tolerated therapies will enable community oncologists to manage various cancer patient at the local level, thereby decreasing the number of unnecessary referrals
- Improve access and visibility of clinical trials for mRCC patients in the community
    - As advancements in oncology research continue to unfold, the role of clinical trials will remain a significant part of patient management
    - Lack of awareness by clinicians regarding available clinical trial enrollment opportunities may limit patients' access to all available treatment options

2. Technical approach

a. Current Assessment of Need in Target Area:

An evolving therapeutic landscape in mRCC

In 1992, interleukin-2 (IL-2) was approved by the US FDA for the treatment of mRCC.[1] Despite the fact that only 5–7% of patients achieved a durable response with treatment, the approval of

[1] McDermott DF, Regan MM, Atkins MB. Interleukin-2 therapy of metastatic renal cell carcinoma: update of phase III trials. *Clin Genitourin Cancer*. 2006;5:114-119.

IL-2 represented a major milestone in mRCC therapy.[2] IL-2 was exclusively administered at experienced centers, given the potential cardiopulmonary toxicities associated with the agent. Patients with newly diagnosed mRCC were therefore frequently referred to academic centers such as City of Hope for IL-2 therapy, and were often simultaneously considered for clinical trials at these sites.

The situation changed dramatically in December 2005, when sorafenib was approved for the treatment of mRCC.[3] This was followed shortly by the approval of sunitinib in January 2006.[4] These vascular endothelial growth factor-tyrosine kinase inhibitors (VEGF-TKIs) abrogate signal transduction pathways that promote tumor angiogenesis, thereby exerting an antitumor effect. In May 2007, temsirolimus was approved for mRCC—this intravenous agent antagonizes the mammalian target of rapamycin (mTOR), downstream of the VEGF receptor.[5] From 2007 onwards, two additional VEGF-directed therapies (axitinib[6] and bevacizumab[7]) and one additional mTOR-directed therapy (everolimus[8]) have been approved. With seven targeted therapies now available, community oncologists have a number of new therapeutic options. In general, the toxicity profile of these targeted therapies is better than that of IL-2[9], and community-based oncologists have achieved a certain comfort level in prescribing these medications.

Treatment of mRCC in the community: Are bad habits emerging?

While the therapeutic index of targeted agents is preferable to that of IL-2, these agents are not free of toxicity. VEGF-TKIs are associated with effects including fatigue, hand-foot syndrome, hypertension, and diarrhea, amongst others.[10] In contrast, mTOR inhibitors are well known to cause stomatitis and metabolic abnormalities.[11] In an effort to mitigate these toxicities, many oncologists have modified the schedule and dose of targeted therapies. Using sunitinib as an

[2] Fyfe G, Fisher RI, Rosenberg SA, Sznol M, Parkinson DR, Louie AC. Results of treatment of 255 patients with metastatic renal cell carcinoma who received high-dose recombinant interleukin-2 therapy. *J Clin Oncol*. 1995;13:688-696.

[3] FDA Approval Letter for Sorafenib. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2005/021923ltr.pdf. Accessed March 2013.

[4] FDA Approval Letter for Sunitinib. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2006/021968s000ltr.pdf. Accessed March 2013.

[5] Hudes G, Carducci M, Tomczak P, et al. Temsirolimus, Interferon Alfa, or Both for Advanced Renal-Cell Carcinoma. *N Engl J Med*. 2007;356:2271-2281.

[6] FDA Approval Letter for Axitinib. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/202324s000ltr.pdf. Accessed May 2013.

[7] FDA Approval Letter for Bevacizumab. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/125085s0168ltr.pdf. Accessed May 2013.

[8] FDA Approval Letter for Everolimus. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/022334s000ltr.pdf. Accessed May 2013.

[9] Hutson TE. Targeted therapies for the treatment of metastatic renal cell carcinoma: clinical evidence. *Oncologist*. 2011;16 Suppl 2:14-22

[10] Grandinetti CA, Goldspiel BR. Sorafenib and sunitinib: novel targeted therapies for renal cell cancer. *Pharmacotherapy*. 2007 Aug;27(8):1125-44.

[11] Malizzia LJ, Hsu A. Temsirolimus, an mTOR inhibitor for treatment of patients with advanced renal cell carcinoma. *Clin J Oncol Nurs*. 2008 Aug;12(4):639-46.

example, common strategies include initiating therapy at a substandard dose of 37.5 mg daily (compared to the standard 50 mg), or utilizing a 3-week on, 3-week off schedule for the agent (compared to the validated 4-week on, 2-week off schedule).[12] Despite the good intentions of the practitioner, these alternative regimens could compromise the efficacy of therapy. A recently published randomized phase II study compared a continuous schedule of sunitinib at 37.5 mg daily to the standard schedule starting at 50 mg.[13] The study suggested a numerically inferior progression-free survival (PFS) with the continuous schedule, suggesting the importance of adherence to dosing guidelines.

Dosing of mRCC therapies has become more complex. As one example, the phase III AXIS study compared axitinib and sorafenib in the second-line setting, and used a novel dosing schema for axitinib.[14] This entailed not only dose reducing for toxicity, but dose increasing for patients who did not incur toxicity after 2 weeks of therapy. While this approach may optimally harness the pharmacokinetic properties of axitinib, it introduces an added complexity for the busy community oncologist. Given that many community oncologists only see 3-4 patients with mRCC each year, it is unsurprising that community oncologists and urologists have revealed a lack of understanding and challenges with appropriate dosing. City of Hope receives nearly 150 consults per year from community practices for RCC and treats approximately 100 mRCC patients annually on an inpatient basis.

City of Hope recently conducted a survey of local community oncologists who will be targeted by this initiative regarding their knowledge on dosing of mRCC therapies, interest in participating in this program, and preferred educational formats. **Results from the survey showed that although majority of participants felt that they were very knowledgeable on the issue of mRCC, most were not able to correctly identify the dosing regimens** (Figure 1). More than half of survey respondents stated that they did not know the dosing for sunitinib and axitinib. None of the respondents were able to correctly identify two ongoing open clinical trials in the Southern California area.

[12] Motzer RJ, Hutson TE, Tomczak P, et al. Overall Survival and Updated Results for Sunitinib Compared With Interferon Alfa in Patients With Metastatic Renal Cell Carcinoma. *J Clin Oncol*. 2009;27:3584-3590.
[13] Motzer RJ, Hutson TE, Olsen MR, et al. Randomized phase II trial of sunitinib on an intermittent versus continuous dosing schedule as first-line therapy for advanced renal cell carcinoma. *J Clin Oncol*. 2012;30:1371-1377.
[14] Rini BI, Escudier B, Tomczak P, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet*. 2011;378:1931-1939.

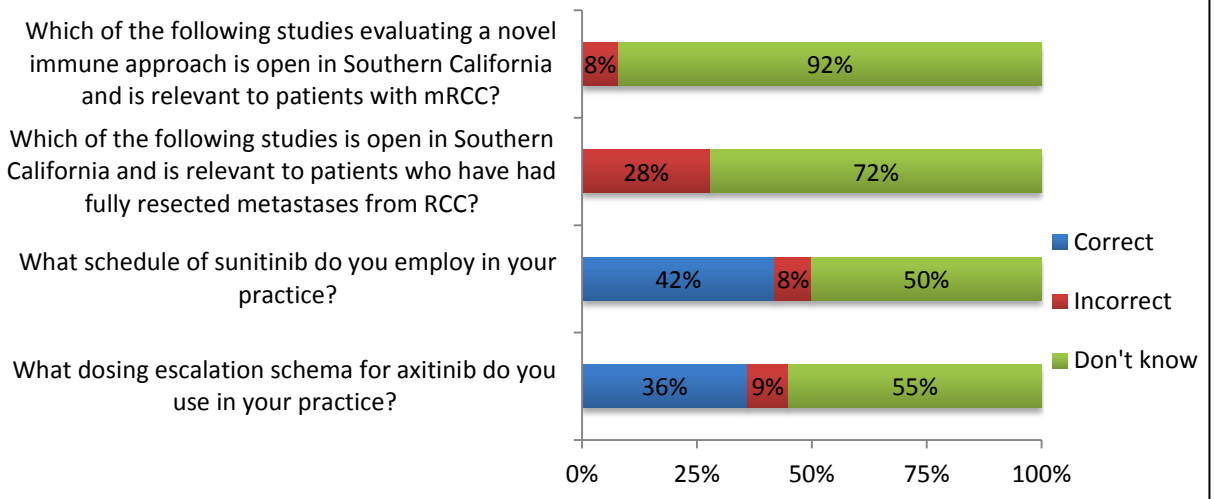


Figure 1: Results from a recent COH survey illustrates the lack of knowledge regarding dosing schedules and available local clinical trails

First-line therapy for mRCC: Moving from academic centers to the community?

Cancer treatment guidelines include clinical trials as an important option for patients with mRCC. With an increasing number of agents that possess a reasonable therapeutic index, patients are increasingly being treated for their illnesses in community-based practices. While patients may certainly receive adequate "standard" care in this setting, the availability of clinical trials is more limited. At City of Hope, we have observed a decreasing proportion of patients referred for first-line clinical trials from 2009 onwards, and many of these patients do not have access to clinical trials within the community-based practices (Figure 2). The current ratio of accrual to first-line studies (accruals: # of studies) is 2:1. In contrast, the ratio of accrual to studies for refractory patients is 9:1. The decrease in clinical trial enrollments is a common theme across many institutions, and poses an impediment to the implementation of new and effective treatment approaches. Unless accrual to first-line studies is improved, it is challenging to envision the initial approach to mRCC improving. Studies are increasingly done outside the United States, as demonstrated by the recent TIVO-1 study (assessing tivozanib as first-line treatment[8]) and it is unclear whether this data is relevant to a US population.

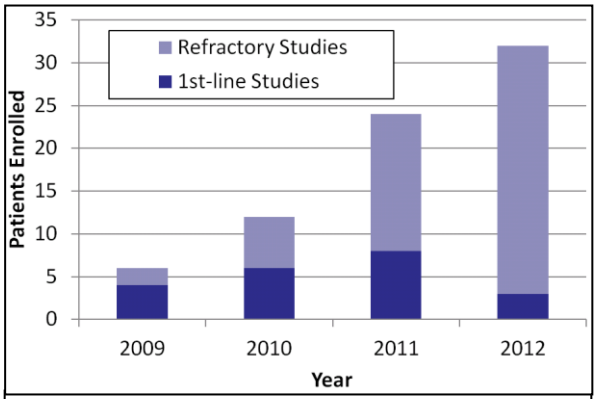


Figure 1: Changing accrual patterns at City of Hope. From 2009 to 2012, a marked decrease in the proportion of patients onto 1st line studies has been observed despite a similar number of available studies for 1st line and refractory patients.

The Primary Audiences: The primary audience for this initiative will be oncologists, urologists and other healthcare providers who are treating mRCC patients. Participants will include, but are not limited to:

- City of Hope clinicians
- Community oncologists and urologists in private practice
- Community hospital oncologists and urologists

Although interested oncologists or urologists from any hospital may participate in the educational sessions, we will focus on 10 community hospitals that represent both the closest hospitals to City of Hope and the largest sources of oncology referrals (see Figure 3). All of these hospitals serve hundreds or thousands of cancer patients annually based on OSPHD data for 2011 and several target a predominantly disadvantaged and underserved population.

- Methodist Hospital of Southern California, a 460-bed facility in Arcadia, serving over 1,300 cancer patients annually
- Queen of the Valley Hospital, a 325-bed facility in West Covina, serving over 800 cancer patients annually*
- Garfield Medical Center, a 210-bed acute care facility in Monterey Park, serving almost 800 cancer patients annually
- Huntington Memorial Hospital, a 625-bed hospital in Pasadena, serving over 2,400 cancer patients annually
- Santa Teresita Hospital
- Foothill Presbyterian Hospital-Johnston Memorial, a 105-bed facility, serving over 400 cancer patients annually*
- Citrus Valley Medical Center, a 193-bed facility in Covina, serving almost 700 cancer patients annually*
- Methodist Hospital
- Beverly Hospital, a 224-bed acute care facility in Montebello, serving over 600 cancer patients annually
- Antelope Valley Hospital, a 420-bed acute care facility in Lancaster affiliated with City of Hope, serving over 1,200 cancer patients annually

*These hospitals are all members of the Citrus Valley Health Partners network, which will facilitate collaborative education and information sharing at these locations.

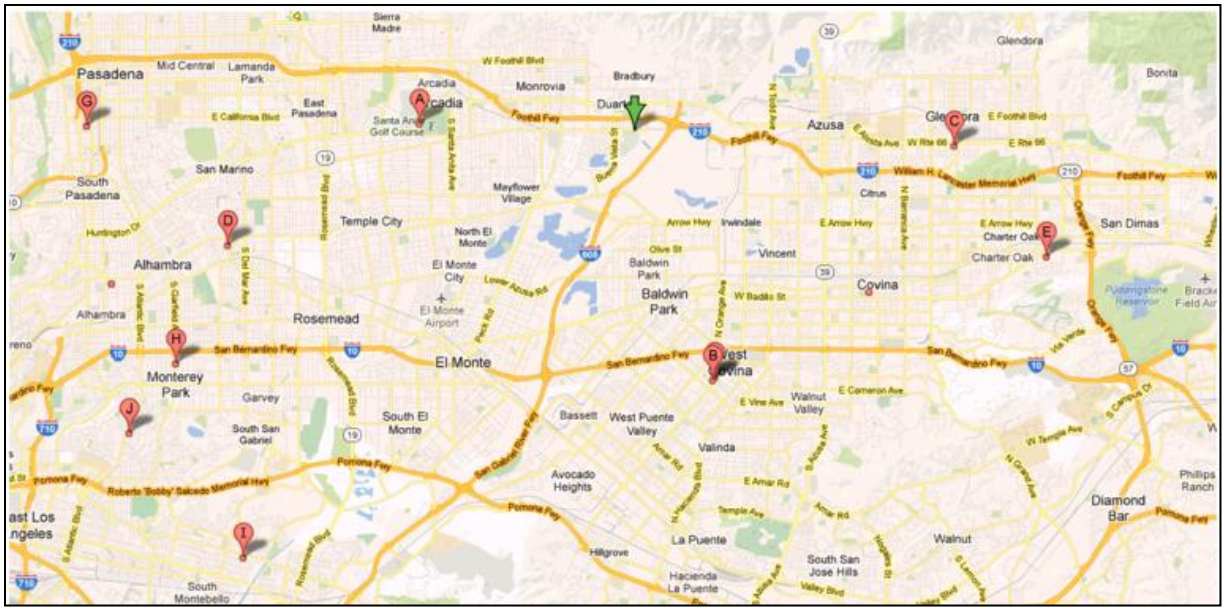


Figure 3: Study site for the proposed intervention. A total of 10 community hospitals that serve as a major source of oncology referrals to City of Hope have been selected (red arrows). These are the nearest hospitals to the City of Hope (green arrow).

b. Intervention Design and Methods:

The proposed educational initiative will be tailored to meet the specific needs of community oncologists. It will be announced via e-blast to 1,775 clinicians who have previously participated in City of Hope's CME programs as well as a purchased list of area oncologists, urologists and select internists. The teaching intervention will address the two deficiencies highlighted in the previous section and will be offered in educational formats selected by the clinicians who responded to our initial survey. During the survey conducted by the City of Hope, local oncologists and urologists identified in-person programming, web-based education with an interactive component, and short podcasts as their preferred methods of receiving information.

Enrollment in the program will require clinicians to participate in at least four of the monthly events, attend a grand rounds lecture, and receive all the additional tools provided by the initiative (app, website, podcast, emails). This initiative will include the following elements:

Steering Committee

A Steering Committee of up to 10 members will be formed to guide the development of this initiative. The Committee members will consist of City of Hope faculty and staff as well as local oncologists who are considered national experts in the field of mRCC. The Steering Committee will meet shortly after grant approval to refine plans for the project. This group of experts will be tasked with outlining the curriculum, identifying guest speakers, defining outcomes criteria, and liaising with community hospitals and oncology practices to promote physician engagement. The steering committee will , ask each hospital make a commitment to participate, publicize the program, and potentially host educational sessions at their medical center

Visiting Professorship: Opportunities to Engage National Experts

As part of our commitment to sharing best practices in the management of patients with cancer and other life threatening diseases, City of Hope hosts an extramural event each month with a nationally recognized faculty speaker. Held on campus on the first Thursday of the month, it is broadcast free online and usually attracts 40-50 participants from the oncology community.

In order to build upon existing educational methods that have a proven track record of attracting learner participation, this initiative will feature presentations on both novel mRCC therapies (i.e., PD-1 inhibitors, MET inhibitors, etc.), practical dosing guidelines and recommendations, and systems based improvements to optimize patient outcomes. One Thursday lecture every quarter will be dedicated to this initiative. Education presenting best practices from individual patient cases will assist in bridging the science of guidelines to real-life cases. Based on past experience with these presentations, participants are interested in learning from national experts and having the ability to ask questions relevant to their practice. Speakers will be a combination of City of Hope faculty as well as nationally recognized leaders in cancer treatment.

While topics and speakers will be finalized by the steering committee, suggested topics for presentations include:

- Overview of RCC (kick-off presentation for the initiative)
- Novel agents for mRCC
- Ongoing clinical trials for mRCC
- Novel mechanisms of RCC pathogenesis: Implications for treatment

Each meeting will be accredited for 1.5 *AMA PRA Category 1 Credits™.*

Live and Archived Webcasts

As participants have identified web-based programming with an interactive component as a preferred educational modality, the Visiting Professorship programs will also be offered as a live webinar where online participants will be able to submit questions in real time to speakers. These webinars will remain available online as archived webcasts. Participants who complete the pre and post education assessments will be eligible for 1 *AMA PRA Category 1 Credits™* per webinar. This is a feature that the City of Hope has offered its CME participants in the past which has been widely successful, based on the number of people accessing these webcasts as well as feedback from attendees.

Grand Rounds

To foster collaboration with community hospitals, each of the 10 targeted hospitals will be offered the opportunity to host an expert speaker. Presentations will specifically be focused on preliminary clinical trial results, availability of trials within the community, and a case-based discussion on the role of clinical trials within the treatment paradigm of mRCC patients.

In order to maintain a sustained level of learning, attendees of the grand round will have the option of signing up on a website created for this initiative and receiving electronic reminders. Grand rounds lectures traditionally attract 50-75 clinician attendees. Each grand rounds lecture will be accredited for 1 *AMA PRA Category 1 Credits™.*

Spaced Education: Podcasts, Apps and Mobile Webpage

Spaced education is a novel, evidence-based form of online education that provides learning reinforcement over time to ensure retention of knowledge and behavior change. Online spaced education following a live CME course has shown to significantly increase the impact of a face-to-face course on providers' self-reported global clinical behaviors.[15] In this initiative, we will use short 5–10 minute podcasts to provide spaced education following participation in one of the live activities. These short updates can inform learners about treatment guidelines using a case-based model. Podcasts will highlight dosing recommendations for each targeted agent, with further selections for recommended dose increases and decreases based on toxicity. These podcasts will be available on a mobile phone or tablet compatible webpage.

Another form of spaced education will be "Rapid Recap" emails that will be sent 5 days following the live lecture. These brief reminders will offer recipients the key points of the lecture in an easily accessible format.

In addition to the podcasts, this website will host other existing resources including a clinical trial identifier app (Clinical Trial SEEK) in which clinicians can input specific features of a patient, yielding a list of clinical trials for which they are candidates within the local area. Supporting educational materials will include: (1) practical and appropriate dosing of medications along with the consequences of inappropriate dosing; (2) National Comprehensive Cancer Network guidelines; (3) clinical trial information ranging from adjuvant therapy to first-line therapy to treatments for refractory disease. To provide maximum access to this website, the City of Hope app will be updated to include special links to this initiative. This app is currently already being used by clinicians and will direct participants to the educational materials and tools provided by this initiative.

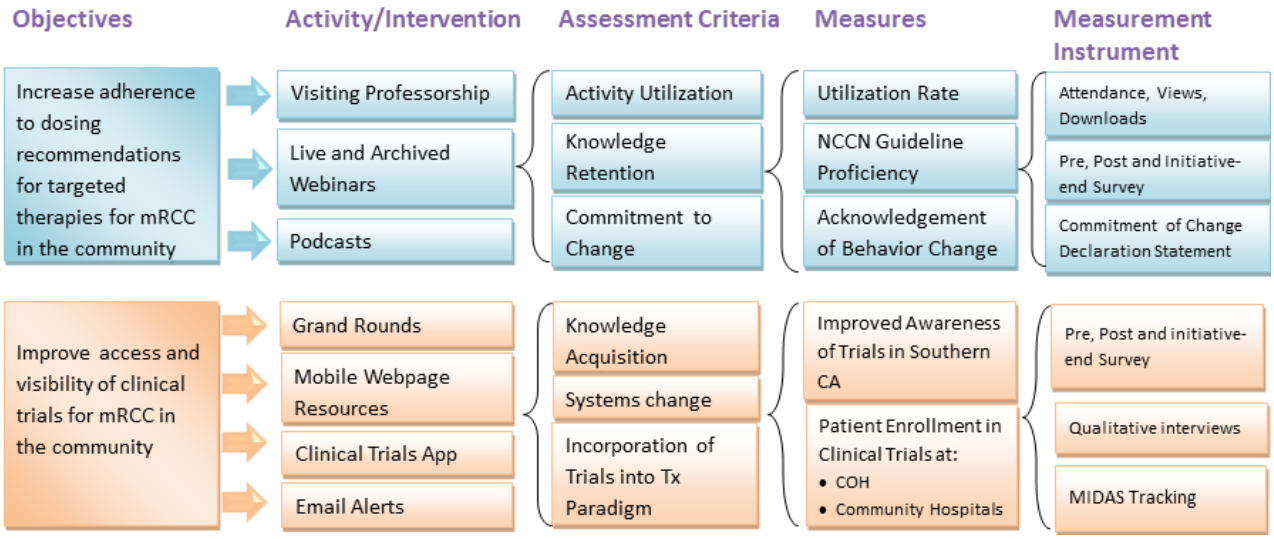
These podcasts and online tools will further support the ongoing decision-making process to assist clinical performance beyond acquisition of knowledge. These tools will be specifically designed to address local clinician needs in order to maximize patient outcomes.

[15] Shaw T, Long A, Chopra S, Kerfoot BP. Impact on clinical behavior of face-to-face continuing medical education blended with online spaced education: a randomized controlled trial. *J Contin Educ Health Prof*. 2011 Spring;31(2):103-8.

2C. Evaluation Design

Our intervention is designed to assist healthcare practitioners in reviewing and integrating clinical data into the patient care setting by building on what learners currently know; giving them ownership of their learning; encouraging interactivity; using multiple modalities to aid learning transfer; and providing reinforcement over time. This educational initiative has been designed based on adult learning principles to ensure that participants not only acquire medical knowledge, but also have the skills and motivation to apply it to every day practice. As illustrated in Figure 4, we have designed a comprehensive evaluation plan to quantify the impact of the initiative on changes in physician knowledge and behavior. Evaluation metrics will include both objective data variables as well as subjective learner self-assessments as outlined below.

Figure 4: A Comprehensive Assessment Plan Designed to Evaluate Initiative Impact



Clinician-Level Outcomes Measurement

A pre- and post-study survey will be administered to the oncology clinicians participating in each activity to assess overall knowledge, competence, and practice behaviors related to their management of patients with mRCC. Assessments will include both quantitative and qualitative evaluations, including changes in physician knowledge; stated changes in physician practice; and an evaluation of commitment to change. Participants will be asked to write down one to three changes that they plan to make as a result of our activities, since these commitments have been shown to predict actual change in practice.[16,17] Post activity surveys go further in measuring change by identifying performance based change. At the end of the initiative, participants will be surveyed again to assess retention of knowledge and whether they have

[16] Lockyer, J, Fidler, H, Hogan, D, Pereles, L, Wright, B, Lebus, C, Gerritsen, C. Assessing Outcomes Through Congruence of Course Objectives in Reflective Work. *JCHEP* 2005; 25: 76-86.

[17] Lockyer, J. M., Fidler, H., Ward, R., Basson, R. J., Elliott, S. and Toews, J. Commitment to change statements: A way of understanding how participants use information and skills taught in an educational session. *J Contin Educ Health Prof*. 2001, 21: 82–89

implemented their commitments to change. Raw scores from surveys at the beginning of each educational program and end of the initiative will be compared using the student's t-test. Descriptive statistics will also be used to demonstrate physicians' varying degrees of behavior change and knowledge gains by subject area (i.e., drug dosing *versus* clinical trial awareness). Descriptive statistics will also be applied to determine which changes in practice have been most profound and any differences by hospital, physician specialty, or other key factors.

The expected level of change from baseline to intervention for the key activities is as follows:

- All participating physicians will demonstrate some increase in knowledge of NCCN guidelines. Current data based on a recent City of Hope survey indicates that less than 40% of community oncologists can accurately identify dosing recommendations. By the conclusion of this initiative, we expect 80% of participants to be able to correctly identify one or more of the follwoing:
    - Axitinib dosing escalation schedule
    - Schedule of sunitinib
    - Dose reduction schema for everolimus
    - Dose reduction schema for temsirolimus
    - Appropriate dosing pattern for pazopanib and sorafenib (i.e. qd and bid, respectively)
- Approximately 65% of clinicians will implement changes in practice based on their commitment to change statements
- All participants will be able to identify at least one clinical trial within the Southern California region by the end of the initiative, versus none of the physicians who completed the survey.

System-Level Outcomes Measurement

Participants enrolled in the initiative will be asked to complete a baseline assessment survey including questions specific to knowledge on guidelines and utilization of clinical trials. These questions will be repeated as part of a final survey along with subjective questions about system level changes including changes in medical care implemented as a direct result of the education received from this initiative. Questions will evaluate variables such as changes in treatment, use of guidelines prompts and apps, involvement of ancillary staff, and patient education. A sample of 10 community oncologists will be invited to participate in a detailed qualitative interview to evaluate their experience with the initiative and to explore further gaps in the community that may prevent optimal patient outcomes. These interviews will evaluate the clinician's subjective reporting of the initiative's effectiveness, applicability to practice, and ability to motivate individual and system level changes. This feedback will help structure any future education initiatives that City of Hope chooses to facilitate.

Community-Level Outcomes Measurement

Clinical trial accruals will also be tracked closely during the intervention period by assessing the numbers of patients accrued at City of Hope; the number of referrals from the 10 community

hospitals; and enrollment into first-line versus refractory studies. Electronic tracing of clinical trial accrual is done via the Medical Information Database Analysis System (MIDAS). This is an online tool that allows for storage of clinical and biologic information. It is also used to regularly generate accrual reports at our institution. The chi-square test for proportions will be used to compare patients enrolled in clinical trials per open trial during the year preceding the intervention (i.e., January–December 2013) as compared to the year following the intervention (i.e., January–December 2015). (Note: Due to budget constraints, this initiative will not include a separate control group. The pre-intervention data will serve as the baseline that the post-intervention data will be compared against.)

Outcomes Reporting

Outcomes will be reported in *Inside Hope,* the hospital's semiannual magazine, featuring the latest advancements in research and treatment, important news and announcements, events, donor and volunteer recognition, and board and executive appointments. Additionally, the principle investigators of this study (Dr. Pal and Dr. Morgan) will work on publishing the results within an oncology journal. We will target journals such as the *Journal of Oncology Practice* which provides oncologists and other oncology professionals with information and tools to enhance practice efficiency and promote a high standard for quality of patient care.

3. Detailed Work Plan and Deliverables Schedules

Fall/Early Winter 2013: Following the execution of the grant agreement with Pfizer, a steering committee meeting will be convened at City of Hope. The goal of the meeting will be to ensure that the overall framework, details, and general timelines are confirmed and in place for this initiative. Outcomes measures and measurement tools will be finalized and a clear action plan for statistical analysis of the data will be outlined. The committee will also draft a list of possible guest speakers and finalize topics for the Grand Rounds and Visiting Professorship lectures.

Winter 2013: Steering committee meeting members will be tasked with promoting the initiative to the local community hospitals and securing physician participation in educational activities. The mobile compatible website and app development will begin. Content for the project website hosted by City of Hope will be updated throughout the initiative duration.

Early Winter 2014–Summer 2015: Six Thursday night lectures and Grand Rounds will be conducted. The France Foundation will assist City of Hope CME staff and faculty in the development of presentations and ensure that they meet the criteria for ACCME accreditation. City of Hope and The France Foundation will assist in the creation of any additional educational materials, under the guidance of the steering committee faculty, including the podcasts, email updates, and mobile website.

Summer 2015: Collection of post intervention survey, clinical qualitative interviews, and clinical trial accrual data will occur. City of Hope and The France Foundation will work together to collect, assess, and create an outcomes document for this project that will be published online and in *Inside Hope*. Based on the outcomes of this initiative, faculty will determine a publication plan including submission of manuscript to relevant journal(s).

	2013	2014				2015		
Deliverables	**Q3/Q4**	**Q1**	**Q2**	**Q3**	**Q4**	**Q1**	**Q2**	**Q3**
Steering Committee	Steering committee meeting; Promotion of program							
Visiting Professorship	Scheduling	X	X	X	X	X	X	
	Development of slides							
Live & Archived Webinars		X	X	X	X	X	X	
Grand Rounds	Scheduling Slides development	X	X	X	X	X	X	
Mobile Webpage App	Programming	Continuous update with available materials						
Podcasts		X	X	X	X	X	X	
Outcomes	Finalize measures; Pre-intervention trial accrual data collection	Pre- and post- education surveys following each program					Final participant survey; Qualitative interviews; Post-intervention trial accrual data collection	Final report