Clinical Trial Design in the Era of Genomic Medicine

A symposium designed to help advocates influence cancer clinical trial design in multi centered research.

SYMPOSIUM SUMMARY

Input from advocates during the design phase has made a difference in the outcomes of cancer clinical trials. Advocates are key stakeholders in clinical trials and are being asked to be involved in the design of clinical trials at earlier stages but need to be prepared and trained for this involvement. On November 20-22, 2013, Research Advocacy Network hosted a symposium for advocates to address this need for earlier advocate input. Conveners invited advocates involved in multi institution clinical trials with the NCI Cooperative Groups and NCI Steering Committees to participate in this unique opportunity.

Objectives for the symposium were to:

- Understand why cancer clinical trials need to be designed differently in the genomic era;
- Identify the elements of clinical trial design that need to change and how;
- Understand the difference between traditional empiric clinical trial design and a rational target-based approach;
- Identify ethical issues that result from these new approaches;
- Improve communication skills to better articulate the patient perspective.

Opening Presentation

The Symposium's opening presentation "Clinical Trial Design in the Era of Genomic Therapy" was delivered by Dr. George Sledge, former President of the American Society for Clinical Oncology (ASCO) and current Chief of Oncology in Stanford's Department of Medicine. Dr. Sledge began by discussing the new challenge we face—one that may seem overwhelming, yet is also full of promise: i.e., *the challenge of the genomic era.* In contrast to 10 years ago, when most treatments comprised local-regional and nonspecific systemic therapies, nearly all new cancer drugs are now targeted agents. Dr. Sledge explained that the numbers of targeted therapeutics that have exploded in the last decade are based on a fairly simple principle: identify the cancer's molecular driver of growth in the laboratory, measure that driver in the laboratory, and disable the molecular driver with a specific targeted therapy. Dr. Sledge also discussed "the implications of the $1,000 genome," where the costs associated with genomic sequencing will continue to decrease and such technology will therefore become more widely available. Every cancer informs our understanding of tumor biology. Dr. Sledge stressed that our traditional clinical trial designs are not designed to address the complicated nature of this new genomic chaos, noting that:

- The emphasis has traditionally been on the study of single agents.
- Combination trials to this point have not been biomarker-based; rather, biomarkers development has been secondary.
- Traditional regulatory mechanisms have been ill-suited to modern biology.
- There is a need for a **"Next-Gen" clinical trials system** with the following components:
    - Therapeutic individualization based on personal genomics
    - Real-time bioinformatics
    - A health information technology (HIT) network supporting clinical trials and cancer care delivery
    - Increased collaboration
    - Trial design focused around multi-targeting
    - Redesign of informed consent for trial participants
    - And a fundamentally different regulatory apparatus

Dr. Sledge shared his final thoughts, quoting words of wisdom from science fiction writer, William Gibson, who was exalted for his ability to depict futures that were right around the corner:

"The future is already here—it's just not evenly distributed."

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Slide Handouts: http://www.screencast.com/t/WdFqrXv2h

Keynote Address

Professor Rebecca Dresser presented the symposium's keynote address on the ethics of clinical trials in the genomic era. Professor Dresser, an expert in biomedical ethics, holds a joint appointment with Washington University School of Medicine, where she teaches law and medical students about ethical and legal issues in genetics, biomedical research, end-of-life care, and additional related topics. She is also an author of a book on patient advocacy and research ethics and serves on the editorial or advisory boards of multiple journals dedicated to bioethics.

Professor Dresser presented a historical perspective on what has been termed the "participatory research movement" and the true ***scientific value*** that results from such engagement of patients in clinical research design and conduct, including:

- The impact on increasing the public health value of the research conducted
- The provision of critical information on **which** health problems should be studied: What is truly important to patients? What questions are worth addressing in clinical research?
- Practical guidance in research design
- Information relevant to an optimal study approach

Professor Dresser emphasized that there are numerous ***ethical reasons*** for inclusion of patients in clinical trial design, conduct, and evaluation, including to:

- Ensure that the interests of the trial participants are **central** to the study.
- Improve the content and methods that are designed in the trial to promote informed choice concerning research participation—i.e., to ensure that patients **truly** understood the potential harms and benefits of participation, the scientific rationale for the trial, and their rights as patients.
- Bring their general knowledge about research from a prospective participant's perspective: What is it actually like to participate in a study?

- Determine whether the research benefits justify any potential risks to trial participants. In bringing their perspectives as engaged patients and research advocates, patients will likely bring an awareness of risks to trial participants that might have otherwise been overlooked.

She also noted several ***practical considerations*** for inclusion of patients in clinical trial design and conduct, including:

- A possible increase in patients' willingness to join clinical studies
- A potential increase in participants' cooperation and adherence with study requirements (crucial for ensuring the quality, accuracy, and robustness of trial data)
- A possible increase in participants' willingness to complete trials (also a critical consideration, since "drop outs" and "loss to follow-up" far too commonly impact the reliability of trial data)

She emphasized that engaging educated patient advocates in clinical trial design may provide an important "reality check" on areas of a protocol that may make patients less likely to participate or to stay in trials. They bring knowledge of what matters to patients and participants, including reasonable study requirements and high-quality research staff.

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Slide Handouts: http://www.screencast.com/t/jHPyULVuyrZG

Overview of Clinical Trials

Dr. Stephen Hirschfeld, Captain of the U.S. Public Health Service and Associate Director for Clinical Research at the Eunice Kennedy Shriver National Institute for Child Health and Human Development (NICHD) outlined the rationale for clinical trials, noting that such trials are the only way to obtain the necessary data, since non-clinical data may not be applicable and/or cannot be extrapolated. He stressed that clinical trials are necessary because "We need the data, and to remove the bias and uncertainty." He also discussed clinical trial design and described different methods of trial analyses including adaptive design.

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Slide Handouts: http://www.screencast.com/t/OHgc5DjajZ

Endpoints in Clinical Trial Design

Dr. Hirschfeld also gave a second presentation, which focused on the **outcome measures** known as **endpoints** in clinical trials. A clinical trial endpoint is a measure that helps to determine whether the hypothesis of the trial should be accepted or rejected. Endpoints are used to determine whether the intervention enables patients to live longer (increased survival), live better (enhanced quality of life), or both when compared to standard therapy. The size of a trial is determined by the power needed to detect a statistically significant difference in the primary (or most important) endpoint. Generally, endpoint data is obtained from observations or reports. Reports may be obtained directly from the patient or indirectly from someone else. In oncology, observations or reports may pertain to the patient, the malignancy itself, or both. Dr. Hirschfeld cautioned that measures of changes in the malignancy may not reflect comparable changes in the patient and vice versa.

In 2001, the National Institutes of Health Definition Working Group defined the following important terms:

- **Clinical endpoint:** a characteristic or variable that reflects how a patient feels, functions, or survives.
- **Biomarker:** a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention.
- **Surrogate endpoint: a** biomarker intended to substitute for a clinical endpoint that should predict clinical benefit or harm or lack of both.

Dr. Hirschfeld explained that biomarkers need to be **qualified,** meaning that the assessment results must be reproducible, consistent, and independent of whom is performing the assessment or where the assessment is done. Surrogate markers also need to be **validated** which requires clinical studies where the biomarkers are measured. Dr. Hirschfeld summarized the challenges associated with the use of biomarkers as surrogate markers. He then discussed the many factors that must be fulfilled in order for an endpoint to be useful in clinical trials. He cautioned that the integration of all evidence is required to understand potential benefit and risk and concluded, ***"Make no assumptions: if something is not measured well, its status is unknown."***

Recorded replay (audio only): http://www.screencast.com/t/sHbEEv1H
Slide Handouts: http://www.screencast.com/t/OHgc5DjajZ

Innovative Clinical Trial Design

Donald Berry, PhD, Professor in the Department of Biostatistics at the University of Texas MD Anderson Cancer Center, Houston, Texas gave an overview of innovative clinical trial design. Dr. Berry stressed that in the genomic era, where we now understand that every cancer has its own unique set of molecular changes, "we're slicing and dicing each disease to the extent that each patient has his or her own disease." With this comes the complex challenge of how to go about developing therapies.

The use of adaptive clinical trial design offers a more appropriate alternative to traditional clinical trials for complex studies that ask multiple questions. In fact, an increasing number of sponsors are adopting adaptive clinical trial design for that reason, since they allow trial-design elements to be modified at predetermined times and under specific conditions outlined prospectively in trial protocols.

With traditional clinical trials, when the results are finally obtained, it's not unusual for such data to suggest that the trial should have been planned differently. In contrast, adaptive design allows those designing the trial to predict what they would wish to have known at the end of the trial—or, said another way, to anticipate what they would have regretted *not* including in the trial design (e.g., different doses). With adaptive design the trial "looks at data as it accrues," sequentially updating what is known about the agent being studied. With every observation, the data changes what we know, providing new information and updating our knowledge. He emphasized that "During the trial, you can look every day at every patient. With the information you obtain, uncertainty becomes less, and precision improves." In designing the trial, "you can ask, 'What is the probability of this future observation (success or failure)? We can ask the question of 'Where is this trial taking me? What is the end result? What is the probability distribution? Could the probability be so small that it's better to move on and do something else?' "And if a success, [this data] promotes graduation to a confirmatory trial."

Bayesian statistics

"Bayesian" refers to a branch of logic applied to decision-making and statistics dealing with probability inference. In other words, Bayesian statistics provides a mathematical method that uses knowledge of prior events to predict future events. In clinical trials, occurrences in prior trials can be used to calculate the probability of the targeted occurrence in future trials.

BATTLE trial in lung cancer

Dr. Berry used the "Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination" trial as an example of the benefit of adaptive randomization in trials. The BATTLE study was the first completed, prospective, biomarker-based, adaptively randomized study in chemorefractory non-small-cell lung cancer (NSCLC) patients. This study showed:

- Adaptive clinical design can be effective in complex studies that investigate multiple biomarkers and several novel agents and require tissue collection from participants.
- Adaptive clinical design can improve clinical trial approaches to simultaneous development of novel agents with matching diagnostic tests and in the identification of those patients most likely to benefit from such agents.
- Real-time core biopsies and molecular biomarker analyses are safe and feasible.
- Biomarker analyses and associated treatment assignment can prospectively guide clinical trial design and direct therapy assignment.
- Trial outcomes data helps to characterize predictive value of biomarkers for agents with associated mechanisms of action.

Basket Trials

Dr. Berry discussed "Basket trials"--where, rather than beginning with multiple clinical trials in different diseases, one trial, "the basket," is established, testing the same novel agent in different cancers based on the same biomarker, enabling enrollment of patients with multiple cancers expressing the target. If one disease group shows a beneficial response, this group may then be expanded; in contrast, if another group is showing no evidence of efficacy, that arm may then be stopped for futility. Such basket trials enable exploration of efficacy of a novel agent early, quickly, and in one trial with multiple diseases.

Decision Analysis and Rare Diseases

Noting the "ever finer grid of biomarker categories" that we're now able to identify for patients' cancers, Dr. Berry noted the "approaching wall," where within 10 years, every cancer patient will essentially have an orphan disease. (The definition of "rare disease" varies from country to country and is related to the population size of the country.) This leads to the critical question of how to develop drugs, establishing safety and significant efficacy, in this setting?

In shifting toward personalized medicine, the goal is to match patients with specific biomarkers to those treatments most likely to be effective. Dr. Berry then discussed **Bayesian hierarchical modeling** of patient subpopulations, where treatment effects in certain subpopulations may provide data concerning treatment effects in other patient subpopulations. A hierarchical model across patient groups allows a decrease in the mean sample size with increased power and is thus likely to correctly determine efficacy or futility and differential effects in different patient subpopulations.

He noted the standard approach used in determining a sufficiently powered patient sample size and how this traditional approach cannot be correct for rare diseases that by definition affect small numbers of patients. Dr. Berry indicated that regulators and investigators have acknowledged this

and have made some necessary adjustments, including accepting smaller studies for rare diseases, considering disease severity, and requiring stronger evidence of effectiveness for highly invasive or toxic agents. Yet the challenges remain: i.e., in determining 1) How small? 2) How severe? 3) How strong?

So for rare diseases, increasingly including cancer patient subgroups based on molecular biomarkers, smaller trials are accepted. But what size is appropriate? Is randomization even possible? Dr. Berry stressed that decision analytics in clinical trials is directed toward delivering good medicine to patients—but he then posed a series of critical questions: "Which patients? How do we determine the size of the trial? You want to learn, but not too much. You want to treat as many patients as effectively as possible. So what would be the ideal sample size? How do we learn but not waste observations?"

Dr. Berry concluded by asking:

"How do we not waste patients whom we could effectively treat?"
"Can advocates influence the way we think about the purpose of clinical trials?"

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Slide Handouts: http://www.screencast.com/t/TJjHturk7X

The NCI's MATCH Trial: Molecular Analysis for Therapy CHoice

Robert Catalano, Pharm.D, vice president for regulatory affairs for the Coalition of National Cancer Cooperative Groups and the regulatory officer for the ECOG/ACRIN Cancer Research Group, and the director of scientific affairs for the Clinical Trials Research Center at the Drexel University College of Medicine, presented information on the NCI's MATCH trial as an example of innovative new trial designs to enhance the quality and efficiency of drug development and approval. Using an umbrella protocol design, the MATCH trial will comprise multiple Phase II single-arm trials where patients whose tumors are in a defined molecular subgroup will be matched to a novel targeted agent.

Dr. Catalano described the MATCH trial as a master screening trial to identify patients with mutations and amplifications in molecular pathways that are targetable by existing therapeutic agents. He characterized the study as **"genotype to phenotype,"** meaning that it will serve to screen molecular features that **may** predict an individual's response to a drug with a given mechanism of action.

The goal of the trial is to molecularly profile 3,000 patients with a validated targeted **next generation-sequencing assay (NGS)** that allows rapid simultaneous analysis of multiple genes for actionable mutations to identify such targets in 1,000 patients. The MATCH trial will serve as an "umbrella" trial for multiple single-arm Phase II trials, with each designed to match an identified molecular lesion of interest to a matching targeted drug defined to target the specific mutation. The plan is to screen as many as 15 actionable mutations with available targeting agents per patient. Those identified targets and matched agents will be dynamic during the conduct of the trial.

The MATCH trial hypothesis of "Patients with tumor mutations or amplifications in one of the genetic pathways of interest are more likely to clinically benefit if treated with agents targeting that specific pathway when compared to historically standard therapies selected without regard to the tumor's molecular characteristics. The rationale for the MATCH trial design is to define the most efficient way to assess tumor context in relation to genotype and therapeutic response via a Phase 2

evaluation that assigns therapy on the basis of genetic alterations predicted to correlate with efficacy **regardless of tumor type.**

MATCH molecular eligibility assessment

Dr. Catalano noted that the NCI will be contracting CLIA-certified labs for genetic analysis of approximately 200 genes, ensuring strict standard operating procedures (SOPs) and concordant test performance. The target for the trial is to have at least 25% of total enrollment comprising patients who have "rare" tumors.

Eligibility criteria

Eligible patients include those with solid tumors whose disease has progressed following at least one line of standard therapy—excluding tumor histologies for which an agent has been approved by the FDA or had shown convincing lack of efficacy with an agent. In addition, the tumor must be accessible to biopsy, and the patient must be willing to undergo biopsy. For patients who fail to respond and progress within the defined 6 month period, no additional biopsies are required and patients who have a second actionable mutation demonstrated on the initial biopsy will be offered the second drug. For patients who respond to the assigned drug, a second biopsy will be requested at the time of progression to assess a mechanism of possible resistance and to look for a second actionable mutation. The biopsy at progression is not a mandatory biopsy and patients may refuse.

The ECOG/ACRIN Cancer Research Group will be the lead NCI Cooperative Group for the MATCH trial. All members of the National Clinical Trials Network (NCTN), Cooperative Groups, NCI-designated centers, and CCOPs may participate. In addition, special participants may request to join the MATCH trial, but they must have a proven track record of receiving CTEP investigational agents. A Central IRB will be required. The plan is that a single Investigational New Drug (IND) application will be required by the FDA. During the conduct of the trial, arms may be added or dropped without affecting the other arms. Initially, only single targeted therapies will be included; however, combination arms may be considered in the future. The targeted therapies selected for the trial may be approved agents for off-label indications or investigational agents. The targeted start date is July 2014. Agents selected could be commercially available or investigational but would have at minimum dose/safety established in phase I trials.

Mike Katz, ECOG/ACRIN patient representative, involved the audience in a survey to provide feedback to the NCI from the audience about the trial's design.

Recorded replay: http://www.screencast.com/t/huugMs8f
Slide Handouts: http://www.screencast.com/t/245upwG4Jtjp

I-SPY 2 and Clinical Trial Innovation

Jane Perlmutter, PhD, breast cancer survivor and cancer research advocate, presented information on NCI's I-SPY 2 breast cancer clinical trial. Dr. Perlmutter reviewed the background of the clinical trial called **"Serial studies to Predict Your therapeutic response with Imaging and molecular analysis 2" or I SPY-2.** Under the sponsorship of the Foundation for the National Institutes of Health's public/private Biomarkers Consortium, the adaptive Phase II clinical trial is testing several oncology candidates from multiple companies in women with newly diagnosed breast cancer that is stage II or higher (with a tumor size at least 2.5 cm). Eligible patients are randomly assigned to standard presurgical (neoadjuvant) chemotherapy, including paclitaxel (Taxol®) followed by anthracycline-based chemotherapy (controls) or paclitaxel in combination with a novel agent followed by anthracycline-based chemotherapy before surgery. She described the trial as an

innovative, biomarker-driven neoadjuvant trial for invasive, nonmetastatic, high-risk breast cancer patients for whom standard chemotherapy is inadequate.

Currently the trial is open at 18 sites across the country and has enrolled approximately 500 patients with plans to treat a total of 800 patients. She described I-SPY 2 as a unique public/private partnership and collaboration between the Foundation for the National Institutes of Health Biomarkers Consortium, the FDA, the NCI, 20 leading academic cancer research centers (researchers and physicians), the Safeway Foundation, QuantumLeap Healthcare Collaborative, and patient advocates.

I-SPY 2 incorporates several highly innovative and unique features, enabling rapid testing of emerging and promising new agents for breast cancer and significantly reducing the time, cost, and number of patients required to efficiently bring new drug treatments to breast cancer patients. The study design utilizes a neoadjuvant treatment approach, where chemotherapy is given to patients prior to surgery, enabling evaluation of tumor response with MRI before surgical treatment. Efficacy is based on assessment of pathologic complete response (PCR), meaning no evidence of tumor in breast tissue and lymph nodes at the time of surgery. Evidence has shown that this approach is as safe and effective as providing chemotherapy after surgery (adjuvant treatment) and allows early assessment of treatment effectiveness.

The study uses a biomarker-driven trial design, where tissue and biomarkers are obtained from cancer patients' tumors to determine patient eligibility for the trial, screen new treatments, simultaneously validate biomarkers and investigational agents, and determine which treatments are most effective for specific breast cancer subtypes. The adaptive clinical trial design enables researchers to "learn as they go," by assessing patient data early in the trial to learn which patients respond better to which therapies as the trial proceeds.

The design allows for the use of a smaller control group, where approximately 20 percent of patients are randomized to receive standard of care (chemotherapy before surgery) and 80 percent are randomized to receive a novel agent in addition to neoadjuvant chemotherapy. Patients are consented in a two-step process where the study doctor and study coordinator discuss the trial with patients and provide a screening consent form that explains the screening study procedures. If patients are found to be eligible for the treatment phase of the study, they will be provided a treatment consent form by their study doctor or study coordinator with information about the agents they have been assigned to receive.

Testing multiple investigational agents in high-risk potentially curable breast cancer patients (i.e., stage 2 and 3 breast cancer) I-SPY 2 enables screening of multiple drug candidates—up to as many as 12 different investigational drugs over the course of the study. The researchers will add new agents as those used initially are either dropped or graduate to Phase III trials, based on their efficacy in targeted patients.

I-SPY 2 is also known for involving educated research advocates in meaningful ways in the design, implementation, conduct, and assessment of I-SPY 2, including:

- protocol development
- informed consent and supplemental educational materials' development
- recruitment and retention plan development and review, ensuring that the I-SPY 2 participants appropriately reflect the diversity of breast cancer patients

- membership on the Data Safety Monitoring Board (DSMB) and External Drug Selection Committee
- membership on all Scientific Working Committees and Advisory Committees
- peer and trial site support at site initiation visits
- advocate training
- dissemination of best practices and dissemination to the public
- assessment of advocate involvement in I-SPY2 through coordinated surveys

Meaningful changes based on advocate contributions

Dr. Perlmutter provided several examples where the insights and perspectives brought by I-SPY 2 advocates as breast cancer survivors themselves resulted in meaningful changes for I-SPY 2 trial implementation and conduct—which may play a vital role in optimally recruiting and retaining patients for clinical trials overall:

- The adoption of a two-stage consenting process (i.e., screening and treatment).
- The decision to inform patients of their treatment during the consenting process (i.e., a non-blinded study).
- The decision to inform patients when the novel agents they are receiving are dropped from the trial—and enabling them to choose whether or not to complete their treatment with such drugs.
- The emphasis on **patient-relevant criteria** into the novel drug selection process.
- Inclusion of data collection concerning the reasons that patients decline to participate in the trial.
- Availability of patient travel reimbursement for research visits.
- Use of a peer support hotline for patients who are considering joining the trial and for those who are currently on trial. Note: Patients or their physician are not informed about what mutations they have. This may deny a patient valuable information for future treatments.

Impact beyond I-SPY 2

Since the development of I-SPY 2, an increasing number of clinical trials have been developed that are now using adaptive clinical trial design in an effort to improve the efficiency and quality of trials, to decrease their cost, and to significantly lower the amount of time required to complete trials and receive FDA approval to bring successful novel agents to those patients who need them. Also, the FDA's guidance on using PCR for accelerated approval was prompted by I-SPY 2. The **Clinical Trials Transformation Initiative (CTTI)**'s Central IRB initiative, where they solicited current perceptions of barriers to the use of single, central IRBs for multicenter clinical trials, despite statements from the FDA, NIH, and Office for Human Research Protections (OHRP) in support to improve efficiency of trial conduct. (CTTI is a public-private partnership of the FDA and Duke University that is dedicated to enhancing the quality and efficiency of clinical trials.) With their Central IRB project, CTTI identified the need for concrete tools to assist research institutions in separating their institutional responsibilities from the ethical responsibilities of an IRB. CTTI is disseminating the project recommendations and tools developed to help facilitate the use of central IRBs in multicenter trials such as I-SPY 2, with the goal of increasing the country's capacity to efficiently conduct high-quality, multicenter trials.

An additional critical impact of I-SPY 2 is the mentorship and development of additional educated cancer research advocates and increased appreciation of the need to work in partnership with advocates to develop and answer research questions of true import to patients.

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Slide Handouts: http://www.screencast.com/t/HGVX50riP

Clinical Trials with Quality of Life and Patient Reported Outcomes

Jeff Sloan, PhD is a Professor of Oncology and Biostatistics at Mayo Clinic's Department of Health Sciences Research. His research focus is primarily on patient quality of life (QoL), with the goal of incorporating patient perspectives on their QoL into clinical trials and personalized clinical care. Cynthia Chauhan is a retired clinical social worker and a two-time cancer survivor who is an active cancer research advocate, serving on the Mayo Clinic Breast Cancer Specialized Programs Of Research Excellence (SPORE), the NCI Patient Advocate Steering Committee, the FDA Oncologic Drugs Advisory Committee (ODAC), and the Patient Advisory Board of the Coalition of National Cancer Cooperative Groups.

Dr. Sloan and Ms. Chauhan reported on their work with Quality of Life and Patient Reported Outcomes in Clinical Trials. A Patient Reported Outcome (PRO) is a measurement of any aspect of a patient's health status that comes directly from the patient. Examples are function, symptoms including intensity and frequency, satisfaction with medication or other interventions, well-being and quality of life. Dr. Sloan described QoL PROs as an integrated vital sign providing additional clinical information that can be incorporated into research and clinical practice. The goal is to improve quality and length of life and reduce time spent in the emergency room. He stressed the importance of establishing scientific validation for patient reported QoL in helping clinicians to address the patient's experience as a crucial component of cancer progression and treatment. It may ultimately lead to exploration of new pathways for improving patient care, increasing overall survival, and enhancing QoL.

Dr. Sloan emphasized several ways to make using PROs both practical and meaningful.

- Make assessing PROs simple to reduce burden, producing data that is readily available and ease to use,
- Make PROs easy to understand,
- Link PROs to outcomes,
- Answer the question, "What do I do with PRO data"?
- Treat PROs like any other vital sign or lab test (i.e., as a routine step in delivering standard of care).

He described tools that support PRO/QoL including:

- PRO/QoL Forms Bank which is a website that provides access to approximately 400 QoL instruments
- Computerized Linear Analogue Self-Assessment (LASA) instrument, which enables user-friendly data collection and simple, robust, readily interpretable Q0L data.

Dr. Sloan felt there were two important endeavors that could be important in the near future: the research efforts to combine PRO/QoL data with survival and the GeneQoL Consortium. The Consortium has been established to explore the genetic underpinnings of pain, mood, fatigue, physical well-being and overall survival. The overall objective is to conduct clinically relevant research to identify and investigate biological mechanisms, potential genes, and genetic variants involved in quality of life. He felt if we can identify patients who are susceptible to poor quality of life, we will be able to better tailor preventive strategies and/or specific support and treatment. He called for collaboration, especially with advocate, to successfully incorporate PROs into clinical practice.

The advocate perspective was offered by Cynthia Chauhan who stated that at the heart of all that we do in assessing PROs is a human being. For her, as for other advocates, it is all about the patient. She felt symptoms could not be separated from health-related quality of life much less quality of life. She also spoke to the importance of the possibility of symptoms affecting choices of treatment. She gave as an example a medication she takes for glaucoma that changes her eye color from blue to brown. She chooses to take the medication to save her eyesight but she spoke to the emotional distress associated with potentially losing what has been a positively defining aspect of self. The eye color change may not qualify as a PRO, but the distress does and it affects her quality of life. Cynthia stressed that the only QoL interpretation that matters is that of the patient.

Recorded replay: http://www.screencast.com/t/ohQE4dXrV
Slide Handouts: http://www.screencast.com/t/upSC3KWMb

Providing the Patient Perspective in Research, Focus Group Summary Report

Elda Railey, co-founder of Research Advocacy Network (RAN), presented results from RAN's 2013 focus group "Bringing the Patient Perspective to Cancer Research" to engage participants in discussion about our current and future efforts as cancer research advocates in the genomic era. The purpose of the focus group was to "gain a deeper understanding of how advocates bring the patient perspective to cancer research." The ultimate goal of the session was to "gather information on the 'who, what, where, when, and how' that could be used as the basis for a future document that would provide insights on how to most effectively, help new advocates establish more dynamic, productive relationships with researchers and help more seasoned advocates expand their activities."

The report identifies critical roles and responsibilities fulfilled by educated cancer research advocates, including:

- **Putting a face on life-threatening diseases** in situations where cancer research is discussed, designed, and implemented
- **For basic and translational research,** helping in the critical transition from the abstract and theoretical to reality and validating the work that researchers are conducting in their labs.
- **Providing researchers with feedback and critical "reality checks"** on proposed trials from the perspective of how meaningful, useful, and safe the suggested actions will be for the patient.
- **Having the ability to point out issues and concerns when researchers may be reluctant** or unable to do so.
- **Identifying potential "red flags,"** such as research questions beginning with, "Wouldn't it be interesting if …" that may intrigue scientists yet offer little or no meaningful benefit—or cause extreme discomfort—to patients.
- **Bringing a sense of urgency** to the research process.
- **Asking questions and pushing back,** particularly concerning complicated schemas that would be difficult to communicate to patients.
- **Keeping research relevant and meaningful.**
- **Acting as the conscience of the group,** redirecting the science away from "interesting scientific questions" to what is meaningful for the ***patient.***

The advocate focus group report also provides information concerning defining and measuring success as cancer research advocates. The focus group participants also shared several critical examples of successes that have resulted specifically due to the efforts of cancer research patient representatives: One example of success was advocate input that helped to reduce central IRB turnaround time from 90 to 30 days for cooperative group trials.

The advocates stressed the importance of earning the respect of researchers by being prepared for opportunities to provide input. Being tenacious and persistent were among the traits of an effective cancer research advocate. Conversely there were factors that interfere with success such as being negative, misinformed or unwilling to collaborate. Though disruptive behavior may in some cases generate positive results, it may more often cause researchers to lose respect. It's important to recognize that patient representatives who are unwilling to collaborate with, mentor, and share strategies with others may also prove to be barriers in having a positive impact on a wider scale. Setting expectations was also discussed as a critical factor.

The education and development of advocates is increasingly resulting in meaningful impact but additional training programs are still needed that will help address the knowledge deficit among some advocates. Due to the nature and background of patient advocates, there may be a high turnover. Recruiting and mentoring of new advocates is needed.

The vision of patient representation in cancer research in the future includes a changing landscape where the cancer research advocacy role will likely expand beyond the research table, thanks in large part to social media and other technology that enables remote online participation in panels. In addition, they emphasized the importance of recognizing this role as a critical stakeholder in the research enterprise—i.e., as a partner member of the research team. But concerns about consolidations, financial pressure, limited resources, and a more complicated research environment have led to a reduced number of research advocates in some cases. The group felt strongly, however, there should be more—not fewer—patient representatives.

Recorded replay: http://www.screencast.com/t/fKbZs7ubPax
Slide Handouts: http://www.screencast.com/t/xQgFHXpzXEE
PDF of Focus Group Report: http://www.screencast.com/t/NZr65K5W1

Communication: How do we get the voice of the advocate/patient heard?

Lidia Schapira, M.D, medical oncologist at Massachusetts General Hospital, and Associate Professor at the Department of Medicine, Harvard Medical School provided insights from her research that may inform how cancer research advocates may be more effective in providing the patient perspective in the research setting.

In her presentation, Dr. Schapira emphasized the importance of communication, negotiation ability and preparation as part of the necessary skill set for effective research advocacy. Much of her research has focused on improving communication between patients and their healthcare providers and how best to fulfill patient needs, overcoming the barriers to communication, and bridging the communication gaps that may serve to deter patients from participating in clinical trials.

The following skills were emphasized as essentials for advocates to be effective patient representatives and cancer research advocates:

- Critical thinking

- Scientific literacy
- Self-awareness
- Assertiveness
- Experience with teamwork
- Perspective
- Trustworthiness

She also presented a Research Advocate Checklist that can be used when engaging in specific advocacy efforts. Other suggestions included: Establishing a curriculum and standards for research advocates and increasing the visibility and expanding the research advocate role through publications and training. Educating researchers about the role, funding, and training of research advocates would help expand the role.

Q & A Session

During the Q&A session that followed, one audience member noted that advocates bring crucial life experience, which may be unstructured in nature, yet he noted that Dr. Schapira's recommendations gave the impression that advocates need to fulfill specific requirements to become research advocates. Another advocate responded, emphasizing that "Most of us come from our passion. But it's not enough for our voices to be meaningful to researchers. We need to bring a skill set to our passion to influence researchers and research design." Another advocate noted, "It really is a process to come into this world."

Several advocates then discussed their efforts to teach researchers about their roles, including:

- Having a "dog and pony show," where the patient representatives went to their cooperative group's disease committees to discuss what they brought to the table.
- Giving grand rounds concerning breast cancer research advocacy as part of their medical training—"It won't necessarily be the most popular topic, but you really have to keep at it. You have to keep showing up."

One advocate noted that a helpful concrete step may be for cancer research advocates to update their NIH biosketches, since this is then speaking in a shared language and is "something that researchers understand." Another emphasized that we need to "Stand up in a non-aggressive, assertive way. Part of the advocate voice is showing them where we fit in." In closing the Q&A portion of this session, another advocate concluded by noting, "I think of it as a coming together of cultures. We need a diverse team: everyone benefits. The conversation is deeper and richer."

Recorded replay: http://www.screencast.com/t/paqdCCGGz6
Slide Handouts: http://www.screencast.com/t/9n9JotIZk

Targeted Therapies: Considerations for Trial Design

David Gerber, Associate Professor, Division of Hematology-Oncology at the Harold C. Simmons Cancer Center, University of Texas Southwestern Medical Center provided comprehensive information on targeted therapies as therapeutic agents and important considerations regarding targeted therapy clinical trial development.

Dr. Gerber began his session by discussing the differences of conventional chemotherapy from targeted therapies. Chemotherapy drugs typically affect processes that occur in rapidly dividing

cells, one of the main properties of most cancer cells (and some may also interface with the unwinding of DNA that is needed to replicate). In addition to killing cancer cells, chemotherapy also harms normal cells that undergo active growth and rapid cell division, including cells in the digestive tract, bone marrow, and hair follicles. Common side effects of chemotherapy drugs therefore include hair loss (alopecia), nausea and vomiting, decreased production of certain blood cells, and inflammation and pain of the mucous members lining the digestive tract (mucositis). Accordingly, symptom management for standard chemotherapy currently may require the use of pre-medications the day before treatment and on the day of treatment, such as steroids and IV Benadryl to help prevent allergic reactions, and antiemetics to manage chemotherapy-related nausea and vomiting. In addition, following administration of chemotherapy, a granulocyte-colony stimulating factor (C-GSF), such as Neupogen®, may be administered to stimulate the production of white blood cells (granulocytes) and to therefore help prevent infection and fevers due to a chemotherapy-induced low white blood cell count (neutropenia).

Targeted therapies

In contrast to standard chemotherapy, targeted agents are designed to affect specific cell markers and pathways required for tumor development and growth. Targeted agents act on specific molecular targets with precision, disrupting the activity of particular cancer pathways. Because targeted therapies are directed against specific molecular targets, they may be associated with fewer or different side effects than standard chemotherapy. Specific cell markers and pathways targeted with targeted therapies should be:

- unique to cancer and not found in normal tissue (e.g., the abnormal tyrosine kinase enzyme produced by the BCR-ABL translocation in CML), or
- mutated in cancer compared to normal tissue (e.g., EGFR mutations in lung cancer), or
- overexpressed in cancer compared to normal cells (e.g., amplification of HER2+ in breast cancer)

Although targeted therapies are generally better tolerated than standard chemotherapy, they may also be associated with adverse effects, often related to the skin, such as rash, and the GI tract, such as diarrhea. In addition, he noted the unique toxicities that can result from agents that target pathways required for normal cellular growth.

In contrasting standard chemotherapy with targeted agents, he also stressed that the FDA has approved only about 10 traditional chemotherapy agents in 10 years, whereas in that same period, more than 30 targeted therapies have been approved.

Monoclonal antibodies and small molecules

Dr. Gerber explained the naming convention that is used to differentiate monoclonal antibodies and small molecules:

- If the generic drug name ends in **"mab,"** the agent is a monoclonal antibody and has an effect outside of cells (e.g., trastuzumab for the treatment of HER2+ breast cancer).
- If the generic drug name ends with **"ib,"** the agent is a small molecule and can enter cells (e.g., lapatinib, also for the treatment of HER2+ breast cancer).

Monoclonal antibodies are laboratory-produced molecules comprised of identical immune cells that are clones of a unique parent cell, which are designed to recognize and attach to specific proteins on the surface of cancer cells.

In the past, early monoclonal antibodies were created by immunizing mice with the target antigen. Because the resulting monoclonal antibodies were entirely comprised of mouse (murine) proteins, they carried a risk of a life-threatening reaction in patients during infusion. In addition, patients treated with murine proteins often developed anti-murine protein antibodies, which could serve to neutralize the effect of the therapeutic antibody. To overcome these important limitations, more recently developed monoclonal antibodies contain an increased proportion of human components and decreased murine components:

- Murine antibodies are 100% murine (identified by the suffix "-momab" in the drug name)
- Chimeric antibodies are 65% human ("–ximab" suffix)
- Humanized antibodies are 95% human ("-zumab" suffix)
- Human antibodies are 100% human ("-mumab" suffix)

The first two—murine and chimeric antibodies--have a relatively high risk of reactions. Dr. Gerber explained that radioactive substances called radioisotopes can be attached to monoclonal antibodies to carry them directly to cancer cells. He noted that one advantage to using murine antibodies is in this context, since they do not stay in the circulation long, so the attached radioisotope will not be circulating in the body for weeks.

Dr. Gerber described monoclonal antibodies as "huge molecules" that are much larger in size than small molecule targeted agents, noting that their size impacts what they can accomplish therapeutically. Monoclonal antibodies achieve their anticancer effects via several mechanisms, including:

- Binding to ligands or receptors, interrupting critical pathways for cancer growth and spread
- Recruiting or activating the patient's own immune system
- Carrying a "lethal payload"--i.e., a potent anti-cancer agent--directly to the targeted cell. This allows the use of very potent chemotherapeutic drugs at low doses because they are delivered right to the cancer cell: Dr. Gerber stressed that these are chemotherapy drugs that we could never use on their own because of their toxicities (e.g., T-DM1 [ado-trastuzumab emtansine], a conjugated monoclonal antibody for HER2+ breast cancer).

Monoclonal antibodies are some of the most highly specific targeted agents. They are delivered intravenously and have half-lives that may range from days to weeks; they are therefore administered approximately once every one to four weeks. In addition, they do not undergo metabolism via the liver, so therefore are not subject to significant interactions with other drugs.

Fourteen monoclonal antibodies are currently FDA-approved for cancer treatment, some of which have been approved for more than one cancer type. He gave the example of bevacizumab (Avastin®), which has been approved for many cancers since blood vessel growth is critical in so many cancers.

He contrasted **small molecules** with monoclonal antibodies in several ways. First, small molecules are manufactured chemically and are usually administered orally. They are metabolized by enzymes in the liver (cytochrome P450 enzymes), which may result in interactions with other drug agents, including certain antibiotics, anticonvulsants, antifungals, and warfarin. Dr. Gerber noted that "we rarely worry about drug interactions with antibodies, but we do worry about this with small molecules, and it may affect the efficacy of small molecules and other agents." In addition, because small molecules typically have a half-life of just hours, they require daily dosing.[8-1]

Small molecule inhibitors typically exert their anticancer effects by blocking the function of tyrosine kinases (TK). They directly bind to and turn off the kinases, preventing them from activating. If the molecular target is within the cancer cell, small molecule inhibitors are necessary, since the larger monoclonal antibodies can only target the outside of cells. He noted that 25 small molecule inhibitors have been FDA-approved, but stressed that small molecule inhibitors achieve less specific targeting than monoclonal antibodies

Considerations in targeted therapy clinical trial development

Several important considerations were presented in the use of targeted therapies in the context of clinical trial development. These included the following:

- **Adherence: A new issue in oncology?** Because small molecule inhibitors are usually given orally, patients are responsible for adhering to what may be complex medication regimens, and available evidence suggests that patient adherence to oral therapy recommendations may be variable and unpredictable.
- **Toxicities:** Chemotherapy toxicities are familiar to oncologists, and dermatologic toxicities are common with the use of EGFR targeted agents, so as Dr. Gerber notes, "We have become experts in managing dermatologic toxicities" (e.g., use of topical and systemic agents, including steroids, dosing changes, and drug holidays). However, he stressed that oncologists are still learning how to recognize and treat other toxicities that result from use of new targeted agents.
- **Efficacy assessment**: Another crucial challenge is that variable radiographic assessments can serve to complicate the assessment of a targeted agent's efficacy. Dr. Gerber noted that with immunotherapeutic agents, the clinical response patterns seen on imaging may actually manifest after a transient radiographic worsening, e.g., an apparent initial increase in tumor burden or what appears to be new lesions and progressive disease due to a massive influx of the body's own immune factors in fighting the cancer. The result is that new response criteria has been developed for the evaluation of antitumor response with such agents, since before immunotherapy, when there was a radiographic increase in size, this was automatically considered progression.
- **Accrual:** Rare subsets of common cancers are in fact rare diseases, meaning that it will be challenging to identify and enroll sufficient numbers of patients to these clinical trials.
- **Eligibility requirements:** Clinical trials of targeted therapies require substantial amounts of archival tissue for biomarker testing, yet for some cancers, this may be difficult to achieve.
- **Costs:** Targeted therapies can be extremely expensive, and covering these expenses raises important questions

Highlighting the shortening interval between discovery and treatment, he noted that the Philadelphia chromosome in CML was identified in 1960; yet targeted treatment was not documented until 41 years later. Full understanding of effectively targeting EGFR required 26 years. Yet on an encouraging note, recognition of the importance ALK mutation in lung cancer in 2007 resulted in effective ALK targeting and inhibition in 2010, collapsing this interval to just 3 years in this case.

Recorded replay(synched to slides): http://www.screencast.com/t/CgzG5htu
Slide Handouts: http://www.screencast.com/t/eaTmRCaNOo1

Research to Practice

Worta McCaskill Stevens, MD, a medical oncologist and Chief of the NCI's Community Oncology and Prevention Trials Research Group, which houses the Community Clinical Oncology Program (CCOP), Minority-Based CCOP, and the Research Bases for cancer prevention and control clinical trials provided an overview of the NCI's Community Cancer Centers Program (NCCCP). The NCCCP is a network of 21 community-based cancer centers in 16 states. The program was initiated in 2007 as a pilot program with the purpose is to extend NCI programs locally in community-based hospitals and to bring the most advanced cancer care and clinical cancer research to our nation's community hospitals. Per the NCI, only about 15 % of U.S. cancer patients are diagnosed and treated at major academic-based Cancer Centers. The vast majority receive their treatment at community hospitals in or close to the communities where they live. She explained that the NCCCP:

- provides access to real-world healthcare delivery systems
- gives access to a larger, more diverse patient population
- tests the feasibility of implementing new interventions and processes

For the latter, she emphasized that the widespread use of sentinel node biopsy and HER2 testing in breast cancer would not have been feasible if their use was not confirmed in community settings.

Dr. McCaskill Stevens noted that the NCCCP has several main goals or "pillars" that are the focus of the NCCCP sites, including the following:

- Increasing access to clinical trials
- Reducing cancer healthcare disparities
- Collecting, storing, and sharing biospecimens for research
- Linking to the NCI's electronic data repository, leading to a national database of electronic medical records
- Enhancing cancer survivorship and palliative care services
  Improving quality of care

NCI's Community Oncology Research Program (NCORP)

Due to the increasing size and scope of these programs, in 2013, the NCI announced the formation of the **Community Oncology Research Program (NCORP)** to consolidate and build on the success, scope, and activities of the NCI's CCOP community sites, MB-CCOP sites, CCOP Research Bases, and the NCCCP by establishing a single national, integrated, community-based research program. The purpose of the integrated network will be to:

- Design and conduct cancer prevention, control, and screening/post-treatment surveillance clinical trials
- Design and conduct cancer care delivery research
- Enhance patient and provider access to treatment and imaging clinical trials conducted under the reorganized National Clinical Trials Network (NCTN)
- Integrate disparity research questions into clinical trials and cancer care delivery research

Since the overwhelming majority of cancer care is provided in community-based settings, and conducting cancer research in the communities where most patients live provides access to larger, more diverse patient populations. Community-based cancer research gives access to "real-world" healthcare delivery systems, providing crucial "reality checks" of feasibility. With our rapidly changing healthcare system, including the Affordable Care Act, the increased number of merging

practices, and accountable care organizations (groups of doctors, other healthcare providers, and hospitals who voluntarily come together to provide coordinated care to Medicare patients), such research will help to fulfill the urgent need for evidence on how such changes impact patient outcomes and disparities in care. Dr. McCaskill Stevens emphasized that our increasingly dynamic healthcare environment necessitates a better understanding of routine oncology care delivery, noting that NCORP will help to fill a key gap by providing a diverse, geographically distributed platform for cancer care delivery research.

Precision medicine that integrates molecular and clinical research and enables directed treatment based on a patient's unique characteristics greatly complicates care. With this changed landscape, there will be fewer trials than in the past that are going to be much more complex. She noted that hypothesis-driven ideas and interventions will be critical for successful applications, as will be "engaging populations on the fringes into all cancer research." Community-based research can help to promote and accelerate the uptake of new interventions and processes into routine clinical practice. Such research also enhances the potential that outcomes will be broadly applicable in practice.

Future research priorities

Dr. McCaskill-Stevens then discussed future research priorities for cancer prevention and control trials, including:

- Molecularly targeted agents
- Post-treatment surveillance
- Over-diagnosis and under-diagnosis
- Management of precancerous lesions
- Mechanisms of cancer-related symptoms
- Biomarkers of risk for treatment-related toxicities
- Enhancement of accrual of racial/ethnic and other under-represented populations

She also stressed the importance of including a focus on cancer disparities research in NCORP, noting the persistent disparities among underserved/underrepresented populations in cancer incidence, cancer mortality, and quality of life as well as in access to and quality of care.

Q &A session

During the Q&A session following Dr. McCaskill Stevens' presentation, one of the attending advocates noted that when "we talk of the underserved, many think traditionally of minorities." Yet he emphasized that the "underserved can also refer to those who suddenly find themselves reaching their insurance cap—and in the continuum of care, all of a sudden, you become underserved." Another advocate cautioned that "When you look around a room, you don't always know who's underserved." In concluding the discussion, a third advocate stressed that "We have a shifting landscape. The underserved population and how we term that is changing. It won't look the same as it did a year ago, and we can't make assumptions."

Recorded replay: http://www.screencast.com/t/LWyGoDpS0j
Slide Handouts: http://www.screencast.com/t/mZqof5pt2r

Grand Rapids Community Clinical Oncology Program

The Grand Rapids Community Clinical Oncology Program (CCOP) model was presented by Connie Szczepanek, RN, BSN, and Pat Gavin, R.Ph. Connie Szczepanek is a nurse and serves as the Director

of the Grand Rapids Clinical Oncology Program (GRCOP). Pat Gavin, a registered pharmacist, is a cancer survivor and cancer research advocate who is a founding member of the GRCOP's Patient Advisory Board.

Originally formed to develop community cancer patient management guidelines, GRCOP changed its focus in 1983 to become one of the first site participants in the NCI's Community Clinical Oncology Program. GRCOP was described as a consortium program funded by an NCI CCOP grant as well as its many Consortium Members and one Affiliate Member in Michigan. Its mission is to assure every person in their service region the opportunity for education and participation in nationwide cancer prevention and treatment clinical trials. GRCOP works to fulfill its mission by working with local hospitals and cancer organizations to provide access to the most advanced, high-quality care for cancer prevention and treatment.

Real answers, real options

The GRCOP's motto is "Committed to Community, Cancer Research, and Education" She emphasized that "We have real answers, real options, real miracles right here in our community, as well as hope for the future." Historically, we had very few drugs to choose from for cancer treatment and the drugs we did have for chemotherapy resulted in terrible side effects. And we had very little for effective symptomatic management. And far too often, what we did have did not work very well. In contrast, in the 1990s and early 2000: We saw an almost explosive number of new drugs. With new therapeutic options, there also came a much stronger emphasis on symptom management for patients. Several large, multi-center Phase III clinical trials were launched. Crucially, we saw significant improvement in survival rates for patients with many types of cancer, including prostate cancer, breast cancer, and leukemia.

Where we are today

Today, cancer drugs are becoming more "patient specific" recognizing that every patient's cancer is driven by unique molecular mechanisms, and tumor profiling is now informing treatment strategies that target these molecular alterations. Large Phase III clinical trials are moving to smaller and more focused Phase II trials. Clinical trials are becoming increasingly "patient centered," with PROs and QoL assessments becoming the norm rather than the exception.

And what will the future bring?

The future, which brings the increasing economic challenge of healthcare, poses several tough questions, including:

- How will we fund everything we need to do in the community setting?
- Importantly, how do we make this affordable for the patient?
- How do we communicate with patients about clinical trials?

Connie stressed that "Changing the enterprise is definitely doable. We have the right seats around the table. However, she there is concern about what happens to patients at the present CCOPs following the restructured system via NCORP. Although NCORP will also include CCOPs, MB-CCOPs, and Research Bases, it is anticipated that no more than 40 Community Site grants and 14 Minority/Underserved Site grants will be awarded, both representing a reduction in current numbers from these programs. In addition, Community Sites will need to accrue at least 80 patients annually onto treatment protocols. She concluded her portion of the presentation by emphasizing that one third of current cancer clinical trial recruitment comes from the communities and that we need to do all we can to help to protect, preserve, and grow the Community Sites.

Pat Gavin, Chair of the GRCOP Patient Advocate Committee

Pat Gavin, Chair of the GRCOP Patient Advocate Committee as well as Chair of the Alliance for Clinical Trials in Oncology cooperative research group (the "Alliance").began his presentation by sharing his personal story as a stage IV pharyngeal cancer survivor. When he was diagnosed Pat was told that his cancer was very aggressive and that his chances of survival were poor. His oncologist recommended that in addition to standard therapy, he consider participating in a clinical trial that included two new drugs showing encouraging results against other cancer types. In addition, as part of the trial, he would receive radiation therapy at the same time as the chemotherapy. His doctor warned Pat that the treatment regimen would be very difficult, but that it was the best option for him as an otherwise healthy man. However, he also explained that it was possible the trial would not help him. But Pat's perspective was that if the trial did not in fact benefit him personally, six months from that point, he "might not be here, and we wouldn't have learned anything." Following months of treatment, scans, and biopsies, Pat visited his oncologist, who said, "We had the experience of witnessing a miracle. We had drugs that worked, radiation therapy that worked, a patient with a great attitude and the support of a loving family and prayers from hundreds of people. Your tumor is gone, and your cancer is in remission." Gavin told the symposium audience that he knows "I am alive today by the grace of God and the fact that I participated in a clinical trial." This statement appears next to his picture on the Grand Rapids Clinical Oncology Program website. Pat puts his convictions into practice through his work as a cancer research and patient advocate, which includes his role as a founding member and current Chair of the Patient Advisory Board for Clinical Research, current Chair of the Alliance NCI cooperative group, and frequent public speaker about his experience as a cancer survivor and an advocate.

Research advocates' role in overcoming current and future challenges

Pat presented several areas where cooperative group research advocates can assist in meeting today's and tomorrow's challenges surrounding clinical trials. He emphasized the importance of introducing standardization between cooperative groups today, with each group having its own forms, formats, reports, and descriptions.

The need for patient-friendly information

Enhanced communication about trials is necessary through summaries in plain language and the development of a common look for trial information that would help patients more effectively locate appropriate information when searching on ClinicalTrials.gov. Pat also emphasized the importance of providing patient-friendly information by clearly, effectively answering questions that patients may have about potential trial participation.

The need for patient-directed educational materials

IRB-ready handouts for cancer centers, doctors' offices, and patient gathering places are needed. Social media-ready information for posting on trial sites or support groups can be offered as well as pre-written email solicitations

The importance of a meaningful accrual plan

Before study implementation, GRCOP does an extensive local feasibility review and troubleshooting. The GRCOP research advocates bring critical perspectives to clinical trial design and implementation and insights into what may encourage or discourage patient participation (e.g., randomization, invasive tests, etc). Advocates should be asking such questions concerning the ability of a proposed study to fulfill the required accrual numbers for a sufficiently powered study.

And "if we're having trouble accruing, why? What changes need to be made?" Pat then shared his favorite questions to PIs:

"Why would my doctor recommend I participate in this trial?"
"Why should I participate?"

Pat concluded his portion of the presentation by speaking about the GRCOP website, which truly shows the "face of the patient"—literally, the faces, voices, and stories shared by Pat and his fellow GRCOP Patient Advisory Board members. More information is available at: www.grcop.org.

Recorded replay: http://www.screencast.com/t/nQqpw9GoBoa
Slide Handouts: http://www.screencast.com/t/teruDPfzPK

Models of Dissemination of Research Results Utilizing Advocate Networks - The Moffitt Cancer Center LATTE Program

Christie Pratt-Pozo, program administrator for the Department of Thoracic Oncology and program coordinator for the Lung and Thoracic Tumor Education (LATTE) program at Moffitt Cancer Center, presented another example of how research advocates work in the community.

LATTE advocacy program

The mission of the LATTE program is "To contribute to the prevention and cure of lung cancer by embracing the patient and family perspective." She emphasized that Moffitt's MDs and nurses decided to develop this educational and supportive program due to their understanding of the need for having patients' and family's perspectives infused into everything they do in the department.

The LATTE Program explores ways to initiate and promote formal means for patient advocacy through which patients and their family members are actively engaged in all decision-making processes concerning Moffitt's thoracic oncology programs. Per the LATTE Education Program website, "Through advocacy, support, education, and community outreach, the Lung and Thoracic Tumor Education program serves as the collective voice of actively involved individuals who share their personal and professional expertise to contribute to the prevention and cure of lung cancer."

LATTE advocates include lung cancer patients, their family members, and other stakeholders who are dedicated to enhancing the conduct of lung cancer research. The aims of the LATTE Advocacy Program include the following:

- Support and incorporate the contributions of advocates in research design, implementation, ethics, and evaluation of the overall clinical trial process.
- Foster active participation of advocates in public education on lung cancer and clinical research, using institutional channels, established networks, and community partners.
- Engage key stakeholders, including patients, family members, clinicians, and researchers in formative research to identify barriers and facilitators of lung cancer research, using these contributions to create new programs. Pratt-Pozo gave an example where stakeholders' perspectives on rapid tissue donation resulted in their proposing the development of a pilot training program to initiate a rapid autopsy program through their institution's Lung SPORE .
- Disseminate translational research findings to patients, stakeholders, and SPORE collaborators.

Through the LATTE Advocacy Program, advocates have the opportunity to become involved in multiple working groups, including research advocacy, outreach and education, legislative advocacy, peer support, and communications and marketing. LATTE's Research Advocacy

Workgroup currently has eight research advocates, who partnered with the Research Advocacy Network to develop training for them. The goal of the training was to provide tools for ongoing education to fulfill their roles of:

- Providing input on all research initiatives through a process that is in place, reviewing all documents, including informed consents, patient diaries, etc.
- Serving as reviewers of SPORE pilot projects, thoracic concept trials, and research trials
- Influencing trial design
- Regularly interacting with researchers to continue to strengthen translational research

In what is now a formalized process, the suggestions of the Research Advocacy Workgroup are compiled into a report that is given to the PI and co-PI, which is then followed by a sit-down conversation to discuss the Workgroup's feedback.

Pratt-Pozo also discussed the Internal LATTE Committee, which includes MDs, other clinicians, social workers, trial nurses, and the advocacy council. She emphasized that, "The researchers are also there to bounce ideas off the advocates: [the result is] two-way communication and a sense of urgency is given to the researchers. Such communication is open and frequent."

Several projects and ongoing initiatives established by the LATTE Program include:

- ***Faces of Lung Cancer Project®,*** traveling photo exhibit, published book, and website, to "educate and increase awareness about the importance of clinical trials, to give a voice to survivors regarding their experiences with lung cancer, and to provide a message of hope."
- ***Community Outreach,*** through which LATTE advocates leverage existing partnerships and actively engage in their own communities to establish new partnerships.
- ***"A Taste of LATTE"*** a regular patient and family newsletter that is driven by the LATTE advocates.
- ***Regularly Providing Trial Updates to Physicians*** throughout the community and state
- ***Web Seminar and Teleconference Educational Series, developed by Moffitt MDs and researchers***
- ***Research Forums and Outreach***
- ***Social media channels***
- ***Behind the Science Video Series.*** Series of interviews with researchers, discussing specific topics in lay language, highlighting advances in translational lung cancer research. iPads are provided to patients in their clinic where they can view these during their visits or accessed directly on the web at http://www.moffitt.org/cancer-types--treatment/cancers-we-treat/behind-the-science-video-series.

The presentation concluded with the following words of wisdom concerning the crucial benefits that result from partnerships between patient advocates, caregivers, clinicians, and researchers:

"Never underestimate the power of partnership and collaboration."

Recorded replay: http://www.screencast.com/t/cAxAbubqeFRo
Slide Handouts: http://www.screencast.com/t/Y2f6GyPfj

Closing Discussion

During the last session of the symposium, advocate Mike Katz, co-chair of the ECOG/ACRIN Cancer Research Advocate Committee, surveyed the advocate participants on several key questions. The

purpose of this interactive session was to generate a robust discussion concerning those areas that the advocates felt important in further strengthening their research advocacy efforts in the genomic era.

The audience was comprised of a seasoned group of advocates; 63% of the group had been in advocacy longer than 10 years and 75% of the attendees were themselves cancer survivors. When asked about if they felt welcomed and valued in their associated research group 72% felt they were valued. Among the group there was a strong sense (45%) that advocate presence and impact has declined due to the consolidation of the cooperative groups; while 20% felt consolidation had strengthened presence and 35% felt there was no significant change. Strikingly, two-thirds of the research advocates in the audience did not believe that the Cooperative Groups are ready for the necessary transition of the clinical trial enterprise into the genomic era.

During the discussion, it was noted that the Cooperative Groups are primarily organized for Phase III trials. Concern was expressed that with the current movement away from these large Phase III trials and towards Phase II trials, the Cooperative Groups have not appeared to embrace the new technology that is needed to make clinical trial design and conduct more efficient. When asked "Compared to Five Years Ago, How Do You Feel About the Pace and the Potential of Cancer Research to Improve Patient Outcomes and Cure Cancer?" 61% were optimistic, while the remainder felt the same or less optimistic than five years ago.

Overall the group responded that they felt well-educated and equipped to be effective in this new era of genomic medicine but also discussed the need for ongoing training and support. Mentoring was discussed as an avenue to improve skills and education and also as a way to recruit and retain new advocates in research. The importance of advocates' reporting back and sharing information within our own communities was stressed.

The group felt strongly (76%) that to become a more effective advocate for cancer research it was most important to have opportunities for advocates and scientists to discuss the issues and strengthen collaboration.

The symposium adjourned with a strengthened sense of community among many of the advocates, shared concerns, new tools, and a deepened commitment to increase the level of collaboration among cancer research advocates, scientists, clinicians, and all stakeholders. Working together we can ensure that the science in this increasingly complex genomic era remains focused on what the patients themselves truly need.

Recorded replay of session: http://www.screencast.com/t/jfqpuesJ

Agenda with links to slide handouts and recorded replays

The following table recaps the agenda and provides links to the slide handouts and recorded replays of the sessions. *Please note: Recorded replays include visuals of the speaker and have not been synched to the slides unless indicated. Please open the slide handouts and listen to the audio.*

Session	Speaker	Link to Handouts/ Recordings
Wednesday, November 20, 2013		
Opening Session	George Sledge, MD *(Presented remotely during opening dinner)*	• Recorded replay http://www.screencast.com/t/3p5u6RLMn9Nu • Slide Handouts: http://www.screencast.com/t/WdFqrXv2h
Thursday, November 21, 2013		
Welcome	Elda Railey	• Recorded replay: http://www.screencast.com/t/1i90lmJqniP7 • Slide Handouts: N/A
Keynote Speaker: Ethics of Clinical Trials in the Genomic Era	Rebecca Dresser, JD	• Recorded replay http://www.screencast.com/t/GJf7uKwUU • Slide Handouts: http://www.screencast.com/t/jHPyULVuyrZG
Overview of Clinical Trial Design	Steven Hirschfeld, MD PhD	• Recorded replay (synched to slides): http://www.screencast.com/t/mskkK88fm6H • Slide Handouts: http://www.screencast.com/t/OHgc5DjajZ
Endpoints in Clinical Trial Design	Steven Hirschfeld, MD PhD	• Recorded replay (audio only): http://www.screencast.com/t/sHbEEv1H • Slide Handouts: http://www.screencast.com/t/OHgc5DjajZ
Innovative Clinical Trial Design	Donald Berry, PhD	• Recorded replay: http://www.screencast.com/t/BXwhAZPflVAE • Slide Handouts: http://www.screencast.com/t/TJjHturk7X
NCI MATCH Audience Survey	Robert Catalano, PharmD Mike Katz, Advocate	• Recorded replay: http://www.screencast.com/t/huugMs8f • Slide Handouts: http://www.screencast.com/t/245upwG4Jtjp
I-Spy 2: How advocates are involved in a trial with an innovative design	Jane Perlmutter, PhD, Advocate	• Recorded replay: http://www.screencast.com/t/lUAyzs3Jxl • Slide Handouts: http://www.screencast.com/t/HGVX50riP
Clinical trials with QOL/PROs	Jeff Sloan, PhD Cynthia Chauhan, Advocate	• Recorded replay: http://www.screencast.com/t/ohQE4dXrV • Slide Handouts: http://www.screencast.com/t/upSC3KWMb

Session	Speaker	Link to Handouts/ Recordings
Thursday, November 21, 2013 (continued)		
Communication: How do we get the voice of the advocate/patient heard? • Focus Group Report	Research Advocacy Network	• Recorded replay: http://www.screencast.com/t/fKbZs7ubPax • Slide Handouts: http://www.screencast.com/t/xQgFHXpzXEE • PDF of Focus Group Report: http://www.screencast.com/t/NZr65K5W1
Communication: How do we get the voice of the advocate/patient heard? • Presentation and Discussion	Lidia Schapira, MD Cynthia Chauhan, Facilitator	• Recorded replay: http://www.screencast.com/t/paqdCCGGz6 • Slide Handouts: http://www.screencast.com/t/9n9JotlZk
Friday, November 22, 2013		
Targeted Therapies	David Gerber, MD	• Recorded replay(synched to slides): http://www.screencast.com/t/CgzG5htu • Slide Handouts: http://www.screencast.com/t/eaTmRCaNOo1
From Research to Clinical Practice -NCI Community Oncology Research Program	Worta McCaskill - Stevens, MD *(Presented remotely)*	• Recorded replay: http://www.screencast.com/t/LWyGoDpS0j • Slide Handouts: http://www.screencast.com/t/mZqof5pt2r
From Research to Practice in the Community - The Grand Rapids CCOP model	Connie Szczepanek, RN and Pat Gavin - Grand Rapids CCOP Advocate	• Recorded replay: http://www.screencast.com/t/nQqpw9GoBoa • Slide Handouts: http://www.screencast.com/t/teruDPfzPK
Model of dissemination of research results utilizing advocate networks	Christie Pratt - Pozo Moffitt Cancer Center LATTE	• Recorded replay: http://www.screencast.com/t/cAxAbubqeFRo • Slide Handouts: http://www.screencast.com/t/Y2f6GyPfj
Closing Session: IDEA STORMING		• Recorded replay of session: http://www.screencast.com/t/jfqpuesJ

About the Conveners - Research Advocacy Network

The mission of the Research Advocacy Network is to develop a network of advocates and researchers who influence cancer research–from initial concept to patient care delivery—through collaboration, education and mutual support.

We believe that patient-focused research holds the greatest hope for improvements in treatment, diagnostics and prevention. Our goals are to:

- Get the results of research studies (new treatments) to patients more quickly
- Give those touched by the disease opportunities to give back to the cancer community
- Help the medical community improve the design of research studies so that more people are willing to participate in clinical trials.

We also believe that dissemination of research results to the medical community and patients can have a major impact on clinical practice.

The Research Advocacy Network (RAN) is a nonprofit (501 c 3) organization formed in 2003 to bring together participants in the research process with a focus on educating, supporting and

connecting patient advocates with the medical research community. For more information, please visit our web site www.researchadvocacy.org

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Research Advocacy Network
Advancing Patient-Focused Research

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Research Advocacy Network is designated as a 501(c)(3) tax-exempt organization by the IRS

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