Patient Reported Outcomes
Scientific and Clinical Research Roundtable
March 23, 2018
Public Meeting Summary

AUTHORS

LUNGevity Foundation
Andrea Ferris
Upal Basu Roy

WSCollaborative
Wendy Selig

Note: This is a public version of the March 23, 2018 meeting summary. Identifying information of meeting participants has been deliberately removed.

OVERVIEW

On March 23, 2018 LUNGevity Foundation (www.lungevity.org) hosted its fourth Scientific and Clinical Research Roundtable, a day-long meeting in Bethesda, MD, bringing together stakeholders from across the lung cancer ecosystem in the US and globally, to discuss issues and opportunities relating to the development and use of Patient Reported Outcomes (PROs) for lung cancer.

Background and Meeting Objective:

There are numerous efforts underway within the field of patient-reported outcomes (PROs) and LUNGevity Foundation has launched a new initiative for its Scientific and Clinical Roundtable (SCRT) focused on this topic. Working closely with leaders at FDA, LUNGevity has identified an opportunity to use lung cancer as a "case study" and engage its SCRT membership in defining best approaches for incorporating patient reported information into the drug development and approval process. The March 23rd meeting was an interactive roundtable designed to elicit key stakeholders' perspectives and consider efforts to leverage opportunities and address challenges associated with measuring and using data from PRO assessments and other patient-experience measures from lung cancer clinical studies. Participants include senior representatives of FDA, NIH, NCI, industry, patient advocacy and the clinical and academic community.

This effort is well-timed as a precursor for an upcoming public workshop co-sponsored by the FDA's Oncology Center of Excellence (OCE) and the American Society of Clinical Oncology (ASCO) on June 22, 2018. According to the public notice, the June workshop will explore PRO assessment in cancer trials (concepts, instruments, and assessment frequency) using a case-based approach to illustrate strategies that can adapt to multiple clinical trial contexts. Following clinical trial design considerations, cases will be used in the afternoon sessions to provide examples of analysis and visualization methods.

Meeting Deliverables:

The March 23rd agenda was designed to identify and elicit discussion about current practice, regulatory expectations and future opportunities with PROs and patient-experience data in lung cancer, including:

- Clarifying and developing shared understanding of key definitions of patient-experience data and measurement approaches
- Identifying commonalities among stakeholders on core patient-centered outcomes to measure
- Level setting regarding regulatory perspectives for considering and evaluating this data

- Identifying potential uses for this data
- Examining approaches to analyze, visualize, and interpret data
- Understanding any limitations/gaps in current practice
- Evaluating opportunities for communication of this data
- Defining potential next steps for the lung cancer community to advance this field

The March 23 meeting was chaired by Andrea Ferris, President & CEO of LUNGevity Foundation, along with a clinician member of LUNGevity's Scientific Advisory Board and an expert in PROs from Oncology Center of Excellence, FDA. Dr. Upal Basu Roy, LUNGevity Director of Translational Research and Patient FoRCe, and Wendy Selig, Founder & CEO of WSCollaborative, assisted in preparation and facilitation of the meeting. Participant snapshot is provided in Appendix A. The detailed meeting agenda is provided in Appendix B. A list of sponsors for the Roundtable is at Appendix C.

LUNGevity Foundation is grateful to its Scientific Advisory Board, Scientific Key Opinion Leaders (KOLs), leaders from the FDA, EMA, NICE, industry sponsors, patients, and all the participants whose collaborative efforts and active engagement created a productive opportunity to advance the field of lung cancer therapy development.

Meeting Overview

In introducing the agenda for the meeting, **Andrea Ferris, MBA** emphasized the goal of promoting discussion and dialogue, using short "level setting" talks by speakers representing multiple stakeholder perspectives (FDA, industry, clinicians, patients) to set up the topic. She charged the meeting participants with focusing on an assessment of:

- Where are we currently with lung cancer PROs?
- Where do we want to be? What is our "ideal" future state? Can we come to consensus about a core set of measures?
- How do we get there? What are areas that can be clarified, either by the FDA or by clinicians, or by sponsors? How do we leverage current opportunities to get where we want to go?
- Given that this topic has been under discussion for many years, what is different now that provides momentum for progress toward that "ideal" future state?

Ferris summed up LUNGevity's interest in this topic by citing a quote from Cindy Geoghegan, a patient advocate, about the importance of generating PROs that reflect direct input from patients:

> "*Patient-reported outcomes data are necessary to enable people to make rational decisions about treatments that balance impact on survival as well as symptoms, overall quality of life and financial impact. Patients need to know what they can expect to feel and how they can expect to function while on therapy*."

Before launching into the first session, Ferris introduced two patient advocate participants in the meeting**, both** Stage IV lung cancer patients who have participated in clinical trials and experienced multiple therapies during their lung cancer treatment journeys. Both provided brief opening comments to the group, emphasizing the importance of directly asking patients to provide their experiences and valuable input on what matters most to them in assessing treatment options. It was noted that there is a disconnect when some companies feel they cannot have patients who participate their trials assist in designing those trials, using the reasoning that experienced patients may be "biased." The reasons behind not engaging current trial participants were not discussed in detail and of the scope of this meeting. Some of the reasons include potential risk of unblinding, influencing or biasing trial results, among other reasons.

Key Takeaways:

1. There is general receptivity to incorporating PROs into clinical trials but PRO experts within industry are seeking a clearer suggestion/expectation from regulators to make the case with company leadership that this information must be gathered.
2. Continued efforts to coordinate and harmonize expectations and requirements among regulators from FDA and their global counterparts is important.
3. It is important to sort through the multitude of different instruments and attributes being studied in oncology (and used for lung cancer) to *develop a core set of questions* to ask lung cancer patients (e.g. focusing on disease related symptoms, treatment related symptoms, and function). In this way, lung cancer could be a "pilot" for oncology.
4. The FDA is currently exploring a core PRO objective of on-treatment descriptive data of the patient experience focusing on symptomatic adverse events, overall side effect bother/impact, and physical function, and disease symptoms
5. Once the broad categories of what should be gathered are agreed upon, engage the patient community to identify the actual questions that are relevant to them ("If you want to know what patients' think, ask them!")
6. There is a need to balance standardization of PRO instruments with a recognition that drug development and clinical trial designs are evolving and there needs to be some flexibility to address and incorporate scientific and technological advances. PROs need to address patient needs, but also reflect the needs of clinicians, sponsors, regulators and HTA officials.
7. Further discussion is needed on the topic of communicating PRO data from cancer trials to patients and clinicians. If data is not in the label, a manufacturer is hampered from disseminating information to the people who need it most. What are other mechanisms to disseminate PRO information such that HCPs and patient can use the information to engage in shared decision making? Is there a data threshold that can be established where the information does not go in the label, but could go in education/marketing materials? How can the trial community make the dissemination of digestible information easy?

Session 1: Importance of PROs and Other Patient-Experience-Data in Clinical Trials

Session Goal: Review general definitions and importance of PROs across oncology, assess the current landscape and present areas of interest for regulators.

The meeting began with overview comments from several representatives of FDA CDER, who provided an overview of the statutory landscape that underpins many of the changes and activities underway at FDA and throughout the community to prioritize and advance patient focused drug development (PFDD). The first speaker traced the recent legislative and regulatory history in which all stakeholders within the drug development ecosystem have recognized that patients are experts on their disease and their input should be used to inform benefit-risk assessments for new treatments.

The speaker described the FDA's activities, including holding the first PFDD meetings and more Recently encouraging others to host externally led PFDD meetings, to solicit directly from patients their "unique perspective about their disease -- what's it like to live with it, what's the worst aspect of living with it, what are their burdens associated with treatment." Through legislative vehicles (including PDUFA V and VI, and 21st Century Cures), additional commitments were made by FDA to advance this initiative, including developing definitions and providing a series of Guidance documents for industry and all stakeholders about how this patient experience data can be collected in a rigorous, fit-for-purpose manner, and ultimately used within the regulatory process. Moving forward under these legislative and regulatory commitments, FDA will be publicly reporting on patient experience data and related information provided by sponsors.

The speaker emphasized an important message to sponsors about timing for collecting patient input for drug development, noting that it is important to start early, even within the discovery phase of product development, to develop the right tools for eliciting this input throughout clinical trials. Additionally, the speaker noted that it is important to continue collecting patient experience information once a product is on the market, describing a vision for the future, where patient experience information "stops being special and becomes normal" and the costs for collecting this information is minimal and not a deterrent for sponsors (especially small companies). The speaker expressed support for attempting to define a standard set of measures that can be used regularly and can be included in product labels to inform patients and providers.

The second speaker presented an overview of work at the Oncology Center of Excellence, noting that in many ways oncology is ahead of other disease areas in the number of available PRO tools and measurement systems. The speaker offered a case for why the "time is now" for making real progress in incorporating patient experience data in drug development. The speaker discussed how clinicians can be surprised by what matters most to their patients, confirming the need to assess *both* clinical outcome measures based on efficacy of therapies

(e.g. survival, response rate) *and* patient reported outcomes based on elements of tolerability of therapies (e.g. side effects, mode of administration etc.) and improvements in disease symptoms. It was also noted that there is movement to re-evaluate "legacy" PRO tools/instruments to assess ways to reduce duplication and redundancy, while becoming more focused on elements that really matter to patients AND are more sensitive and relevant to the primary objective of commercial clinical trials- to demonstrate the safety and efficacy of the therapy under study. In addition, the speaker pointed to advances in technology that are helping to fuel progress in this area (electronic data capture in the controlled clinical trial as well as "real world" setting, wearable devices, etc.), and the fact that payers are engaging in efforts to gather information and evaluate patient experience.

The speaker concluded with the hope that the stakeholder community will be able to focus on a core set of measures that will reflect patient priorities, including symptoms and toxicities, side effect burden, ability to function, carry out one's activities, go to work and take care of oneself and one's family. If that core can be developed and operationalized, then additional PRO measures to address additional trial-specific outcomes can be added to the "core" as needed. The speaker stressed that any "core" group of patient concepts must be useful for multiple international stakeholders including regulators, payers, clinicians and patients.

Discussion

Introducing a theme that resonated multiple times throughout the meeting, the group discussed ways in which the FDA could be even more proactive in encouraging sponsors to develop and provide patient experience data as part of their clinical trials. It was noted that a stronger approach is needed by FDA in communicating an expectation for receiving this data as part of a regulatory package, to advance the shift in business processes of sponsors and ultimately make the collection of patient experience data the norm in clinical trials.

Additional discussion focused on the need to make this work seamless for clinicians and doable for patients, who while generally willing and eager to provide their input, should not be repeatedly asked duplicative or irrelevant questions as part of the process.

Session 2: What Should be Measured

Session Goal: Focusing on lung cancer, understand concepts to be measured, discuss relevance to the patients, seek group consensus on core data sets to be measured to address interests of multiple stakeholders (e.g. industry, regulators, payors, physicians, and patients).

In recognition of the global nature of drug development and oncology clinical trials, this session began with an overview from officials from MHRA, UK (Medicines and Healthcare Products Regulatory Agency) and NICE, UK (The National Institute for Health and Care Excellence).

The MHRA speaker provided a brief overview of the UK regulatory network, which functions Under the umbrella of the European Medicines Agency (EMA). Within the committee structure, There are several working parties, including one focused on oncology, whose role is providing guidance to industry on regulatory review requirements for drug approvals. A recent guideline appendix was issued to address issues relating to Patient Reported Outcomes, with emphasis on the importance of assessing patients' points of view on their health status, including how they function and their sense of well-being. This information provides a complement to efficacy and safety data. The speaker noted the trend in Europe with patients increasingly participating in face-to-face meetings of the scientific advice working party of the EMA.

In addressing what should be measured, the speaker provided some overall criteria, Noting that the inclusion of the PRO endpoints should add value to the clinical trial, should be considered early in the development program and should involve the patient in the study design. An endpoint should be stated in specific clinical trial objectives with clarity about what the endpoint is trying to measure. Any of the instruments should be administered at clinically relevant time points, and this should not be an undue burden to the patient. The instrument should be sensitive enough to capture both the anticipated and the unanticipated effects. In summary, the speaker emphasized that any claims made on PRO should be based on robust data and analysis from well-designed studies with relevant instruments that are really going to capture the objectives of the study. It was stressed that PRO instruments and assessments should detect clinically meaningful effects and provide this added value of understanding better how the drug is being used within the clinical study and how it might benefit the patients. The speaker strongly recommended that drug developers seek the advice of regulatory and HTA officials as they do this work.

The NICE speaker provided a global payer's perspective, offering an overview of NICE's Structure and authorities in the UK, noting that NICE is usually assessing the same evidence as that being reviewed by the EMA regulators, but with a goal of answering different questions. Once a regulatory decision has been made to make a drug available, then NICE makes the positive or a negative decision for this to be reimbursed in the healthcare system by trying to answer two questions: 1) how cheap must the therapy be to be cost effective, and 2) how clinically effective does the therapy need to be worth paying for. These decisions are generally made based on survival and quality of life, with quality of life playing a significant role.

This speaker reviewed distinctions among multiple types of PRO tools, focusing on the differences between generic tools and disease specific tools. The speaker stressed that for NICE, generic tools are of paramount importance because they allow derivation of utilities for economic modeling. Disease-specific instruments are used and can provide complementary information to that obtained with the generic tools, however it is a problem for NICE when a company only uses a disease-specific instrument (e.g. lung-cancer specific validated PRO tools). It is in a company's best interests to always include data generated with a generic instrument (e.g. EQ5D). To underscore her point, the speaker provided several real-life examples of recent NICE evaluations of lung cancer therapies.

It was noted that sometimes sponsors move quickly toward conditional approval of therapies and bring phase 2 data for regulatory review, with incomplete or no PRO data. This creates a problem for NICE. The speaker made a plea to industry to include PROs early in their drug development programs to address this problem.

Next two FDA speakers provided the Agency perspective on what to measure. The first speaker gave an overview of FDA's process in reviewing a new drug application, including two aspects: completing the benefit-risk framework and evaluating the patient experience data (from PRO's). It was noted that, where the patient experience data is robust and shows a Clinically meaningful benefit, that evidence can be included in the benefit-risk framework.

This speaker walked through a series of key questions that reviewers ask in assessing the Patient experience data they receive, including whether the sponsors fully understand the symptoms of the underlying condition, whether they have chosen the right tool to assess the patient experience with the condition, whether the sponsor has considered the toxicity profile and ease of administration of the drug, the duration and setting of the treatment, and how the treatment compares with the standard of care. The speaker went on to discuss reviewers' considerations with respect to the clinical trial itself, including: Is it a well-controlled adequate trial that can answer the question? Or is it just a single-arm trial, but has a good sample size? Is there a clear statement of the PRO objective? Can it distinguish the effect of the drug from other influences? And, are the tools well-defined and reliable tools?

Lastly, this speaker described regulators' interest in the sponsor's goal for use of the PRO data, including:

- Does the sponsor seek to use PRO data as supportive data for overall benefit/risk assessment?
- Or is the sponsor interested in including descriptive patient experience data into the label?
- Or does the sponsor seek to make a claim for treatment benefit in the label?

It was noted that it can be frustrating for regulators when the PRO endpoint lacks clear objectives. In general, for a PRO endpoint to be included in a label it must have some statistical hierarchy and analysis. The speaker concluded her remarks by suggesting this is more likely to be accomplished with PROs that focus on symptoms that are relevant to the specific disease and the therapy under review.

The next speaker began by reminding the group that several "legacy" PRO instruments in active use today, were first developed in the 1990's. It was noted that for FDA, what is most proximal to the drug effect is symptom status and functional status, which are elements that could possibly be labelled. FDA's interest in health-related quality of life is focused on the patient's ability to function, symptomatic adverse events (overall side effect impact) and

disease symptoms. The speaker noted that, when considering physical function, there are important distinctions related to disease setting that can be obscured with the use of a standard set of measures. Additionally, s limitations of those "legacy" PRO tools in that they over emphasize side effects associated with more traditional therapies (e.g. chemotherapy) yet they do not capture adverse events associated with more novel therapies (e.g. immunotherapy and its distinct side effects).

An industry participant commented that having a trial with a PRO as a primary endpoint is still a long way off from where the field is today. This participant underscored the point made by previous speakers about the speed with which oncology drug development is occurring (e.g. accelerated approvals, breakthrough designations, single arm studies etc.), and the impact that is having on the traditional phases of clinical trials and the reduction in numbers of randomized controlled clinical trials being undertaken.

This industry speaker noted interest in standardizing what is measured in oncology trials, and focusing on developing PRO endpoints (not just the tools to measure them). It is important to focus on defining the outcome of interest in the trial as it is designed and evaluating the structure of the trial, as necessary for determining the best way to develop the relevant patient experience evidence. This participant encouraged pre-competitive collaboration among sponsors in developing conceptual disease models, and concluded with a brief discussion about opportunities to integrate what is learned through PRO's in clinical studies into clinical practice.

A seond industry noted the use of the term "Patient-Centered Outcomes Measurement" rather than patient-reported. In expressing support for a core set of measures, this participant noted that many of the elements of patient experience data are interdependent, and that standards of care and patient expectations/wants/needs are continuously evolving. This poses challenges with trial design, as sponsor need to consider not just what patients want and need today, but what they might want and need in 4-5 years when a trial reads out.

This partiipant went on to emphasize that just because something is "patient-reported" that does not mean it is "patient-centric." In fact, patients are often asked to respond to questions about how they feel or function that do not reflect things that truly matter to them. This participant stressed that survival remains important to patients, and it should be viewed as a patient centered outcome.

It was sugested that, while industry evaluates their drug pipelines and companies consider go/no-go decisions about specific drugs, they may want to consider relevance to patients, along with proof of concept and proof of mechanism.

Discussion:

The two survivor participants in the meeting discussed what "quality of life" means to them, chiefly being able to participate in the elements of their lives, noting that this may mean

different things to different patients. They commented about being surveyed about their side effects relating to investigational therapies as part of clinical trials. Both felt that the surveys had been missing key elements relating to their experience with the therapies being studied. For example, as surveys are given in the doctor's office and often weeks apart, when patients are asked "how are you feeling today", this does not account for the days leading up to the doctor visit (when they may have been feeling much worse, or much better).

Additionally, they underscored the importance of understanding a potential treatment's impact on quality of life and of having detailed information available in a format that is understandable and digestible for patients that can be used in for discussion with a physician about possible side effects (specifically how patients experience the therapy) of a treatment option being considered. The importance of being able to support these doctor-patient discussions with good information about patient experience with a therapy was underscored by one of the clinician participants.

The importance of terminology in this discussion was emphasized, as "health-related quality of life" is not synonymous with "side effects." There is often discussion about quality of life, yet what is being measured in a survey is specific to pain. One of the FDA participants stressed that the focus of a core set of PRO measures should be the "side effect burden," so that a variety of aspects could be measured to assess tolerability and impact on quality of life.

The concept proposed for consideration by the participants is a modular approach of establishing a core set of patient experience measures and then adding to those for specific situations using "item libraries" populated with concepts and related questions (e.g. PRO-CTCAE). In this way, the approach can be both standardized and flexible. The group briefly discussed asking a patient to evaluate their experience by choosing from a menu of concepts based on "goal attainment," in recognition of the fact that patients often value different things.

The group discussed the goal of developing well defined functional domains (ie: physical role function and selections of certain disease and side effect symptoms) that make sense for a trial and can be statistically valid. Clinicians, cooperative groups, and industry sponsors will all need to agree to this type of approach, which could include agreed-upon core outcome sets, with the opportunity for a more tailored overlay for a specific trial. There is an opportunity to coordinate with the International Consortium for Health Outcomes and Measurement (ICHOM), which creates standard sets of measures for different diseases that are treatment agnostic and include patient reported outcomes and clinical outcomes.

The participants discussed distinctions between measuring disease symptoms (the underlying symptoms of lung cancer and its progression) and the side effects (or toxicities associated with a therapy, e.g. its tolerability). It was noted that these are often two sides of the same coin from a patient's perspective in how they feel and function, although it is necessary to keep

them separate in terms of clinical trial design and measurement of clinical benefit.

Lunch Session: PRO CTCAE Update/Friends of Cancer Research Activities

A speaker from the NCI provided an overview of the Patient Reported Outcomes of the Common Terminology Criteria for Adverse Event Reporting (PRO-CTCAE) initiative for patient reporting of symptomatic adverse events in clinical trials.

While clinicians are evaluating patients in trials for safety and clinical outcomes using the traditional CTCAE to assess safety signals, patients are focused on the tolerability of a therapy (i.e. its impact of the therapy on their day-to-day lives). There is an important distinction between safety and tolerability, and increasingly the field understands that physician-reported assessment of tolerability of a therapy is not the same as assessments by patients themselves.

This speaker noted that NCI is including the PRO-CTCAE (an item library) in its trials (there were 20 last year) to ensure that patients' assessments of side effects from treatment are collected and aggregated with the physician assessments to provide a more complete picture of the impact of a therapy. The PRO-CTCAE includes 78 items, which each have 1-3 questions associated with them, relating to severity, interference, and presence/absence. NCI has released a funding opportunity specifically focused on tolerability, asking the investigator community to design best ways to analyze these data and accurately measure "side effect bother" for patients. Additional efforts are underway to expand the use of PRO-CTCAE and encourage all physicians to use it, not only in clinical research but also to improve clinical care.

Next, a Friends of Cancer Research Participant provided an overview of recent work by Friends relating to tolerability. The speaker reviewed a 2015 Friends event which identified multiple challenges with PROs and specifically the PRO CTCAE, including: trial designs not being optimized for inclusion of PROs, difficulty in aligning PROs with the development timelines, particularly with accelerated approvals and breakthrough therapy designations, lack of standardization in data analysis and presentation, difficulty in operationalizing this work in a multi-national setting due to language barriers in some of these tools, operational challenges around item selection, minimizing the patient burden and duplication of questions, and mechanisms for sharing the results to ensure the data gets to patients to inform their decisions.

To address thesechallenges, the PRO-CTCAE Industry Working Group was established to provide a pre competitive space for companies to work together. Leveraging this effort, Friends is leading a process to develop a manuscript to propose a more granular, working definition of tolerability that is more patient-centric, can inform best endpoints and trial design, and that can ultimately be embraced by the community. He concluded his remarks by suggesting the need for better ways to provide this information to patients, including considering a patient experience section for labeling.

Session 3: How to Measure PRO Concepts

Session Goal: Generate discussion and shared understanding of various methods for measuring lung cancer PROs/patient experience data, identification of which measurement tools are acceptable and how best to validation those tools.

A participant from FDA presented an overview of FDA perspectives regarding how to measure PRO concepts, noting the importance of using a fit-for purpose instrument. The definition of fit for-purpose in this context means that it follows good measurement principles, including: the assessment is appropriate for its context of use; that it measures the most important concepts to patients; that its contents or concepts are well defined; that it can generate consistent and reproducible data; it measures what it is supposed to measure; it's sensitive to detect change; and the score change that is observed is interpretable and is also reflective of meaningful change. The speaker noted that it is alsoimportant that the instrument yield data that can be communicated in a way that is accurate, interpretable and not misleading.

This speaker discussed ways in which the FDA works with sponsors to evaluate instruments, encouraging efforts to reduce redundancies, address issues with timing and recall, assess scoring approaches, discuss mode equivalence, and evaluate study design (especially length of study, impact of open label study on patient's assessments, whether meaningful change is observed, effect of concomitant medications etc.).

An academic expert on PROs spoke about practical considerations of doing PRO assessments. This speaker noted the importance of evaluating the patient population, disease settings, and treatments within the trial, as well as the intended concepts for measurement and if/how they are changing over time. This may influence where assessments should occur, if they need to happen in clinic or while the patient is at home, or if they should be measured multiple times a day, etc. The speaker outlined multiple factors that clinicians consider in selecting a PRO tool for use in a trial, including that it: measures the intended concepts, has suitable measurement properties, is relevant for the study patient population (e.g. has desired language translations, is age appropriate), has reasonable costs, is consistent with comparative trials, and poses an acceptable burden on the patient.

The speaker also commented on three examples of item libraries – PRO-CTCAE, PROMIS and EORTC – and evaluated some of their pros and cons. It was noted that PRO-CTCAE and PROMIS Have components that can use computer adaptive testing instead of static forms, which can be beneficial but also are still being evaluated for comparability. In closing, this spekaer expressed support for developing a core set of concepts to measure and then supplementing with an item library.

Next an industry participant discussed challenges faced by industry in assessing patient experiences, including time constraints, limited financial resources, issues with trial design, the

properties of existing measures, as well as the varying needs of our stakeholders. This speaker noted that, in an era of accelerated approval and breakthrough therapy designation, it is more challenging to implement innovative assessment models. For example, it can take 12 weeks to implement computer adaptive testing (E-PRO) into a trial which may be more runway than the development timelines will allow. There is often not the time to do the legwork and item development early on in a development program that is moving quickly. It was noted that, in oncology specifically, with more small, single arm, open label studies, this is even more challenging. There are also issues with validation and missing data/data completeness, especially when it comes to requirements of global regulators (e.g. Germany has strict rules about missing data and has expressed questions about PRO-CTCAE).

This speaker concluded by proposing several questions for the group, including:

- Could we have more guidance related to the appropriate uses of off-the-shelf measures in oncology trials?
- Can we align on specific scales that we are comfortable with?
- Or, if not, come up with a very specific guidance on modification approaches that may be deemed acceptable.
- How can we better target measures to address the profiles of study-specific comparators?
- Are there any initiatives to align FDA and EMA so that sponsors can formulate one strategy to satisfy both agencies?

Discussion:

The participants discussed these questions, and specifically considered ways to evaluate the domain concept of "symptom bother" or "side effect bother" to develop an overall evaluation of the patient's assessment of a therapy's tolerability. This can provide a single question, which is much easier to assess and evaluate for meaningful change than a complex, cascading series of questions across multiple instruments. Achieving this type of streamlined approach is a goal of the PRO-CTCAE Industry Working Group, which involves 12 companies attempting to create a framework so that when patients look at labels, if everyone in industry's using PRO-CTCAE, and displaying the data in a similar way, it'll be much easier to look across labels and make comparisons for the tolerability of side effects. The group also discussed nuances of using paper vs. electronic instruments and ways to ensure data can be reconciled across modes.

Efforts are continuing to encourage all sponsors to use PROs and provide tolerability assessment evidence. The group discussed ways that the FDA could be more proactive in indicating that this evidence is expected by regulators, to advance the goal of having all trials collect and report this information. Additionally, efforts to get all sponsors to do this work will be more successful if there is further alignment and harmonization among global regulatory agencies.

There was discussion about the value and challenges associated with collecting patient experience data post-progression, especially when patients are no longer coming into the clinic. While the FDA does not require post-progression PRO evidence, other stakeholders, especially regulators in other countries, modelers and payers, do ask for this information as they want to understand durability of symptoms and response over time (e.g. with I-O therapies).

Relating to concerns about correlation between clinician adverse event reporting and the reporting associated with the PRO-CTCAE. Participants discussed industry concerns with monitoring risk and inspection issues with physician under-reporting of AE's. There is a paper coming out that clarifies that PRO data does not need to be reported as safety data and the FDA recognizes that there will be discrepancies within a trial between reported safety data and PRO data. FDA does not ask for clinical monitoring of PRO data.

Session 4: Analysis, Interpretation and Presentation of Data

Session Goal: Generate discussion to further define how patient experience data can be used, and to deepen understanding and types and amount of data needed, analytical methods and data presentation formats.

An FDA participant discussed the Agency's requirement to report on patient experience data submitted to the Agency and its approach to standardizing, reviewing and describing that information. This speaker presented examples of graphic presentations for several concepts, including patient disposition, completion rate, item-level response, categorical PRO's and patient progression from baseline while on therapy. The speaker summarized FDA's approach as using pre-specified PRO analyses and focusing on descriptive summaries of patient experience while on therapy, noting this is still a work in progress with statistical methodology or visualizations driven by the research objective.

An industry participant provided an overview of analytical approaches to PRO data and cited published sources. This speaker discussed the advantages and disadvantages of various approaches for evaluating PRO data using a longitudinal model (linear mixed model with repeated measures) and a time-to-event model (time to quality-of-life score deterioration). Longitudinal models have well-established methodology and are robust to missing data but do not account for response shift and may not be easy for some clinicians to understand. Time-to-event models can provide clinically meaningful results and death can be taken into account but need enough measurements to be meaningful and depend on the definition of deterioration (of which there are several). A Rasch model was shown to enrich interpretation of PRO scores. An example was given with the Functional Assessment of Cancer Therapy-Kidney Symptom Index-Disease-related Symptom Scale (FKSI-DRS) where its scores were mapped to the chance of not having each of its nine symptoms, forming a profile of favorable

responses across the nine symptoms of FKSI-DRS. Furthermore, a person-item map (from a Rasch rating scale model) for 10 items on s physical functioning scale was illustrated to inform about the relationship between item difficulty and person ability on physical functioning. Also noted were challenges when different PRO measures within a study are based on different scales with different ranges and the interest centers on their relative magnitude of treatment effect. To address this, standardized effect sizes can put the different measures on the same metric (standardized deviation units). Additionally, distinctions were made between "minimally clinical important difference" and "minimal important difference" on the one hand and "clinical important difference" (CID) and "clinical important responder" (CIR) on the other hand. The CID can be used as threshold for the relevance of a treatment group difference, while the CIR can be used as a responder definition for within-subject change. Finally, to illustrate the process for teasing out the interrelationship of multiple factors, this speaker used an example where approximately one-quarter of the treatment effect on reduced self-reported sleep disturbance was occurring indirectly through the mediating effect of self-reported pain reduction, with the remaining three-quarters occurring directly through other factors.

Discussion:

Participants emphasized that successful ability to determine meaningful change through statistical analysis depends first on having the necessary data, which is predicated on ensuring that the right questions are asked of patients within trials. Analysis gets ever more complicated when multiple items are being evaluated at the same time (and even more so with combination therapies), so it can be more streamlined and less complex to evaluate single items in a PRO using scales that show meaningful change. It is important to evaluate data and ultimately present it in a way that physicians and patients can understand it and incorporate it into shared decision-making.

The group agreed it is necessary to combine the expertise of statisticians, with clinical expertise and the input of patients to arrive at a process of evaluation that defines meaningful change and yields useful analyses. Additionally, it is important for sponsors to engage with FDA early in the process for defining their approach. FDA is anticipating, after its summer workshop, to be able to provide sponsors with its preferred standard approach for measurement of acute and subacute patient experience that is a well-defined and reliable tool. Industry patient experience experts noted the importance of having FDA expecting and utilizing this data in helping to drive culture change within their companies.

Session 5: Communication

Session Goal: Generate discussion and feedback about how and where patient experience data that is collected and analyzed can and will be communicated.

An industry participant provided an industry perspective on opportunities for communicating patient experience data. This speaker expressed support for the emerging consensus among participants for a core set of items to measure, focusing on symptom improvement, adverse events (side effects), and the impact of those on a patient's quality of life. The speaker presented an overview of the multiple stakeholders and end-users of industry efforts to communicate this type of data (from a clinical development and medical affairs perspective). He discussed the multiple channels that exist for communication of this information, from publications to labeling to online (social media) activities, and the importance of presenting the information in ways that are understandable to key audiences (especially physicians and patients). Technology is offering patients a way to communicate with each other and compare experiences. This should be part of the process, not a work-around because the existing system is failing to deliver what patients really need.

It was noted that having the information in a product label, perhaps in the form of a patient-specific label, would be "the ideal world" situation, as it would ensure the information reaches providers and patients and would provide comfort to companies, who worry about off-label communications (ie: discussing anything that is not within the label).

A clinician participant provided a clinician's perspective on the topic of communication, underscoring the importance to doctors of listening to patients and understanding "how they feel and what they can do in living their lives." Regarding the functional assessment, clinicians want their patients to live long and be able to pursue their lives as they would like to live. As this is a personal decision for individual patients, PRO data can help inform this discussion.

An FDA participant concluded the session with a summary of what FDA is doing to promote communication of patient experience data, including putting this information in its reviews and working to address opportunities for label inclusion and other approaches leveraging technology (online channels to facilitate wider accessibility for the information). This speaker noted that the label may not be the only (or best) opportunity for communicating this data, while acknowledging feedback from industry participants on its importance to them and company leadership.

Discussion:

Participants focused on steps that could be taken to encourage and broaden communication of PRO information. It was noted that often publications of patient experience data come much later than publication of the efficacy data for a trial. The group agreed it would be better to have all relevant information to a therapy's impact presented together.

There was significant discussion about the need for culture change within company leadership, for embracing the value and importance of PRO data. This culture change could be driven

faster by clear communication from FDA regarding its expectations for receiving and communicating patient experience information, whether in the label of by other means.

Industry participants emphasized the need for strong, clear guidance form the Agency on these points, with specific focus on labeling opportunities and requirements. Additionally, it was noted that there is more work to do within the scientific and medical communities to drive understanding and acceptance of the validity of this data as critical components of clinical trial results that should be presented along with primary endpoint analyses.

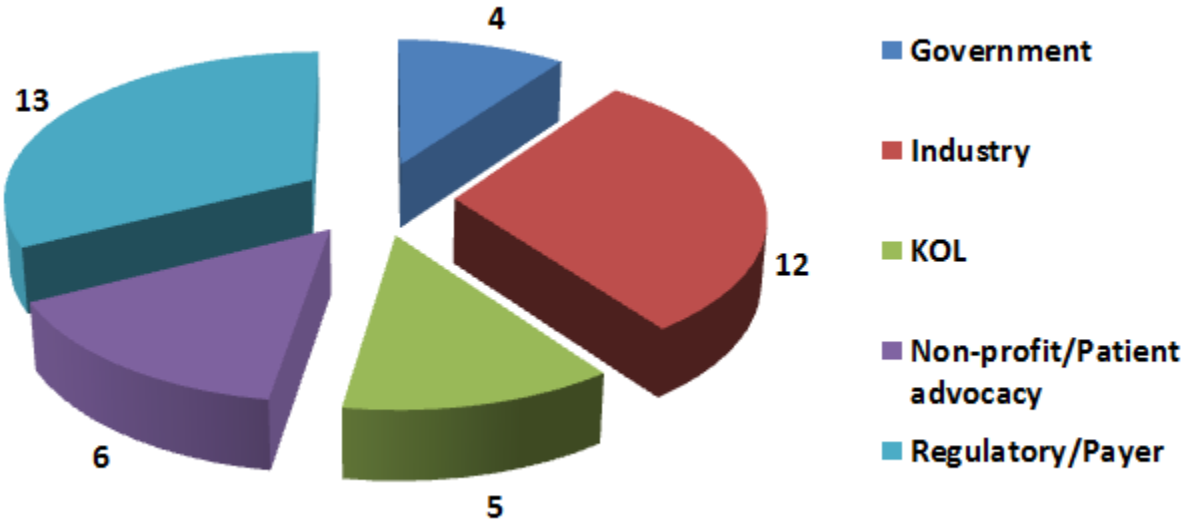
Finally, the group touched on opportunities to incorporate data from wearables into this work. It was noted that data from wearables can provide an additional piece of supplementary evidence to support what the patient reports (e.g. exact number of steps, amount of sleep etc.).

Wrap Up and Next Steps

FDA will incorporate feedback from this meeting as it prepares for its June workshop, during which it will presents its proposed framework for what to measure (symptomatic adverse events, overall side effect impact, symptoms of the disease, physical function) and trial design issues including how frequently to assess PRO questions. During this workshop, PRO experts will develop trial designs to accomplish this using several existing PRO tools and measurement systems and discuss several ongoing efforts to develop standard analysis and presentation methods. Dr. Kluetz also mentioned plans for a manuscript stemming from the workshop as well as a Draft Cross-Center Guidance which is under development with goal date within the next 1-2 years.

LUNGevity will launch a project to review PRO Instruments most commonly used in lung cancer trials, compare the questions, and develop a consolidated document that can be circulated by LUNGevity to its patient population for input on what is important to them. LUNGevity will create a Patient-Advisory Board for the project; conduct qualitative interviews; circulate the questions for weighing; compare with what is currently being gathered; and make recommendations on what SHOULD be gathered. This will then be distributed as a survey to the March 23rd meeting participants as a step toward establishing a relevant core set of measures and concepts for the item library.

Appendix A - Participant snapshot



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Appendix B – Meeting Agenda

9:00 – 9:45	**BREAKFAST AND REGISTRATION**
IMPORTANCE OF PRO'S AND OTHER PATIENT -EXPERIENCE DATA IN CLINICAL TRIALS	
10:00 – 10:30	Introduction and Overview • Definition of PROs – why are they important, how are they used and by whom? • Current landscape • Clarify and describe utility of current PRO data reported: Benefit Claim, Supportive Claim, Descriptive Data, Inform Safety and Tolerability • What are regulatory agencies interested in and why?
WHAT SHOULD BE MEASURED	

10:30 – 12:30	• Overview
	• What PRO concepts should be measured?
	  ○ Symptoms
	  ○ Physical Function
	  ○ Role Function
	• What is relevant to a patient?
	• Can we agree on a core?
	• What are HTA interested in?
	• US & Global considerations of regulatory agencies (FDA? EMA?)
	• Pharma? Treating Physicians?

12:30 – 1:30	**Working LUNCH (Overview of FOCR work and PRO CTCAE)**

HOW TO MEASURE PRO CONCEPTS	

1:30 – 2:30	• Overview
	• How should PROs be measured?
	  ○ Trial Design
	  ○ Instrument issues
	  ○ Timing and frequency of observations
	• What tools are acceptable?
	• How are tools validated?
	• Can data/individual items from different tools (e.g. paper and electronic) be pooled?

ANALYSIS, INTERPRETATION AND PRESENTATION OF DATA	
2:30 – 3:30	• Overview • How will the information be used? • What and how much data is required? • How will data be analyzed? • How will data be presented?
COMMUNICATION	
3:30 – 4:30	• Overview • What is important for HCPs and patients to know? • What vehicles are available to use (e.g. publications, label, marketing materials, other) • If not in the label, where?
4:30 – 4:45	**WRAP-UP & NEXT STEPS**

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Appendix C – List of sponsors

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SCIENTIFIC AND CLINICAL RESEARCH ROUNDABLE

PATIENT REPORTED OUTCOMES 2018

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