WORKSHOP ON
CLINICAL OUTCOME ASSESSMENTS (COAs)
IN CANCER CLINICAL TRIALS

April 26, 2016  ■  Silver Spring, MD

Co-sponsored by
WELCOME

WORKSHOP ON
CLINICAL OUTCOME ASSESSMENTS (COAs)
in Cancer Clinical Trials

April 26, 2016 • Silver Spring, MD

Paul G. Kluetz, MD
OHOP

Stephen Joel Coons, PhD
PRO Consortium

FDA

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Registration Packet Contents

- Welcome Letter
- Workshop Agenda
- Presenters and Panelists Biographical Sketches
- Pre-Registrant List
- Workshop Feedback Form
Active Participation is Encouraged

Before you speak, please step to a microphone or let us bring a microphone to you.

The workshop is being audio recorded.

Please turn off cell phones or set to vibrate.
Overall Goals of the Workshop

• Provide a forum for international drug development stakeholders to hold an open and constructive dialog in an evolving area of regulatory and health care policy

• Discuss methods to thoughtfully and scientifically incorporate the patient voice into cancer drug development to better inform regulatory, reimbursement, and treatment decisions

• Encourage a sustained collaborative effort to continue to work toward improved alignment and strategic use of PRO measures in cancer trials
Workshop Sessions

**Session 1:** Reviewing the Patient-Reported Outcome (PRO) Data Needs of Stakeholders: What Questions Are We Asking?

**Session 2:** Using Multiple Instruments to Create a Comprehensive PRO Assessment Strategy in Cancer Trials

**Session 3:** Existing Options for Assessing Patient-Reported Physical Function

**Session 4:** Physical Function Data in Cancer Trials: Data Collection, Analysis, and Interpretation
Session 1
Reviewing the Patient-Reported Outcome (PRO) Data Needs of Stakeholders: What Questions Are We asking?
Disclaimer

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Session Participants

**Chair**
- Stephen Joel Coons, PhD – C-Path

**Presenters**
- Paul G. Kluetz, MD – FDA
- Daniel O’Connor, MD – MHRA and EMA
- Keith Tolley, MPhil – Tolley Health Economics Ltd.
- Joseph O’Connell, MD – InventivHealth

**Panelists**
- Mary Lou Smith, MBA, JD – Research Advocacy Network
- Naomi Aronson, PhD – Blue Cross Blue Shield Association
- Chiun-Fang Chiou, PhD – Janssen
Patient-Reported Outcome Measures in U.S. Regulatory Review of Cancer Products

Paul G. Kluetz
Office of Hematology and Oncology Products
U.S. Food and Drug Administration
• This talk represents current thinking in an evolving area of scientific and health care policy

• The views expressed do not necessarily reflect the official position of the U.S. Food and Drug Administration
FDA’s Use of PRO Data in Oncology

- FDA reviews the safety and efficacy of cancer therapies
  - Primary and secondary endpoints of submitted trials are most commonly radiographic measures and overall survival

- PRO data most commonly exploratory endpoints
  - Reviewed as important supportive data during the benefit:risk determination

- Inclusion of PRO results in product labeling has been challenging
Patients Would Like to Know How They May Feel and Function When Taking a Cancer Therapy

- FDA labeling is only one potential source of PRO and COA data obtained in a clinical trial

- **FDA clinical and statistical reviews** for new drug and biologic products available online

- **Published literature**- Rigorous PRO and other COA data can and should be published contemporaneously with primary efficacy and safety manuscript
U.S. Drug Labeling Allows for Drug Marketing and Promotion

Federal Food, Drug & Cosmetic Act (FD&C Act)

- Prescription drug promotion must...
  - Not be false or misleading
  - Have fair balance
  - Be consistent with the approved product labeling
  - Include claims substantiated by adequate and well-controlled clinical studies
FDA Labeling Considerations

• If claiming treatment benefit (Drug X decreases cancer pain)
  – Requires substantial evidence with pre-specified endpoint definition, statistical testing and control of Type I error
  – Requires well-defined and reliable assessments in adequate and well-controlled trials

• Whether a claim of benefit, or describing safety data, labeled data must be interpretable and effects should be related to the drug
  – “Purpose of conducting clinical investigations of a drug is to distinguish the effect of a drug from other influences…”
  – “…Adverse events for which there is some basis to believe there is a causal relationship between the drug and the occurrence”

Reference 21 CFR 314.126, 21 CFR 201.57(c)(7)
Integrating More of the Patient Experience in FDA Labeling

• Labeled PRO data has typically been generated from “proximal” symptom and functional outcome assessments more directly related to the effect of the drug (Rock 2007, PMID: 17991927)

• We are interested in exploring opportunities for PRO assessments in cancer trials that may be suitable to help inform patients and providers in product labeling
Proximal symptom and functional outcome assessments

For labeling considerations, proximal symptom and functional outcome assessments are favored and are important components of HRQoL.

Proximal concepts are not the only PRO data to assess or measure, but they have been the focus of our analysis to consider for potential inclusion in product labeling.

Figure from Kluetz et al., Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials: Symptomatic Adverse Events, Physical Function, and Disease-Related Symptoms, 2016, Clinical Cancer Research, Epub 2016, Jan 12.
Patient Reported Outcome Data

- Held to the same standard as any other data that supports the safety and efficacy of a treatment

- What is the objective of a PRO assessment?

- If primary or key secondary endpoint to determine efficacy, trial design should be consistent with that goal
  - Blinding
  - Enrichment for symptomatic or functionally impaired patients
  - Example: Jakafi (ruxolitinib)
Safety in a Changing Therapeutic Context

**Prior** Drug Development Era:

- Mechanism: Cytotoxic Chemotherapy
- Intermittent Intravenous Administration
- Shorter Duration of Treatment
- Adverse events typically Neuropathy, Mucositis, Bone Marrow Suppression, Fatigue, Nausea/vomiting, Diarrhea, Hair Loss, Taste Changes

**Current** Drug Development Era:

- Mechanism: Diverse, including Cytotoxic, Immune, Antibodies, Small Molecule targeting Various Pathways.
- Continuous Daily Oral Administration becoming more common
- More Prolonged Duration of Treatment
- **Adverse events can differ depending on mechanism and target.**

Systematic PRO assessment of symptomatic adverse events with a flexible PRO instrument could be of value
Safety and Tolerability

- “How will I feel and function while taking this therapy?”

- While there is a role for efficacy assessment with PRO, FDA is also evaluating new and existing PRO measures to inform safety and tolerability.

- Descriptive data on symptomatic adverse events and how patient’s function and carry out their activities while on cancer treatment.

Safety and Tolerability is a PRO measurement Opportunity(3,6),(996,991)

- Safety is a key trial objective across all stages of drug development.
- Systematic assessment of symptomatic adverse events can add important descriptive data to complement existing clinician reported safety assessments.
- Can physical function describe the tradeoff between efficacy and toxicity?
Panel 1 will hear perspectives from several key stakeholders who incorporate patient reported outcome data in their decision making.

Figure from Kluetz et al., Focusing on Core Patient-Reported Outcomes in Cancer Clinical Trials: Symptomatic Adverse Events, Physical Function, and Disease-Related Symptoms, 2016, Clinical Cancer Research, Epub 2016, Jan 12.
The Goal for PRO Measures

• **Common Goal that We All Share:**
  – Reliable and responsive PRO assessments that help inform a drug’s effect on patients is EVERYONE’s goal
  – Optimizing PRO data is not a regulatory issue, it is a scientific issue

• **Exploring Clinical Outcome Assessments (COA) including PRO measures in the Evaluation of Oncology Therapies**
  – Increasing FDA statistical, COA staff and clinical reviewer resources and expertise related to COA measurement in oncology
  – Interacting with COA academic and international policy stakeholders
  – Continuing to learn from patients in patient-focused drug development meetings and other interactions
Reviewing the Patient-Reported Outcome (PRO) data needs of stakeholders: What questions are we asking?
- EU regulator’s view

Dr Daniel O'Connor – Medical Assessor - MHRA
Disclaimer

The views expressed do not necessarily reflect the official position of the MHRA, the EMA or their committees
European regulatory framework

- Member States (MS) have one or more medicines Competent Authorities
  - UK authority is the Medicines and Healthcare products Regulatory Agency
- MS & the European Medicines Agency (EMA) work together in a regulatory network
- EMA is the medicines regulatory agency of the EU, the EMA co-ordinates, through its scientific committees the evaluation of new oncology medicines
- Scientific Committees are made up of experts from the EU countries, as well as representatives of patient and healthcare-professional organisations
  - Working parties are convened to carry out specific tasks in their respective fields
  - Scientific Advisory Groups provide independent scientific recommendations
- Scientific advice is given by the Scientific Advice Working Party
- There is an extensive collection of EU scientific/ regulatory guidance documents
- In total, the EMA works with a network of over 4,500 ‘external’ European experts
Involving the patient in regulatory activities

- The Patients' and Consumers' Working Party (PCWP) provides a platform for exchange of information and discussion of issues of common interest between EMA and patients and consumers
- Patient involvement in regulatory activities is growing and diversifying year on year
- The inclusion of patients in protocol assistance procedures began in 2005
- Patient experiences adds a valuable dimension

Guidelines

- Guidelines provide a basis for practical harmonisation of how MS/EMA interpret & apply the requirements for the demonstration of quality, safety & efficacy (questions we are asking)

- Main oncology guideline is the ‘Guideline on the evaluation of anticancer medicinal products in man’

- The revised 2012 guideline refers to a proposed Appendix 2, PRO measures in oncology
Appendix 2: PRO measures

• The oncology working party held a workshop on health-related quality of life (HRQL) in 2012, bringing together relevant experts to help inform on the content of the new PRO appendix in oncology.

• The appendix will be imminently published following a public consultation and extensive revision of a reflection paper.

Key message

‘The importance of the patient’s point of view on their health status is fully acknowledged and such information may be used in drawing regulatory conclusions regarding treatment effects, in the benefit risk balance assessment or as specific therapeutic claims’
Use of PRO measures in oncology studies

• The PRO appendix has 19 pages, 8 sections and 53 references

• The appendix covers general aspects of the use of PRO endpoints in oncology studies:
  o Specific sections on symptom PRO measures and Health Related Quality of Life (HRQL), clinical trial design and clinical importance
  o PRO: A PRO includes any outcome evaluated directly by the patient himself or herself and is based on patient’s perception of a disease and its treatment(s)
  o PRO measures (PROMs) are the tools and/or instruments that have been developed to ensure both a valid and reliable measurement of these PROs

Key aim

• ‘By outlining broad principles of scientific best practice rather than prescribing a particular approach to PRO selection and application, the appendix aims to encourage developments in the methods and application of PROs in the oncology regulatory setting’
Why include PRO assessment?

• Provide a patient focused assessment of the burden and impact of disease, by understanding how a treatment impacts on patient functioning and well-being.

• Add information on the clinical benefit of a therapy by complementing efficacy and safety data with patient-reported evaluation.

• Assess the relationship/agreement between clinical reported endpoints and other patient-reported endpoints.

• Attempt to differentiate two treatments, where the primary endpoint is an objective measure.

• Provide information to facilitate more accurate future patient-physician communication in terms of the quality of the survival time remaining for the patient and the burden of treatment-related morbidities and disease-related patient impacts.
General recommendations for PRO measures

• An assessment or rationale for the extent to which the inclusion of PRO measures can provide added value in the clinical trial setting

• Consider whether the collection of PRO data can detect meaningful effects and make a difference to the study conclusions and benefit risk balance assessment

• A clear hypothesis lead strategy is strongly recommended and measures should be selected based on the scientific rationale

• PROM should be considered early in the development programme

• Consideration should be given to patient involvement in the study design process and in the evaluation of study feasibility

• PRO data reporting should be adequately performed and PRO data should be treated with the same importance as other clinical data
Which instrument(s) to choose?

- There are many instruments in the published literature

- The new PRO appendix does not cover the validation of instruments nor does it make specific recommendations regarding which instrument to select, but:
  
  - Important to select the most appropriate instrument(s), in line with the study objectives and the characteristics of the patient population
  - The most appropriate and valid PRO measures have often involved patients in their development
  - PRO measures should be acceptable to the population in which they will be administered, both in terms of the questions they ask and the overall burden to the patient
  - PRO instruments and assessments should be capable of detecting clinically meaningful effects
  - Consider special populations (children, adolescents & young adults, elderly, palliative setting, patients with rare diseases) and linguistic and cultural validation
EMA HRQL guidance is also available

- Discusses the place that a HRQL may have in the drug evaluation process and gives some broad recommendations on its use in the context of already existing guidance documents (2005)

- HRQL goes beyond efficacy and safety assessments, which are the basis for drug approval

- 2016 Oncology WP work plan:
  - This is an overarching guidance in need of updating
  - A Concept paper to be agreed Q2 2016
Clinical importance and added-value

• The importance of the patient’s point of view on their health status is fully acknowledged and such information may be used in drawing regulatory conclusions

• However, poorly defined PRO objectives and lack of a priori specification of the expected effect have hampered the usefulness of PROs in regulatory decision making

• But PRO information can enhance decision making by providing a better understanding of the potential impact of both the disease and treatment on a patient

• PRO instruments and assessments must be capable of detecting clinically meaningful effects

• Added value may be derived if patients and clinicians have a more complete picture of the expected impact of a treatment on the patients’ perception of adverse reactions and on disease related symptoms
What (questions) are we asking for?

• We want to capture the patients’ perspective during the drug development process and at regulatory approvals

• This is reflected by increasing patient involvement in scientific advice, EMA committees and the launch of a specific PRO appendix in oncology
  • PRO appendix aims to encourage developments in the methods and application of PROs in the oncology regulatory setting

• PRO measure should be considered early in the development programme

• Careful planning and an in-depth analysis of whether the inclusion of PROM is likely to make a potential difference to the study conclusion should be made

• PRO data should be treated with the same importance as other clinical data

• Scientific advice at the EMA (+ parallel with FDA) can help with the challenges
Thank You

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A European Health Technology Assessment Perspective

Keith Tolley
Director, Tolley Health Economics Ltd.

Workshop on Clinical Outcome Assessments (COAs) in Cancer Clinical Trials

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Overview

• What role does PRO evidence play in HTA of new cancer pharmaceuticals in Europe (UK, Germany as examples)?

• What might change the role of PRO measures and their inclusion in HTA?

• 11 years experience as an assessor with one of the UK HTA bodies (Scottish Medicines Consortium) and extensive work supporting and advising company submissions to the National Institute for Health and Clinical Excellence (NICE)
HTA: the classic ‘4th hurdle’ for market access!

Policy Level:
1. Regulatory
2. National and regional levels
3. Budget management: Volume agreements
4. Patients / dynamic pricing

Steps:
1. Safety
2. Efficacy
3. Quality
4. Reimbursement
5. HTA / economic evaluation
6. Budgeting
7. Protocols and restrictions
8. Patient cost sharing
9. Value based pricing

**HTA in UK and Europe**

- Network of HTA organisations in Europe appraise new technologies for value assessment on behalf of public payers:
  - NICE (National Institute for Health and Clinical Excellence) in the UK, IQWiG in Germany,
  - CVZ and TLV in Sweden, AHTAPol in Poland, and ‘emerged’ HTA in Russia, Slovenia, Romania

- Support negotiations on reimbursement and value based pricing of new pharmaceuticals

- Anti-cancer pharmaceuticals are routinely subjected to HTA in the UK:

  "*The PD-1 inhibitor **Opdivo** (nivolumab) has been turned down as a treatment for locally advanced or metastatic squamous non-small cell lung (NSCLC) whose disease has progressed after prior chemotherapy, with NICE saying it is simply too expensive” (Dec 2015)."

  "*NICE's final rejection of **Kadcyla** (trastuzumab emtansine) for HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane comes despite Roche offering undisclosed discounts on the drug's £90,000-a-year list price, and after the drug was also turned down by the Scottish Medicines Consortium (SMC)” (Dec 2015)."

  *NICE supported the use of **Xtandi** (enzalutamide) in patients whose prostate cancer has spread after the failure of first-line therapy but for whom chemotherapy is not yet necessary. [The drug] can delay the need for chemotherapy, is well-tolerated and improves survival, said NICE, and is an appropriate use of NHS resources, with an incremental cost-effectiveness ratio of £34,500 compared to best supportive care” (Dec 2015)."
Patient-relevant outcomes in cancer HTA

• A core principle of Value Assessment of new pharmaceuticals conducted by HTA bodies such as NICE and IQWiG is that the benefits of treatments are patient relevant.

• Methods guidance for both bodies state this means evidence to support:
  – Mortality benefits
  – Patient Reported Outcomes (PRO) measures – describing how the patient feels and functions:
    • Morbidity/disease symptoms
    • Health related quality of life (HRQoL): impact on physical, psychological and social wellbeing as perceived by the patient.
    • Treatment satisfaction/convenience
  – Extent of harm/adverse events
NICE and IQWiG

- **NICE**: Remit is to assess comparative clinical and cost-effectiveness of selected health technologies in order to offer guidance to the National Health Service in England and Wales:
  - Perform technology appraisals of all new cancer drugs (from 2016): recommend for use, for coverage with evidence development or not recommend

- **IQWiG**: Remit is to conduct therapeutic benefit assessment and health economic evaluation in order to support Ministry of Health (G-BA) decisions on reimbursement of new pharmaceuticals and pricing negotiations in Germany
  - Categories: major additional therapeutic benefit, considerable, minor, unquantifiable, unproven, none, less

- Both HTA bodies review the drug trial evidence base to assess and appraise PRO data
  - so for cancer this primarily includes the HRQoL impact of experiencing symptoms of disease and disease progression, being in remission (PFS) with complete or partial response, adverse events associated with treatment.

- However, qualitative input from patients plays an important part!
But diverging approaches!

- Common desire for PRO evidence AND RCTs are primary source of treatment effect data = A high need for a range of COAs in cancer drug trials
- However, the reality is somewhat different...........
- For NICE, PRO measures usually quantify an impact on HRQoL that translates (with survival) into Quality Adjusted Life Years (QALYs) for the evaluation of cost-effectiveness (NICE Methods Guidance, 2013).
  - Evidence base should include a generic HRQoL instrument/questionnaire (e.g. EQ5D)
  - NICE allow mapping from other health-related quality of life measures or health-related benefits observed in the relevant clinical trial(s) to EQ5D
  - Disease-specific utility instruments have been developed but little expressed in NICE methods guidance
    - The EORTC-8D is a subset of the QLQ-C30 that has had an algorithm developed to convert responses into utility estimates (Rowen et al, 2011)
- For IQWiG, economic evaluation plays a smaller role and they do not state a preference for QALY outcomes (although they do allow it)!
  - IQWiG methods guidance (April 2015) states that “Parallel to the use of a generic instrument, disease-specific instruments to determine quality of life in clinical studies should be applied. The mapping of disease-specific to generic instruments is therefore discouraged”.
Case studies: (1) Kadcyla

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<th>Assessment of Kadcyla (trastuzumab emtansine)</th>
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<td><strong>Comparator</strong></td>
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<td><strong>NICE recommendation</strong></td>
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<td><strong>IQWiG benefit assessment</strong></td>
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<td><strong>Cost-effectiveness (NICE)</strong></td>
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<td><strong>PRO/HRQoL measures in trial</strong></td>
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<td><strong>Impact of PRO on HTA appraisal: NICE guidance (TA371, Dec 2015)</strong></td>
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<td><strong>Impact of PRO on HTA appraisal: IQWiG Extract report (Mar 2014)</strong></td>
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Case studies: (2) Xtandi

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<th>Assessment of Xtandi (Enzalutamide)</th>
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Limitations of using PRO data in cancer HTAs

• In the UK at least all roads lead to the QALY, for HTA-based decision-making with the dominance of the EQ5D

• The German benefit assessment approach naturally places a greater emphasis on results from PRO measures for HTA,
  – but impact still limited in relation to the impact of traditional clinical endpoints in cancer trials, in particular survival.

• Historically, PRO endpoints and measures have not been routinely included in clinical trials or well specified (designed for regulatory or HTA approval)
  – A systematic review of RCTs in breast cancer 1990-2009 found only 24% included a PRO measure, and mostly as a secondary endpoint (~80%) (Brettschneider et al, 2011)
  – Most common instrument was cancer specific EORTC questionnaires (~50%) (Brettschneider et al, 2011)
  – A systematic review of 75 most recent HTA focussed trials in the UK up to 2013 found only 33% included PRO measures, and of these 61% were incomplete (e.g. in terms of PRO rationale, data collection methods, training, interpretation in relation to traditional endpoints) (Kyte et al 2014)

• Trials increasingly appear to be including the EQ5D and QLQ-C30 or FACT questionnaires, but are often sub-optimal for the needs of HTA
  – e.g. Only administered up to 28 days beyond treatment end = does not provide data to assess HRQoL beyond disease progression.
What could improve wider PRO measure use and impact within HTA?

1. Continued work to improve the inclusion and specification of validated PRO measures in clinical trial protocols (e.g. aided by Appendix 2, ‘PRO measures in oncology’)

2. An agreed common set of cancer specific and generic (utility based) measures for inclusion in cancer RCTs (as key secondary endpoints):
   – Area for EMA and HTA collaboration?

3. More real world/observational studies and pragmatic RCTs in cancer with a range of validated PRO measures

4. There is movement towards coverage in evidence development or other post launch managed access schemes in Europe for cancer drugs (e.g. 2016 cancer drugs fund in UK), hence PRO measures need to be integrated into the post launch data collection aligned to these schemes.
References

• Brettschneider et al. Informative Value of Patient Reported Outcomes. GMS Health Technology Assessment 2011; Vol 7; 1-15

• Kyte et al. Systematic evaluation of the Patient-Reported Outcome (PRO) content of clinical trial protocols. Plos-one 2014; Vol 9 (10); 1-12

• Rowen et al. Deriving a preference based measure for cancer using the EORTC QLQ-C30. Value in Health 2011; Vol 14 (5)
An Industry Perspective
“Caught in the Middle”

Joseph O’Connell, MD
VP, Hematology Oncology Area Lead InventivHealth Clinical

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Disclosures

• I have no conflicts to disclose
• I will not be discussing any information related to specific ongoing clinical research projects which inVentiv Health supports
Historic perspective

Development Planning for pharmaceutical companies’ assets often relegates PRO/ HEOR to a diminished importance:

- Leadership for development of the overall Clinical Plan is in the hands of a Clinician or Asset Lead with an MD or PharmD background;

- Input to Phase 1 design: key roles for Pharmacology and Safety;

- Phase 2 planning: Regulatory Strategy and Commercial Projections become more relevant.

HEOR is largely seen as necessary to satisfy regional regulatory strategy (e.g. EU), and inform economic analyses in highly regulated healthcare environments, not as information that is valuable to prescribers and patients.
Why the traditional resistance to early collection of PRO data in the course of clinical development?

On the Sponsor study team

• Unfamiliarity with the terminology and conceptual basis:
  Concepts such as ‘content validity’ and ‘minimally important difference’ are not part of the training and education of clinical, statistics and commercial colleagues;
• US-centric approach: Lack of impact on FDA label equates with minimization of the importance of PRO endpoints.
• Culture of lack of commitment to ‘doing it right’ compromises the output (improper administration and missing data).

For the Sponsor Budget:

• Cost of administration, monitoring, analysis is seen as not worth the $ that alternatively could go to pK analysis, central radiology reading and other competing budgetary priorities.

At the Site:

• Perception that patients are burdened by too many questions;
• Site resistance due to interruption in patient flow at the clinic.

The Historic Reality:

• The impact of a new drug on PRO is minimal when the clinical benefit is a relatively small increment on the patient with metastatic cancer!
PRO measure implementation complicates the conduct of studies

- Deciding on which PRO measure to deploy.
- Obtaining and distributing translations.
- Instructing sites at Site Initiation Kickoff
  - When to collect; How to collect: Who responds, etc.
- Additional monitoring burden in data-heavy Phase 1 trials
  - Baseline not missing; All questions answered; Timing prior to other procedures.
- Data Output and Statistical analysis require a resource commitment, when the major focus is on establishing safe dose and estimating efficacy.

Prior to Phase 2 readout and Proof of Concept: is it worth the effort?
The value of PROs to patients and prescribers

The efficacy of chemotherapy in incurable malignancies is usually assessed through response rates, toxicity, disease-free survival, and OS. However, these parameters do not allow for an assessment of the overall therapeutic benefit because they do not provide information about the clinical condition of the patients, their experience while undergoing treatment, or the quality of their survival.

Treatment choices that patients make are influenced by numerous factors, including the value they place on potential improvements in survival.

Studies have shown that cancer patients want to have QOL information to help in their decision making, and that most oncologists are unwilling to prolong survival at the expense of worsening QOL, although QOL considerations play a relatively small role in treatment decisions in current practice.

Andrea Bezjak et al. JCO 2006;24:3831-3837
Case Study: Erlotinib in Non-small Cell Lung Cancer

Tavceva label:

‘*Tarceva is also indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen.¹*

The Registration Study, BR.21:

Double-blind phase III trial
Previously treated NSCLC
Randomly assigned to erlotinib 150 mg daily or placebo
Primary study outcome = Overall Survival
QOL:

- EROTC QLQ-C30
- EORTC QLQ-LC13

‘The primary end points for QOL analysis were time to deterioration of three common lung cancer symptoms: cough, dyspnea, and pain.’²

² Andrea Bezjak et al. JCO 2006;24:3831-3837
BR.21 PRO outcomes in a positive P3 study
Or The bad old days of incremental benefits

Time to quality-of-life deterioration for
(A) cough (B) dyspnea (C) pain.

‘Patients with advanced NSCLC who have previously been treated with (and progressed during or relapsed after) chemotherapy are expected to deteriorate.
In that clinical setting, a benefit may be defined not only as an improvement in baseline symptoms, but also as a delay in progression of symptoms.’

‘Couldn’t we have predicted this deterioration??
P2 results: ORR 12.3 %, PFS 9 weeks;
P3: PFS 2.2 vs 1.8 month for placebo

1Andrea Bezjak et al. JCO 2006;24:3831-3837
2 Perez-Soler JCO August 15, 2004
©2006 by American Society of Clinical Oncology
The present: Erlotinib and ‘Personalized Medicine’

Erlotinib in unselected patients (BR.21\textsuperscript{1}): Median PFS 10.3 weeks

Erlotinib versus chemotherapy in First Line patients with EGFR mutations (EURTAC\textsuperscript{2})
Median PFS 9.7 months

1Shepherd, NEJM, July 2005
2 Rosel, Lancet Oncology; March 2012
Improved drug targeting = Changing Times in Drug Development: Increased Expectations for Benefit

Pre-2005

New Therapies with Incremental Benefit.

Measurable improvement in symptoms are neither expected nor sought

2005-2013

Targeted Therapies move the Goalpost for achievable and meaningful Clinical Benefit

PROs are frequently included in publication and presentations of trial results

Future

“American Society of Clinical Oncology Perspective: Raising the Bar for Clinical Trials by Defining Clinically Meaningful Outcomes”
Ellis, JCO, March 2014
No longer seen as substantially benefiting patients unless there tumor has a sensitizing EGFR exon 19 deletion or exon 21 point mutation.

Approved in 1st line due to improved PFS compared to standard chemotherapy:

- Erlotinib
- Gefitinib
- Afatinib

Margins of benefit in symptoms and QoL measures are similarly more robust than in unselected patients (next slide)

1 Shepherd, NEJM, July 2005
2 Rosel, Lancet Oncology; March 2012
Impact of an EGFR TKI on QoL in appropriately selected population

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<tr>
<td>Global health status/QoL (QLQ–C30: Q29–30)</td>
<td>-3.18 (-5.75 to -0.61)</td>
<td></td>
<td>.015</td>
</tr>
<tr>
<td>Functional scales</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical (QLQ–C30: Q1–5)</td>
<td>-4.80 (-7.47 to -2.13)</td>
<td></td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Role (QLQ–C30: Q6–7)</td>
<td>-4.40 (-7.40 to -1.40)</td>
<td></td>
<td>.004</td>
</tr>
<tr>
<td>Emotional (QLQ–C30: Q21–24)</td>
<td>-0.87 (-3.20 to 1.46)</td>
<td></td>
<td>.462</td>
</tr>
<tr>
<td>Cognitive (QLQ–C30: Q20 and 25)</td>
<td>-3.16 (-5.47 to -0.85)</td>
<td></td>
<td>.007</td>
</tr>
<tr>
<td>Social (QLQ–C30: Q26–27)</td>
<td>-1.11 (-3.94 to 1.72)</td>
<td></td>
<td>.442</td>
</tr>
</tbody>
</table>

Results from the longitudinal analysis of global health status/quality of life (QoL) and functional scale domains for afatinib compared chemotherapy.
Accelerated approval provides opportunities for sponsors — but requires a different development paradigm.

**Standard Development Paradigm**

- **2014-2015**: Phase 1
- **2016**: Phase 2
- **2017**: Phase 3
- **2018**: Proof of Concept
- **2020-2021**: Registrational Intent
- **2022**: NDA
- **2023**: Launch

**Accelerated Pathway**

- **2014**: Dose Finding
- **2015**: Ex
- **2016**: ESOE
- **2017**: GO/NO-GO
- **2018**: Proof of Concept
- **2019-2020**: Registrational Intent
- **2021-2022**: NDA
- **2023**: Launch

**KEY:**
- Ex = Expansion Phase
- PD/RR = Pharmacodynamic/response rate
- ESOE = Early sign of Efficacy

Circa 24 MONTH DIFFERENCE BETWEEN STANDARD AND ACCELERATED PLANS
Case Study: Phase 1 study of nivolumab (2012)

A maximum tolerated dose was not reached.
Initially, 5 expansion cohorts of ~16 patients each were enrolled:
melanoma, NSCLC, renal-cell cancer, prostate cancer, colon cancer

On the basis of initial signals of activity, additional expansion cohorts of approximately 16 patients each were enrolled for:
- melanoma (doses of 1.0 or 3.0 mg/kg, followed by cohorts randomly assigned to 0.1, 0.3, or 1.0 mg/kg);
- lung cancer (randomly assigned to a dose of 1.0, 3.0, or 10.0 mg/kg);
- renal-cell cancer

2015 Press Release: “The U.S. Food and Drug Administration today approved Opdivo (nivolumab) to treat patients with advanced (metastatic) renal cell carcinoma”

Q: Will the opportunity to learn about PRO impact in P1/2 be lost, due to the rapidity of the development path??

Where to fit in PRO Measures?
New US reimbursement environment and emergence of ‘Value’ criteria: an emerging impact on PRO strategy

There is a multiplicity of rapidly emerging therapeutics for payers to evaluate:

• Myeloma: 5 new drugs in 2015. Overall Survival improved dramatically in last decade, and up to 7 new submissions expected in next 2 years
• Multiple new indications for PD-1/ PD-L1 antibodies;
• NSCLC: 8 new approvals in last 18 months;
• On the horizon: CART-cell therapy, new Antibody-drug conjugates; etc., etc.
• $$$

Payers and Physician Groups seek to devise optimal Clinical Pathways, as physicians are placed at risk for the Total Cost of Care.

Focus on Value.
Outcome / Cost = Value

Whose Quality (Payer? Patient? Society?)
What measure of Outcome: OS? PFS/ ORR?
Who speaks the ‘Patient Voice’?
Caught in the Middle: Changes in Efficacy, Approval Process and Access intersects with Clinical Development

Pre-2005

- New Therapies with Incremental Benefit.
- Improvement in symptoms little attended in development

2005-2013

- Accelerated Approvals In Oncology

The Middle

- Targeted Therapies move the Goalpost for achievable and meaningful Clinical Benefit
- PROs are frequently included in publication and presentations of trial results

Future

New Reimbursement Environment

“Quality” “Value”

Voice of Advocacy
PRO moves front and center

Summary:
- Clinical Development plans are changing as we look for bigger gains.
- Pharma and Regulatory Agencies collaborate on more rapid approval process.
- Patients and Payers are gaining a Voice in what should be paid for.
- Q: How and When do Sponsors collect valid and relevant PRO data???
Panel Discussion

Reviewing the Needs of all Stakeholders: Where are They Similar and Where do They Differ?
Session Participants

Chair
– Stephen Joel Coons, PhD – C-Path

Presenters
– Paul G. Kluetz, MD – FDA
– Daniel O’Connor, MD – MHRA and EMA
– Keith Tolley, MPhil – Tolley Health Economics Ltd.
– Joseph O’Connell, MD – InventivHealth

Panelists
– Mary Lou Smith, MBA, JD – Research Advocacy Network
– Naomi Aronson, PhD – Blue Cross Blue Shield Association
– Chiun-Fang Chiou, PhD – Janssen
WORKSHOP ON CLINICAL OUTCOME ASSESSMENTS (COAs) IN CANCER CLINICAL TRIALS

April 26, 2016  ■  Silver Spring, MD

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