PAYER AND HTA PERSPECTIVES ON CLINICAL OUTCOME ASSESSMENTS (COAs)

Peter Black, Senior Scientist, ERT Consulting Services
Marta Andreykiv, Sr. Consultant, Quintiles
Stefan Holmstrom, Dir. HEOR, Astellas Pharma Global Development
Erin Tomaszewski, Clinical Outcomes Research Scientist, Quintiles Outcome

Presenters

• Peter Black, Senior Scientist, ERT Consulting Services
• Marta Andreykiv, Sr. Consultant, Quintiles
• Stefan Holmstrom, Dir. HEOR, Astellas Pharma Global Development
• Erin Tomaszewski, Clinical Outcomes Research Scientist, Quintiles Outcome
Objectives

• High level overview of topics
• Understand key methodological considerations for design and implementation of clinical outcome assessments (COAs; including PROs, ClinROs, and ObsROs)
• Evaluate select payer perspectives of use of COAs
• Explore some examples of application of COAs

What will you learn...

• Basics of COA methodology, in light of EMA and FDA guidance
• What can be learned from HTA’s
• What has worked and what has not worked for application of COAs in clinical trials
Structure

• Four presentations
  – Clinical Outcome Assessments (COAs) and Endpoint Strategies
  – General payer requirements and overview
  – CRPC Example
  – Examples of COA application
• 15 minutes for questions at the end

Clinical Outcome Assessments (COAs) and Endpoint Strategies

Peter Black,
ERT Consulting
Challenges and Opportunities

• Difficult to demonstrate substantial improvements in efficacy over approved products
  – value of modest effects is difficult to interpret
• Many products don’t fail until late in development process, which dramatically increases R&D costs
• Increased scrutiny from regulators and payers
• Joint HTA and regulatory agency scientific advice in Europe (now) and US (future?) influence payer acceptance
• Variance between EMA and FDA, and within EMA given the variety of agencies that touch the reimbursement world

Objectives

• COA nomenclature definition
  – EMA - FDA differences in assessing COAs

• Define and describe value of an endpoint strategy using COAs

• Review select methodological tools to facilitate development of COAs to support endpoints with an emphasis on the payer
Clinical Outcome Assessments (COA)

- **Patient Reported Outcome (PRO)**
  - A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of particular aspects of or events related to a patient's health condition.

- **Clinician Reported Outcome (ClinRO)**
  - An assessment that is determined by an observer with some recognized professional training that is relevant to the measurement being made.

- **Observer Reported Outcome (ObsRO)**
  - An assessment that is determined by an observer who does not have a background of professional training that is relevant to the measurement being made, i.e., a non-clinician observer such as a teacher or caregiver.

Source: FDA Website

Role of COAs

- To provide evidence of a specific treatment benefit
- Treatment benefit is a favorable effect on a meaningful aspect of how a patient feels, functions, or survives

- COAs measure a ‘concept’ that is meaningful (and name of COA doesn’t necessarily communicate the underlying concept)
- Feels = A patient’s physical sensation or perceived mental state related to health within typical ‘daily’ life
- Functioning = A patient’s ability to perform an activity that is a meaningful part of typical ‘daily’ life; not isolated physiological process
- Effectiveness and/or safety
COAs in Medical Product Lifecycle

• COAs are primary and key secondary efficacy endpoints
• COAs are also used for safety:
  – Adverse events
  – Tolerability
  – Suicidality
• COAs are effectiveness endpoints

COA Endpoints in Product Lifecycle

• **What?**
  – Create the messages you want to deliver at the end your work
  – Identify the *concepts*, or what you want to measure, that will support your messages
  – What to measure depends upon:
    • Who is in your target patient population
    • Who you want to influence with your results – regulators, *payers*, clinicians, and/or patients themselves

• **How?**
  – Only select instruments after deciding on what concepts to measure
  – Select instruments that measure exactly what you want to measure
PRO Guidance: FDA “vs.” EMA

FDA

Guidance for Industry
Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

December 2009

Olivier Chassany, 2010

PRO

HRQL

EMEA

Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on the regulatory guidance for the use of health-related quality of life (HRQL) measures in the evaluation of medicinal products

Draft agreed by the efficacy working party
September 2006

Adoption by CHMP for release for consultation
November 2006

End of consultation (deadline for comments)
February 2007

Agreed by the efficacy working party
July 2007

Adoption by CHMP
January 2008

Date for coming into effect

PRO assessment: FDA versus EMA

FDA

• SEALD group dedicated to PRO reviews
• Training of Divisions in PRO issues continuously ongoing
• Less likely to accept HRQL
• Alignment between SEALD and the Divisions

EMA

• No dedicated internal HRQL/PRO expertise
• “Outsource” HRQL reviews to academic or clinical research organizations depending on reporter country
• Challenges in the harmonization of reviews within EMA and across various national agencies
Depth of appraisal of a PRO dossier may differ between FDA and EMA

**FDA reviews PRO dossier:**
- Is it validated and relevant for the population under study?
  - Content validity
  - Item generation (verbatim of patients’ interview)
  - Recall period
  - Modification of a questionnaire
- Is the difference between groups meaningful?

**EMA currently asks for any endpoint (including PRO):**
- Is it validated and relevant for the population under study?
  - is the symptom well-known?
  - Publications
  - Previously used in dossier submission?
  - Already used in a claim (summary of SPC)
- Is the difference between groups meaningful?

**Select Methods**

- Endpoint Strategy
- Endpoint Development Process
- Conceptual Model
What is an Endpoint Strategy?

• A plan that describes how trial endpoints will be used to clearly demonstrate the *treatment benefit* of the investigational product to *relevant stakeholders*

• What it is NOT:
  – Only based on regulatory approval
  – Only based on input from limited resources within company
  – Routine, “paint by numbers” process

• Identify endpoints for Payers as key stakeholders

• Should be considered *early* in development process (pre-phase 2)

---

**Endpoint Strategy Matrix**

(“Stakeholders”)

<table>
<thead>
<tr>
<th>Market</th>
<th>Product Labeling</th>
<th>Payer/Promotional</th>
<th>Provider Communication</th>
<th>Patient Communication</th>
</tr>
</thead>
<tbody>
<tr>
<td>“EU”</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etc…</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• Cells include key endpoints for each strategic objective
Endpoint Development Process (EDP)

- Patient Perspective
- Expert Input
- Literature/Label Review

<table>
<thead>
<tr>
<th>Measure Available</th>
<th>Measurement Strategy</th>
<th>No Measure Available</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Implementation Strategy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Internal Communications</td>
<td>Regulatory Interaction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>External Communications</td>
</tr>
</tbody>
</table>

Conceptual Model

- Drug Action
- Patient Population
- Low Back Pain
- Diagnosis
- External (e.g., Anxiety)

- Signs/Symptoms
  - Aching
  - Burning
  - Tingling
  - etc

- Disease Related Impact
  - Physical Function
  - Absenteeism/Presenteeism
  - Depression
  - Functional Impact
Conclusions

COAs are essential methods for establishing the direct treatment benefit of new products and supplying evidence to **payers**

- An Endpoint Strategy is useful in developing a treatment benefit and payer argument early in a development program
  - start early
  - consider key strategic and methodological questions
  - consider all stakeholders

- In the U.S. Key methodological considerations specifically outlined for PROs also apply to other COAs
  - Context of use, content validity, psychometrics, responder definitions

- Start early! (pre-phase 2)

General payer requirements
Commentary on COAs

_Marta Andreykiv, Quintiles Consulting_
Some agencies are more specific than others about their requirements and expectations

IQWiG’s latest General Methods document provides certain details on expected COAs*

As the benefit of an intervention should be related to the patient, this (benefit/harm) assessment is based on the results of studies investigating the effects of an intervention on patient-relevant outcomes. In this connection, “patient-relevant” refers to how a patient feels, functions or survives.” (General Methods, p. 28)

This translates into patient parameters:
- Increase in life expectancy
- Improvement in health status
- Improvement of quality of life
- Reduction in disease duration
- Reduction of adverse effects

IQWiG sees these parameters in following outcomes:
- Mortality
- Morbidity (symptoms and complications)
- Health-related QOL
  - In the assessment of QoL, patient satisfaction only
  - instruments should be used that are suited for application in clinical trials and have been evaluated accordingly.
- Time and effort invested in relation to the disease and the intervention (supplementary)
- Treatment satisfaction (supplementary)

Further details:

Patient-reported outcomes (PROs): can also cover other dimensions of benefit, for example, disease symptoms; RCTs are best suited to demonstrate an effect. For quality assessment of PROs, IQWiG refers to FDA.

Surrogate Endpoints:
“Most surrogate endpoints are [...] unreliable”, statistical proof for their validity is required; if this is not possible, it is also possible to apply the “surrogate threshold effect (STE) concept”.

Other highlights:

Review of the guidance from various HTA agencies reveals further preferences of COAs

Eunetha guidance

Endpoints used for REA of pharmaceuticals: HEALTH-RELATED QUALITY OF LIFE and UTILITY MEASURES

- August 2012 EunetHTA published the draft guidance on HRQoL used in relative effectiveness assessments.
- The primary objective is to focus on methodological challenges that are encountered by HTA assessors while performing a rapid relative effectiveness assessment of pharmaceuticals.
- It has been elaborated by experts from KCE, reviewed and validated by HAS and all members of the EunetHTA network: the whole process was coordinated by HAS. As such the guideline represents a consolidated view of non-binding recommendations of EunetHTA network members and in no case an official opinion of the participating institutions or individuals.

A general recommendation applicable to all types of Relative Effectiveness Assessment irrespective of their particular purpose is to require the inclusion of a disease- or population specific and a generic HRQoL measure for most adequately capturing the impact of a disease on daily life. In case there is a need for the calculation of QALYs, a utility measure or generic HRQoL instrument associated with a reference set of utility values needs to be used.

REAs performed for informing resource allocation decisions across indications should primarily be based on HRQoL data obtained with a generic HRQoL instrument, encompassing all HRQoL dimensions in which improvements are considered important by the general public.
Case Study 1: HTA Landscape of Rheumatoid Arthritis treatments

<table>
<thead>
<tr>
<th>Drug</th>
<th>Agency</th>
<th>Date</th>
<th>Main reason for rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certolizumab pegol</td>
<td>CADTH</td>
<td>May 2010</td>
<td>High proportion of withdrawals in trial</td>
</tr>
<tr>
<td></td>
<td>INESSS</td>
<td>Feb 2010</td>
<td>No data on maintenance of effect</td>
</tr>
<tr>
<td></td>
<td>INESSS</td>
<td>Jun 2010</td>
<td>No data on maintenance of effect</td>
</tr>
<tr>
<td></td>
<td>INESSS</td>
<td>Feb 2011</td>
<td>High proportion of withdrawals in trial</td>
</tr>
<tr>
<td></td>
<td>INESSS</td>
<td>Oct 2011</td>
<td>No data on maintenance of effect</td>
</tr>
<tr>
<td></td>
<td>NCPE</td>
<td>Sep 2010</td>
<td>High proportion of withdrawals in trial</td>
</tr>
<tr>
<td></td>
<td>SMC</td>
<td>Jun 2010</td>
<td>Uncertainties with indirect comparison and duration of response</td>
</tr>
<tr>
<td>Golimumab</td>
<td>INESSS</td>
<td>Feb 2010</td>
<td>Lack of data on slowing radiologic progression</td>
</tr>
<tr>
<td></td>
<td>INESSS</td>
<td>Jun 2010</td>
<td>Lack of data on slowing radiologic progression</td>
</tr>
<tr>
<td></td>
<td>INESSS</td>
<td>Feb 2011</td>
<td>Lack of data on slowing radiologic progression</td>
</tr>
<tr>
<td>Abatacept</td>
<td>NICE</td>
<td>Aug 2011</td>
<td>Uncertainties around subpopulation</td>
</tr>
<tr>
<td></td>
<td>SMC</td>
<td>Sep 2011</td>
<td>Uncertainties around subpopulation, uncertainties with indirect comparison</td>
</tr>
<tr>
<td></td>
<td>UVEF</td>
<td>Sep 2011</td>
<td>Route of administration, cost offset not robust, uncertainties with indirect comparison</td>
</tr>
<tr>
<td>Tocilizumab</td>
<td>SMC</td>
<td>Apr 2012</td>
<td>Patient population not reflective of clinical practice</td>
</tr>
</tbody>
</table>

Certolizumab pegol was rejected by INESSS (Canada) several times as no data on the maintenance of effect for up to two years was available. Additional data was submitted, but the STA was still rejected for the same reason. Other concerns discussed were use of an unlicensed dose and concerns around a high proportion of withdrawals in the trial (caused by the low methotrexate dose used). Similarly, concerns around the high proportion of withdrawals in the trial was the same reason both CADTH (Canada) and NCPE (Ireland) rejected certolizumab pegol. Golimumab was also rejected several times by INESSS due to data on the slowing of radiologic progression not being presented. The company resubmitted several times, but only managed to convince the agency after additional data became available. Tocilizumab was rejected by SMC (UK) due to concerns around the trial population not reflecting the population in UK clinical practice.

Case Study 1: What is Payers perception of COAs used in Rheumatoid Arthritis studies?

“While almost all HTA reports on rheumatoid arthritis refer to PRO, this is only the case in about half of the reports on breast cancer.”

“The outcome measured, mean change from baseline in HAQ (Health Assessment Questionnaire) at six months, was not a primary outcome in any of the studies and is also not normally used by clinicians in practice.”

“SMC’s Abatacept assessment August 2011”

“The Committee noted that the manufacturer’s mapping of HAQ scores to EQ-5D utility values resulted in the possibility of clinical scenarios where having rheumatoid arthritis would be worse than being dead.”

“NICE’s Abatacept for the treatment of rheumatoid arthritis after the failure of conventional disease-modifying antirheumatic drugs August 2011”

“The EQ-5D has only five dimensions and three levels in each dimension, therefore this outcome measure is sensitive to significant changes in one domain and there is more potential for one dimension to overstate the effect of clinical measures. The PBAC noted the variability in the baseline EQ-5D scores which suggested that this measure was less sensitive than the QoL.”

“PBAC review of biological disease-modifying antirheumatic drugs December 2009”
Case Study 2:  
HAM-D as the primary outcome in clinical studies of antidepressants

The Hamilton Rating Scale for Depression (HRSD), also known as the Hamilton Depression Rating Scale (HDRS) or abbreviated to HAM-D, is a multiple choice questionnaire that clinicians may use to rate the severity of a patient’s major depression.

There is no consensus as to what constitutes a clinically significant difference between treatments:

- NICE required a difference of at least three points as a measure of clinical importance.
- SMC referred to NICE’s requirements (assessments of Valdoxan (agomelatine) in Oct 2009 and Aug 2010):
  "...the reported difference between agomelatine and placebo was 2.93, which would suggest a borderline clinically significant outcome."
- HAS did not provide specific requirements regarding a clinically significant difference between treatments (the assessment of Valdoxan (agomelatine) in Nov 2009):
  "One study versus fluoxetine demonstrated significantly greater efficacy for agomelatine than fluoxetine: 1.49 point difference [95%CI: 0.20; 2.77] p=0.024 in terms of HAMD17 score after 8 weeks."
- PBAC did not provide specific requirements regarding a clinically significant difference between treatments, however, FLAC noted that 1.49 points difference was marginal and unlikely to be clinically important (the assessment of Valdoxan (agomelatine) in March 2012):
  "There was a statistically significantly larger mean reduction in HAM-D17 score in the agomelatine arm versus the fluoxetine arm (mean difference -1.49; 95% CI -2.77, -0.20). However, the PBAC noted that the clinical evaluator stated that the clinical relevance of the finding was marginal. ... PBAC considered that the differences were unlikely to be clinically important."

Key Takeaway Messages

- The majority of HTA agencies are explicit in their preferences on COAs; Reviewing agencies’ guidelines allows to extract that information.
- The need for consistency of submissions to HTA agencies is acknowledged to ensure comparability of methods and results between appraisals of different technologies and over time. Recently published EUnetHTA document on HRQoL is a step towards the harmonization of the payers requirements.
- Certain level of similarities can be already observed between different HTA agencies as to what COAs they prefer to see in the submissions (e.g., generic HRQoL instruments), however, reviewing the historical HTA publications indicates that majority of the assessments are evaluated on the case-by-case basis and have to be interpreted separately.
- HTAs often weigh patient-reported measures, which clinical trial outcomes do to a lesser extent. The type and frequency of PRO used in clinical trials largely depend on the disease analyzed. The HTA-community seems to pursue the utilization of PRO proactively—in case of missing data the need for further research is stated.
CRPC Example

Stefan Holmstrom,
Astellas Pharma

HTA landscape of CRPC

In recent years treatments for Castration Resistant Prostate Cancer have attracted a lot of attention from HTA agencies worldwide.

- 90 HTA agencies websites were scanned to identify HTAs of new medications for the treatment of CRPC published from 2005 to present.

- There are 46 relevant assessments published in 12 different countries.

- The majority of these reports are evaluating the cost-effectiveness of new medications - Docetaxel (6), Cabazitaxel (12) and Abiraterone (18) - for treatment of CRPC.
### HTA agencies critique regarding COAs

*Lessons learned from HTA cost-effectiveness evaluations of new castration-resistant prostate cancer medications*

<table>
<thead>
<tr>
<th>Country</th>
<th>Topic</th>
<th>Decision/Reason for Rejection</th>
</tr>
</thead>
<tbody>
<tr>
<td>DE</td>
<td>Abiraterone</td>
<td>IQWiG commented on insufficient QoL data and restrictions in subgroup analysis for both cabazitaxel and abiraterone. G-BA accepted both drugs based on the corresponding IQWiG assessments.</td>
</tr>
<tr>
<td></td>
<td>Cabazitaxel</td>
<td></td>
</tr>
<tr>
<td>GB</td>
<td>Docetaxel</td>
<td>NICE (England &amp; Wales) accepted docetaxel and abiraterone, and rejected cabazitaxel due to considerable uncertainty in the utility values. SMC (Scotland) rejected docetaxel due to uncertainty around survival gain and failure to consider QoL of patients treated, rejected cabazitaxel partly due to unrealistically high utility values, and rejected abiraterone due to an unacceptably high ICER and the use of non-standard measure for estimates of progression free survival.</td>
</tr>
<tr>
<td></td>
<td>Abiraterone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cabazitaxel</td>
<td></td>
</tr>
<tr>
<td>CA</td>
<td>Cabazitaxel</td>
<td>INESS rejected cabazitaxel due to an unacceptably high ICER and <em>missing QoL data from the clinical trial</em>. INESS accepts abiraterone but commented on the uncertainty around the utility values used.</td>
</tr>
<tr>
<td></td>
<td>Abiraterone</td>
<td></td>
</tr>
</tbody>
</table>

Overall, uncertainty regarding HRQoL measures was the most often cited negative comment: For both docetaxel and cabazitaxel, the absence of quality of life measures from the main phase III trials and uncertainty around utility values were cited as reasons for rejection by NICE, SMC, PBAC, and INESS. The CVZ accepted cabazitaxel for temporary reimbursement on the understanding that further subpopulation analysis and more data on utilities will be needed. The IQWiG assessments of abiraterone and cabazitaxel commented on insufficient QoL data and restrictions in the subgroup analyses.

### Cabazitaxel Assessments

*Data on health related quality of life were not collected in the cabazitaxel trials; The majority of HTA agencies commented in their report on the absence of Quality of Life data; For some of the agencies it was one of the main decision-drivers for rejection of cabazitaxel.*

<table>
<thead>
<tr>
<th>Critiques</th>
<th>HTA Agencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>➢ Data on (health-related) quality of life not collected</td>
<td>✔️ ✔️ ✔️ ✔️ ✔️</td>
</tr>
<tr>
<td>➢ Trial not powered to detect differences in adverse reactions</td>
<td>✔️</td>
</tr>
<tr>
<td>➢ Open label study susceptible to bias in the subjective outcomes included in progression-free survival, such as pain and deterioration in symptoms.</td>
<td>✔️ ✔️</td>
</tr>
<tr>
<td>➢ Dose intensity of cabazitaxel treatment in the TROPIC trial may not be reproducible in clinical practice</td>
<td>✔️ ✔️</td>
</tr>
<tr>
<td>➢ ECOG performance score of 2 may not be offered to patients in clinical practice as they may not be well enough to tolerate the drug</td>
<td>✔️</td>
</tr>
<tr>
<td>➢ There are insufficient data to support the efficacy of cabazitaxel compared to second-line treatment with docetaxel.</td>
<td>✔️ ✔️</td>
</tr>
</tbody>
</table>

*NICE, UVEF, NCPE and SMC have provided negative recommendations for cabazitaxel*
Abiraterone Assessments

Quality of life measures using the Functional Assessment of Cancer Therapy-Prostate (FACT-P), brief pain inventory short form (BPI-SF), and the brief fatigue inventory short form (BFI-SF) questionnaires were applied in the abiraterone studies. Several HTA agencies have raised issues about uncertainty around utility values, especially the mapping of FACT-P scores to EQ-5D.

<table>
<thead>
<tr>
<th>Quality of Life critiques</th>
<th>NICE</th>
<th>NCPE</th>
<th>SMC</th>
<th>TLV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Utility values for the pre-progression state differed according to treatment, and were derived from an algorithm that mapped FACT-P scores to EQ-5D utility values from a separate cross-sectional dataset.</td>
<td>✔</td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Uncertainty about the true difference in utility values between the pre-progression and post-progression states in the economic model (i.e. Utility value for post-progressive state identified from the literature).</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Manufacturer mapping algorithm had not been externally validated or subject to peer review.</td>
<td></td>
<td></td>
<td></td>
<td>✔</td>
</tr>
<tr>
<td>No data available comparing QoL for abiraterone vs. cabazitaxel.</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

“*The manufacturer had not provided EQ-5D values for health states obtained directly from patients, which would have been in line with the preferred methods recommended by NICE”

NICE’s Abiraterone appraisal, June 2012

TLV, NCPE and SMC have provided negative recommendations for abiraterone

Key take away messages

Lessons learnt from Health Technology Assessment Reports in CRPC indication:

- There is a demand from HTA agency reviews for research on the QoL of patients treated with anticancer therapies.
- Despite the fact that most HTA agencies’ preferred framework for economic evaluations is cost-utility analysis with quality-adjusted life-years (QALYs) as the main measure of health outcomes, the review of available assessments showed that none of the CRPC clinical trials used in the reviewed HTA submissions collected utilities directly from patients.
- There is clear need to include comprehensive quality of life measures in phase III trials for new drugs to treat CRPC, and to use robust mapping algorithms of FACT-P to EQ-5D when utility data directly collected from the patients is not available.
- Currently, several (ongoing) RCTs are assessing QoL for CRPC, and these will address some of the recommendations and unmet needs arising from the current lack of HTA information in CRPC.
Examples of application of COAs

Erin Tomaszewski,
Quintiles Outcome

Objectives

• Examples of implementation of COAs
• Feedback examples
  – The link between the messages and the evidence provided
Landscape

- Use of PROs, ClinROs, and ObsROs: *Does the landscape change due to the new COA-focus? (It does provide a window for payers to be more critical of effectiveness/etc. evidence using ClinROs.)*
  - Minimal shift, payers continue to listen to the clinician for advice on what to reimburse
  - More emphasis is put on PROs, specifically, but ClinROs remain the focus

Stakeholders

- Are the instruments used in the treatment’s studies validated and interpretable?
- Does the PRO data show that patients status is better, or at least as good as the comparators, and more effective than placebo?

Strategic Research: A practical handbook for Phase IIIb and Phase IV clinical studies. Hugo Stephenson. 2005
Provenge

• Medicare Central Coverage Decision to cover individuals with all of the following characteristics:
  1. A good performance level (ECOG* 0-1); and
  2. An estimated life expectancy greater than 6 months; and
  3. No visceral disease (lung, liver, or brain metastases); and
  4. No or minimal symptoms defined as no moderate to severe prostate cancer-related pain or no use of narcotics for cancer-related pain; and
  5. Serum prostate-specific antigen (PSA) level of 5 ng/ml or more; and
  6. Serum testosterone level less than 50 ng/dl (17 nmol/l); and
  7. Progressive disease based on imaging studies or PSA measurements; and
  8. No treatment within the previous 28 days with systemic glucocorticoids, external-beam radiation (EBRT), surgery, or systemic therapy for prostate cancer (except medical or surgical castration); and
  9. No chemotherapy within the previous 3 months; and

Increasing trend to consider the patient as part of coverage decisions

From: https://www.healthnet.com/static/general/unprotected/pdfs/national/policies/Provenge_Sipuleucel-T.pdf

Avastin Case Study

• Initially indicated as first line treatment of metastatic breast cancer
• Indication withdrawn by FDA in 2010
• FDA clearly highlighted importance of PROs in decision to withdraw indication

“FDA considers additional measures of direct clinical benefit to include amelioration of disease-related symptoms, a delay in symptoms or improvement in patient-reported outcomes, including health-related quality of life measures.”

“No evidence has been provided ...that [it] improves patient symptoms or patient-related outcomes.”

Regulatory Decision to Withdraw Avastin (bevacizumab) Firstline Metastatic Breast Cancer Indication,” Dec 15, 2010
EMA Refusal to Extend Indication for TARCEVA to Pancreatic Cancer (2006)

- What were the major concerns, which led the CHMP to recommend the refusal of the change to the marketing authorisation?

- The major concerns of the CHMP were that:
  - The benefit on patients’ survival seen in the study was very limited and it did not outweigh the risk associated with the combination of erlotinib and gemcitabine, given the side effects of the treatment.
  - The study did not show any improvement in the quality of life of the patients treated.
  - Other measurements such as progression-free survival, and objective response rate, also showed a similarly small effect.

Bristol-Myers Skin-Cancer Drug Yervoy Rejected by U.K. Health Cost Agency

Bristol-Myers Squibb Co. (BMY)’s Yervoy drug was rejected by the U.K.’s health-cost agency, which suggested the company consider lowering the price of the skin-cancer treatment. (14 Oct 2011)

- Regulatory approval and fanfare, but NICE rejection, because could not make effective argument to support costs
- Effective endpoint strategy may offer sponsors ability to more adequately communicate value to payers
FDA Warning Letters

- About 12% of letters issued (2002-2011) by OPDP cite inappropriate health economic promotions
- Common warning letters:
  - overstatement of efficacy
  - omission and minimization of risks
  - broadening of indication
  - testimonials that went beyond clinical evidence
  - unsubstantiated claims
  - promotion of an unapproved drug
  - “false and misleading” statements


Prostate Cancer

- Eligard (leuprolide), a palliative for advanced prostate cancer
- FDA warning letter cited non-factual promotions
  - ‘overstatement of efficacy’ and lack of ‘substantial evidence’


**Luvox**

- FDA reviewed a patient brochure promoting Luvox CR (fluvoxamine) for social anxiety/obsessive-compulsive disorder
- Liebowitz Social Anxiety Scale (LSAS) scores do not improve in the magnitude demonstrated by the results of the clinical trials. The drastic improvements in social functioning suggested by the patient brochure do not correlate with the results of the clinical trials. The LSAS does not measure academic performance.

**Provigil**

- Provigil (modafinil) to improve wakefulness in persons that experience excessive sleepiness

"...it does not necessarily follow that Provigil is beneficial with respect to occupational function associated with shift-work sleep disorder"
Summary

• Substantial evidence must exist to support messages from COA instruments
  – Linking the message to the instrument
• As a general trend, gaps exist in what is being recommended, and what is being implemented

Thank you!

Questions....
Contact Information

• Peter Black, Senior Scientist, ERT Consulting Services, Peter.Black@ERT.com
• Marta Andreykiv, Sr. Consultant, Quintiles, Marta.Andreykiv@quintiles.com
• Stefan Holmstrom, Dir. HEOR, Astellas Pharma Global Development, Stefan.Holmstrom@astellas.com
• Erin Tomaszewski, Clinical Outcomes Research Scientist, Quintiles Outcome, Erin.Tomaszewski@quintiles.com