Evolving Benefit-Risk Management

A New Approach to Benefit-Risk Assessments

16 December 2014
Webinar

Better outcomes
Connecting insights
Superior delivery

Improve your probability of success™
Your Presenters

**Mary Mease**  
Senior Director, Benefit-Risk Management Safety Knowledge and Reporting, Quintiles

Ms. Mease has 17 years of experience in signal detection and validation, risk management, and benefit-risk communication. She has served as a Benefit-Risk Analyst at Quintiles for 6 years. Since joining Quintiles, Ms. Mease has completed projects including post-marketing surveillance, signal detection and verification, portfolio-wide benefit-risk assessments, Risk Management Plans (RMPs), Risk Evaluation and Mitigation Strategies (REMS), and specialized risk management commitments and she serves as an internal consultant for signal detection services, REMS, RMPs, post-marketing regulatory safety concerns, and a breadth of regulatory compliance. Prior to joining Quintiles, Ms. Mease was employed by the FDA for 11 years where she authored many postmarketing signal detection and analyses reports.

**Stella Blackburn**  
Vice President, Global Head of Risk Management, Real-World & Late Phase Research, Quintiles

Dr. Stella Blackburn develops multidisciplinary benefit risk management services, reviews and assists customers with interpretation of pharmacovigilance legislation, and ensures compliance with regulations and best practices in the conduct of pharmacovigilance and risk management activities for the company’s real-world and late phase research efforts. With more than two decades of experience in the pharmacovigilance and pharmacoepidemiology fields, Dr. Blackburn joined Quintiles from the European Medicines Agency (EMA) where she served for more than 16 years. Dr. Blackburn was responsible for designing and implementing risk management public policy and processes used throughout Europe.
Today’s Webinar Audience

- Academia
- Biostatistician
- Clinical Operations
- Epidemiology
- Medical Affairs
- Market Access
- Regulatory Affairs
- Risk Management
- Other
Polling Questions

A small number of polling questions have been added to today’s webinar to make the session more interactive.
Webinar Agenda
Benefit-Risk Management

The benefit-risk management philosophy

Opportunities in innovative benefit-risk programs to optimize patient populations

Meeting European and US regulatory requirements to deliver cost-effective, value-added tools for monitoring and measuring benefit-risk

Case Studies

Q&A
Disclaimer

The views expressed should not be taken to represent the views of Dr Blackburn’s former employer: the European Medicines Agency.
Benefit-Risk Assessment

Definition, Influencing Factors & Philosophy
Why Talk About Benefit-Risk Assessments?

Significance

• Benefit-risk balance is the cornerstone of the regulatory approval process
• Key to protecting public health and individual patients

Challenges

• No standard methodology
• Each combination is different and evolves (drug, adverse event, therapeutic indication, alternative treatments)
• Perceptions
• Systems (value systems, healthcare systems)
Benefit-Risk Assessment

Definition and its intersection with many other disciplines

The comparative evaluation or weighing of benefits (positive effects) and risks (potential harm) of various medical options for treatment, prophylaxis, prevention or diagnosis

- Benefit-Risk management
- Comparative effectiveness
- Evaluation of a new drug
- Post-marketing safety reviews
- Comparison studies
When is the Benefit-risk Balance Acceptable?
Benefit-Risk Assessment Framework

Decisions influenced by many factors

Judgment

Physician
Scientist
Pharma
Payor
Pharmacist
Regulator
Patient

Benefit-risk assessment

Social & behavioral sciences

Legal & regulatory requirements

Science, medicine, & policy

Benefit-risk management
Risk Management
An iterative process for balancing risk-benefit profile

Risk Management Cycle

Identify & Analyse
risk quantification and benefit assessment

Select & Plan
risk characterisation / minimisation and benefit maximisation techniques

Evaluate
Benefit risk balance and opportunities to increase and/or characterise

Implement
risk minimisation / characterisation and benefit maximisation

Collect Data
monitor effectiveness and collect new data

Evidence Continuum for a Drug

Post-launch, efficacy and safety are translated into benefit and risk
Regulations/Guidance in the US and the EU

Requirements for benefit-risk assessments
US Regulatory Environment

Where it is today

**When?** NDA submission and regulatory review, post-market safety reviews

**How?** There is no standard framework to guide benefit-risk assessments

- **July 8, 2012:**
  - Food and Drug Administration Safety and Innovation Act (FDASIA)
    - Amends section 505(d) of the Federal Food Drug and Cosmetic Act (FD&C Act)
    - Requires FDA to “implement a structured risk-benefit assessment framework in the new drug approval process to facilitate the balanced consideration of benefits and risks; a consistent and systematic approach to the discussion and regulatory decision-making, and the communication of the benefits and risks of new drugs. Nothing in the preceding sentence shall alter the criteria for evaluating an application for premarket approval of a drug.”
  - Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making,
    draft Feb 2013; part of PDUFA V Plan (FY 2013-2017)
  - PDUFA Reauthorization Performance Goals and Procedures: Fiscal Years 2013 through 2017
PDUFA V Goals

Important Sections: IX, X, and XI

IX. ENHANCING REGULATORY SCIENCE AND EXPEDITING DRUG DEVELOPMENT

A. Promoting Innovation Through Enhanced Communication Between FDA and Sponsors During Drug Development
B. Advancing the Science of Meta-Analysis Methodologies
C. Advancing the Use of Biomarkers and Pharmacogenomics
D. Advancing Development of Patient-Reported Outcomes (PROs) and Other Endpoint Assessment Tools
E. Advancing Development of Drugs for Rare Diseases

X. ENHANCING BENEFIT-RISK ASSESSMENT IN REGULATORY DECISIONMAKING

XI. ENHANCEMENT AND MODERNIZATION OF THE FDA DRUG SAFETY SYSTEM

A. Measure the Effectiveness of REMS and Standardize and Better Integrate REMS into the Healthcare System
B. Sentinel as a Tool for Evaluating Drug Safety Issues That May Require Regulatory Action
C. Conduct and Support Activities Designed to Modernize the Process of Pharmacovigilance
D. Information Systems and Infrastructure

# PDUFA V Goals

*Section X excerpts*

## X. ENHANCING BENEFIT-RISK ASSESSMENT IN REGULATORY DECISION-MAKING

A description of FDA’s intended approach to build on the Agency’s current efforts to integrate a structured benefit/risk framework throughout the lifecycle of human drug development.

A plan to conduct two public workshops on benefit-risk considerations from the regulator’s perspective that will begin by the first quarter of FY 2014. The first workshop will be primarily informational by focusing discussion on the various frameworks and methods available and their application to regulatory decision-making. The second workshop will focus on the results and lessons learned in implementing frameworks at regulatory agencies in the pre- and post-market drug review process.

An evaluation plan to ascertain the impact of the benefit-risk framework in the human drug review process. The evaluation will consider the utility of the framework in facilitating decision-making and review team discussions across disciplines, risk management plan decision-making, training of new review staff, and communicating regulatory decisions. In particular, the evaluation will consider the degree to which the framework supports or facilitates balanced consideration of benefits and risks, a more consistent and systematic approach to discussion and decision-making, and communication of benefits and risks.
PDUFA V Implementation Plan on Benefit-Risk Assessment

Structured Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making
Draft PDUFA V Implementation Plan - February 2013
Fiscal Years 2013-2017

Figure 1: FDA Benefit-Risk Framework

<table>
<thead>
<tr>
<th>Decision Factor</th>
<th>Evidence and Uncertainties</th>
<th>Conclusions and Reasons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis of Condition</td>
<td></td>
<td></td>
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<tr>
<td>Current Treatment Options</td>
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<tr>
<td>Benefit</td>
<td></td>
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<tr>
<td>Risk</td>
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<tr>
<td>Risk Management</td>
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</tbody>
</table>

Benefit-Risk Summary Assessment

Structured Benefit-Risk Assessment

Progress

PDUFA V Commits FDA to 2 Public Workshops

1st Workshop held Spring 2014: Characterizing and Communicating Uncertainty in the Assessment of Benefits and Risks

- Acknowledged uncertainty
- Discussed methods for dealing with uncertainty
  - Statistics
  - Patient perspective
  - How to communicate and the impact of communicating uncertainty

2 Major Areas of Uncertainty

- The transition of pre-market clinical trial data to the post-market setting
- New finding identified post-market for which the sources have various levels of rigor (e.g. case report, observational study)

Key Considerations

- Improve human judgment rather than replace it with an automated process
- Qualitative and quantitative components
- Acknowledge the uncertainty (clinical, methodologic, statistical)
- Recognize knowledge gaps
- Patient perspective

Source:
http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm378861.htm
### XI. ENHANCEMENT AND MODERNIZATION OF THE FDA DRUG SAFETY SYSTEM

#### A. REMS

By the end of FY 2013, FDA will develop and issue guidance on how to apply the statutory criteria to determine whether a REMS is necessary to ensure that the benefits of a drug outweigh the risks.

By the end of FY 2013, FDA will hold one or more public meetings to include the pharmaceutical industry, other government healthcare providers, patient groups, and partners from other sectors of the healthcare delivery system to explore strategies to standardize REMS, where appropriate, with the goal of reducing the burden of implementing REMS on practitioners, patients, and others in various healthcare settings. To move towards increased integration of REMS into the healthcare delivery system, FDA will issue a report of its findings by the first quarter of FY 2014 that will identify at least one priority project in each of the following areas including a work plan for project completion: pharmacy systems, prescriber education, providing benefit/risk information to patients, and practice settings.

By the end of FY 2013, FDA will initiate one or more public workshops on methodologies for assessing whether REMS are mitigating the risks they purport to mitigate and for assessing the effectiveness and impact of REMS, including methods for assessing the effect on patient access, individual practitioners, and the overall burden on the healthcare delivery system. FDA will issue guidance by the end of FY 2014 on methodologies for assessing REMS. This guidance should specifically address methodologies for determining whether a specific REMS with elements to assure safe use (ETASU) is: (i) commensurate with the specific serious risk listed in the labeling of the drug and (ii) considering the observed risk, not unduly burdensome on patient access to the drug.
Standardizing and Evaluating REMS

Progress and the September 2014 Report

FDA convened several workshops 2010-2013

• September 2014 report: Standardizing and Evaluating Risk Evaluation and Mitigation Strategies (REMS)

• Four priority projects identified
  › Improve prescriber-to-patient counseling tools
  › Include REMS healthcare provider education as Continuing Education (CE)
  › Standard format of REMS information and inclusion into Pharmacy Systems
  › Provide a central source of REMS information for stakeholders

PDUFA V Goals

Section XI excerpts (continued)

B. Sentinel as a Tool for Evaluating Drug Safety Issues That May Require Regulatory Action

FDA will use user fee funds to conduct a series of activities to determine the feasibility of using Sentinel to evaluate drug safety issues that may require regulatory action, e.g., labeling changes, PMRs, or PMCs. The activities will be selected and designed to focus on issues that affect classes of drugs or multiple products.

Explore using the Sentinel System to evaluate other types of signals in population-based databases. The following are examples of potential activities:

a) Expanding the active surveillance mechanisms begun for the H1N1 pandemic to substitute for the information gathered in large ad hoc, manufacturer-conducted studies
b) Evaluating risk for class-wide adverse events (e.g., cardiovascular events, suicidality)

By the end of FY 2017, FDA will conduct (or fund by contract) an assessment to evaluate the strengths, limitations, and the appropriate use of Sentinel for informing regulatory actions (e.g., labeling changes, PMRs and PMCs) to manage safety issues.
Sentinel Initiative

Progress and Next Steps

• Mini-Sentinel underway for about 5 years
  › FDA has been tapping the Mini-Sentinel System to provide information to complement other information to make regulatory decisions
  › Protocols posted for comment in advance

• Achieved goals 6 months in advance of target timelines

• Now >150 million electronic health records surpassing the 100 million goal

• 7th Annual Sentinel Initiative Public Workshop is February 5, 2015
  › Transition from the Mini-Sentinel pilot to full Sentinel System
  › National Data Infrastructure
EU Regulatory Environment

Risk Management Plans (RMPs) vs. Periodic Safety Update Reports (PSURs)

**PSUR**
- Main focus is benefit-risk evaluation:
  - Ensure benefit risk balance remains favorable
  - Signal detection and evaluation
  - Ensure product information up to date
  - Establish and publish the known risks of a substance

**RMP**
- Main focus is planning:
  - Risk minimization
  - Data collection
  - Ensuring effectiveness of measures
  - Safety & Efficacy studies

GVP Module VII
- PSUR
GVP Module V
- RMP
Objective of the PSUR

• To present a comprehensive and critical analysis of new or emerging information on the risks and, where pertinent, new evidence of benefit to enable an appraisal of overall benefit risk.

• To contain an evaluation of new relevant information that became available to the MAH during the reporting interval, in the context of cumulative information:
  › Examine whether new information is in accord with previous knowledge of the benefit risk profile
  › Summarizes relevant new safety information that may impact the benefit risk profile
  › Summarizes any important new efficacy and effectiveness information
  › Conduct an integrated B/R evaluation (where new important safety information has emerged)

• PSUR Section 18: “Integrated Benefit Risk Analysis for Approved Indications”: overall integrated analysis of key benefits and risks as used in clinical practice

Acronym Key:
PBRER - Periodic Benefit Risk Evaluation Report
MAH - Market Authorization Holder
B/R – Benefit Risk
EU Regulatory Benefit-Risk Framework
CHMP 2008 review of benefit risk evaluation

Conclusions on current practice of evaluation

• Synthesis of available evidence
• Qualitative assessment
• Subject to biases
• Difficult to communicate

Recommendations

1. Revision of current benefit risk part of CHMP AR
   › Structured list of risks and benefits

2. Explore methodologies for benefit risk analysis
Working groups

WP 1  current practice
› involving different regulatory agencies
› ideas for improvement

WP 2  applicability of current tools and processes
› literature review (non pharmaceuticals)
› Dealing with uncertainty
› Accommodating multiple benefits and risks and trade-offs
› Resolving differences in perspective
› Managing complexity

WP 3  Field test using ongoing assessment
› Benefits and risks
› Evidence base
› How differential importance was considered
Working groups and impact

WP4  Development of benefit tool and process

WP5  training package for regulatory assessors

Expected impacts

• Improve quality of regulatory benefit risk assessment
• Improve transparency of benefit risk communication
• Increase public confidence in regulatory decision making
• Make benefit risk assessments more predictable
• Contribute to harmonisation across the EU
<table>
<thead>
<tr>
<th>Effect</th>
<th>Short Description</th>
<th>Unit</th>
<th>Placebo</th>
<th>Vandetanib</th>
<th>Uncertainties/Strength of evidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (HR)</td>
<td>From randomization to progression or death (blinded independent review)</td>
<td>N/A</td>
<td>1</td>
<td>0.46</td>
<td>95% CI: (0.31, 0.69) Large effect in overall population. Consistent and significant effect on PFS but not OS (too early?) Only a very low number of patients with definite RET mutation negative status at baseline. Lower efficacy? No clear effect on PRO/QoL (missing data)</td>
<td>See Discussion on Clinical Efficacy. Single-arm study in RET negative patients post-approval.</td>
</tr>
<tr>
<td>PFS (median)</td>
<td>Weibull model</td>
<td>Mo</td>
<td>19.3</td>
<td>30.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>Proportion of complete or partial responders (&gt;=30% decrease unidimensional) RECIST</td>
<td>%</td>
<td>13</td>
<td>45</td>
<td></td>
<td>See Discussion on Clinical Efficacy.</td>
</tr>
</tbody>
</table>
Case Studies
Case Example: Portfolio Benefit-Risk Assessment
Portfolio Benefit-Risk Assessment

*Company A*

Executed a benefit-risk assessment of 220+ compounds.
› Multiple acquisitions over many years
› Refocus priorities
› Advancements in certain therapeutic areas

Process
› No roadmap
› Subjectivity based on science

Information
› Qualitative assessment based on available scientific information
  » Clinical Practice Guidelines
  » Pharmacology of compound and class
  » Literature—published clinical trials; epidemiology of risks
› Consideration of local medical practice
› Regulatory Agency actions and opinions

Actions
› No change
› Updates to labels
› Discontinue marketing in select regions
› Discontinue manufacturing altogether

**Key Learnings:**
• Limited talent pool for conducting Benefit-Risk Assessments
• Time consuming
Case Example: Practical example of EU regulatory challenges with managing benefit risk of natalizumab
The initial evaluation

EU Application for natalizumab received 3rd June 2004

- Formal evaluation procedure started on 24th June 2004
- Rapporteur’s first AR report circulated on 30th August 2004
- Co-Rapporteur’s first AR report circulated on 3rd Sept 2004
- CHMP agreed on the LoQ during the 18-21 Oct 2004 meeting
- LoQ sent to the Applicant on 21st October 2004
- Approved in the US November 2004
- February 2005 letter received from MAA announcing suspension of Clinical Trial programme due to (initially) 2 cases of progressive multifocal leukoencephalopathy (PML)
- Companies announced voluntary suspension of marketing in US
Next steps

- CHMP expert attended MAA meeting in March 2005
- CHMP adopted an addendum to the LoQ March 2005
- Response received from MAA 6th October 2005
- Scientific Advisory Group convened Jan 2006
- CHMP adopted list of outstanding issues Jan 2006
- Oral explanation April 2006
Tysabri  B/R  April 2006

68% ↓ in annualised relapse rate
83% reduction in new or newly enlarging T2 hyperintense lesions

Dizziness
Hypersensitivity reactions – 4%  anaphylactoid 0.4%
Injection site reactions
Headache/flu like symptoms
Opportunistic infections

**PML**
3 cases  but  4,500 person years exposure in MS and Crohn’s
Poll Question 1

Do you think it should be authorized?

- Yes
- No
Authorisation

• Positive Opinion April 2006

Tysabri is indicated as a single disease modifying therapy in highly active relapsing remitting MS for the following patient groups:

Patients with high disease activity despite rx with a β interferon (see 5.1)

or

Patients with rapidly evolving severe relapsing remitting multiple sclerosis (see 5.1)

• Commission Decision 27th June 2006
Tysabri risk minimisation

Restricted indication

Use by specialised physicians in neurology

Centres with timely access to MRI

Physician information

- Restricted indication to most severely affected patients
- Risk of atypical opportunistic infections including PML
  - MRI before initiation of treatment (usually within 3/12)
  - Diagnosis of PML
  - Differentiation between PML and MS relapse
  - PML management algorithm
  - Information about other adverse reactions
  - Need to inform patients about B/R
  - Patient alert cards
August 2008

Confirmed PML cases

PML cases

- Jun-06
- Oct-06
- Feb-07
- Jun-07
- Oct-07
- Feb-08
- Jun-08
- Oct-08
- Feb-09
- Jun-09
- Oct-09
- Feb-10
- Jun-10
- Oct-10
- Feb-11
- Jun-11
- Oct-11
- Feb-12
- Jun-12
- Oct-12
- Feb-13
- Jun-13
- Oct-13
- Feb-14
- Jun-14
- Oct-14
September 2008

• During variation CHMP consults SAG on PML
  › Early detection of PML
  › Adequacy of revised SmPC and RMP

• Change threshold of PML investigation in SmPC & RMP
  » Suspend treatment and investigate on any new exacerbation if any possibility that it is not a MS flare up
  » Only restart natalizumab once a diagnosis of PML is excluded (may need repeated tests until certain)

• Add information in SmPC about effects of PLEX

• Modify patient alert card to warn that changed behaviour may be symptom of PML
Article 20 referral

October 2009  European Commission asked CHMP to review benefit risk

January 2010  – 31 confirmed cases of PML
23 in patients treated > 2 yrs
↑ ~ 1/1000 after 2 years or more

Risk minimisation augmented

- Increased warnings in SmPC and PL
- Baseline MRI and then yearly
- Assessment of patient at each monthly infusion  ?MRI
- Beware negative CSF PCR JCV
- MAH should discuss continuous monitoring with MSs
- Treatment initiation and continuation forms after 24 months
- Updated patient alert card
Poll Question 2

What do you think the CHMP should have recommended?

• Keeping it on the market
• Suspending the Market Authorisation
• Withdrawing the Marketing Authorisation
October 2010

Confirmed PML cases

PML cases

0 25 50 75 100 125 150

79
### October 2010

- Analysis of 52 cases showed that prior IS is a risk factor

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Incidence PML with prior IS exposure</th>
<th>Incidence PML without prior IS exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+ infusions</td>
<td>1.89 (1.20-2.83)</td>
<td>0.45 (0.29-0.66)</td>
</tr>
<tr>
<td>13+ infusions</td>
<td>3.01 (1.89-4.55)</td>
<td>0.77 (0.50-1.12)</td>
</tr>
<tr>
<td>25+ infusions</td>
<td>4.70 (2.79-7.42)</td>
<td>0.95 (0.55-1.52)</td>
</tr>
</tbody>
</table>

Information added to SmPC and educational material
April 2011

Confirmed PML cases

PML cases
April 2011 Renewal & Variation

Analysis of PML cases showed antibodies to JCV risk factor

<table>
<thead>
<tr>
<th>Anti-JCV Ab status</th>
<th>Negative</th>
<th>Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0.2/1000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Exposure** | **No prior IS** | **Prior IS**
---|---|---
1-24 months | ~0.4/1000 | ~1.2/1000
25-48 months | ~2.6/1000 | ~8.3/1000

Information on risk stratification added to SmPC and educational material
April 2012

Confirmed PML cases

PML cases

2012 Variation

Updated information on risk stratification in SmPC and educational material

Anti-JCV Ab status

<table>
<thead>
<tr>
<th>Exposure</th>
<th>No prior IS</th>
<th>Prior IS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-24 months</td>
<td>~0.5/1000</td>
<td>~1.5/1000</td>
</tr>
<tr>
<td>25-48 months</td>
<td>~3.9/1000</td>
<td>~10.6/1000</td>
</tr>
</tbody>
</table>
October 2012

Confirmed PML cases

PML cases
Variations

• October 2012

  Recommendation to test anti-JCV antibody in seronegative patients every six months instead of 12

  Information added to SmPC and educational material

• January 2013

  Warning that PML has been reported in patients following discontinuation of Tysabri in patients who did not have findings suggestive of PML at the time of discontinuation

  Information added to SmPC
Benefit of Tysabri as assessed May 2013 during Variation II/0059

B. ARR reduction per yearly interval overtime

Figure 15-1.1 Overall ARR in TOP compared to AFFIRM

Source: Table 11 and Polman et al (2006)
Current situation

Confirmed PML cases

Current estimates of rates of PML

Anti-JCV Ab status

Negative

Positive

0.1/1000

<table>
<thead>
<tr>
<th>Exposure</th>
<th>No prior IS</th>
<th>Prior IS</th>
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<tbody>
<tr>
<td>1-24 months</td>
<td>0.7/1000</td>
<td>1.8/1000</td>
</tr>
<tr>
<td>25-48 months</td>
<td>5.3/1000</td>
<td>11.2/1000</td>
</tr>
<tr>
<td>49-72</td>
<td>6.1/1000</td>
<td>Insufficient data</td>
</tr>
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Data from Multiple Sclerosis Research http://multiple-sclerosis-research.blogspot.com/2014/01/january-2013-natalizumab-pml-update.html
Poll 3

If you were a patient, would you like to have the choice of taking this product?

- Yes
- No
The Regulator’s dilemma

• Natalizumab is an effective treatment

• PML serious disease with considerable morbidity and mortality

• Because of the risk, treatment should be given to those likely to benefit most
  » But are these the patients who are most at increased risk?

• Cannot predict who will or won’t get PML within risk strata

• Only risk minimisation for PML is constant update of information about risk and risk factors and stopping treatment if any suspicion of PML

• Number of PML cases continues to rise
Case Example: WP5 of PROTECT

Looking at data at approximately the time of the referral in 2010

With thanks to Professor Ashby and WP5 for some of the slides
The Innovative Medicines Initiative (IMI)

- Mission
  - The Innovative Medicines Initiative (IMI) is Europe's largest public-private partnership aiming to improve the drug development process by supporting a more efficient discovery and development of better and safer medicines for patients.
  - IMI supports collaborative research projects and builds networks of industrial and academic experts in order to boost pharmaceutical innovation in Europe.
Call No. 6: Strengthening the monitoring of Benefit and Risk

PROTECT

Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium
Work Package 5: Objectives

• To investigate methods of collating data on benefits and risks

• To develop novel modelling approaches allowing continuous benefit-risk modelling along the lifecycle of products

• To build an easy-to-use and understand graphical representations of benefits and risks of medicinal products for use by patients, healthcare prescribers, regulatory agencies, and drug manufacturers, along the lifecycle of the products
# Work Package 5 of PROTECT (membership)

<table>
<thead>
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<th>Public</th>
<th>Private</th>
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<tr>
<td>EMA</td>
<td>AstraZeneca</td>
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<tr>
<td>DKMA</td>
<td>Bayer</td>
</tr>
<tr>
<td>AEMPS</td>
<td>GSK</td>
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<td>MHRA</td>
<td>Lundbeck</td>
</tr>
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<td>Imperial College (co-leader)</td>
<td>Merck KGaA (co-leader)</td>
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<td>Mario Negri Institute</td>
<td>Novartis</td>
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<td>GPRD</td>
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<td>WHO Uppsala</td>
<td>Pfizer</td>
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<tr>
<td>IAPO</td>
<td>Roche</td>
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<td></td>
<td>Sanofi-Aventis</td>
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<td></td>
<td>Takeda</td>
</tr>
</tbody>
</table>
How do you assess benefits and risks?

Global chance of being struck by lightening
1: 300,000

Chance of being struck by lightening in the UK
1:1,000,000 – 1: 2,000,000

↑ In hot, humid areas

↑ If outdoors

↑ If you are tallest object in vicinity!

Risk is multifactorial
How do you assign value?

Many things are subjective
Classifications of approaches

- Benefit-risk assessment framework
  - PROACT
  - URL
  - ASF
  - BRAT
  - CMR-CASS
  - FDA
  - BRF

- Metric indices for B-R assessment
  - NNT
  - NNH
  - AE-NNT
  - RV-NNH
  - Impact numbers
  - MCE
  - RV-MCE
  - MAR
  - NEAR

- Health indices
  - QALY
  - DALY
  - HALE
  - Q-TWiST

- Trade-off indices
  - UT-NNT
  - INHB
  - BRR
  - GBR
  - Principle of three
  - TURBO
  - Beckmann Model

- Estimation techniques
  - DAGs
  - PSM
  - CPM
  - ITC
  - MTC
  - CDS

- Main categories
  - Sub-categories
  - Utility survey techniques
    - SPM
    - CV
    - CA
    - DCE

- All B-R assessment approaches
  - Approaches excluded and not appraised
Steps

1. Define problem
2. Value tree
3. Evidence synthesis
4. Assign value to each criterion
5. Assign weight to each criterion
Problem

Is the benefit-risk profile of natalizumab still positive following the identification of PML as an adr?

(Data from EC Referral - concluded Jan 2010)
Value tree

Benefit-risk balance

Benefit
- Reduction in relapse rate
- Slowdown in disability progression

Administration

Risks
- Severe side effects
  - PML
  - Reactivation of serious herpes viral infections
  - Seizures
  - Abortion or congenital abnormalities
- Mild side effects
  - Transaminases elevation
  - Infusion or injection reactions
  - Hypersensitivity reactions
  - Flu-like reactions
Then a Miracle Occurs

"I think you should be more explicit here in step two."
Assigning a value

Number of relapses per 1000 patients at one year
## Assigning a Weight

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Worst</th>
<th>Best</th>
<th>Rank</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of relapses per 1000 patients</td>
<td>400</td>
<td>80</td>
<td>2</td>
<td>40</td>
</tr>
<tr>
<td>Disability</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with EDSS score increase ≥ 1</td>
<td>270</td>
<td>100</td>
<td>1</td>
<td>100</td>
</tr>
</tbody>
</table>
The Benefit-risk is the product of the weight and the value.

Most of the Benefit-risk contribution is coming from prevention of relapses.

Infusion reactions are the worst risk.
Challenges

Balancing benefits with risks is complex, as it involves:

- uncertainty (difficult to estimate probability of desirable and undesirable effects, effect size, etc. due to limited and sometimes conflicting data),
- differences in perspectives (patient, societal, regulatory perspectives),
- heterogeneity of effects across patient populations.
- ill-defined preferences and utilities of outcomes,
- the difficulty of trading off effects of differential importance,
- lack of agreement on what valuation criteria to use
Thank you
Previous & Upcoming Events

Quintiles experts run regular webinars on Real-World & Late Phase services.

Topics include:

- OBSERVATIONAL RESEARCH
- HTA & MARKET ACCESS
- MAXIMIZING VALUE AND QUALITY IN PHASE IV
- COMPARATIVE EFFECTIVENESS RESEARCH
- CLINICAL OUTCOME ASSESSMENTS

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Conferences include:

- **SCOPE Summit for Clinical Ops Executives**, Feb 24-26, Miami, FL

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