Medical Outcome Trials Webinar

May 30th, 2012
Phil Galtry
Mel Blackwood
Phil Galtry
Senior Director, Clinical Project Management, Cardiovascular Metabolic, Quintiles

Phil has over 23 years of experience working in Clinical Research with the last 16 years in project leadership managing large global/multi-national programs and studies across Europe, South Africa, Asia, Australasia, North and South America. He has significant experience working in the cardiovascular therapeutic area, including hypertension, acute coronary syndrome, hypercholesterolemia and heart failure but has also had experience in brain injury, heartburn, and pain. Phil has been responsible for the Project Management and oversight of a number of large and complex Phase 3 and 3b multi-national cardiovascular outcomes trials including up to 41 countries across 1,000 sites, and including over 15,000 patients. Philip's current role combines line management of Clinical Project Management staff and programme management. Philip's current program management responsibilities include liaising with the customer and third party contractors, as well the co-ordination and management of the entire project team on a program of two large and complex studies and smaller imaging studies. Phil also gained the Project Management Certification (PMP), as set by the Association of Project Management Professionals.

Mel Blackwood
Vice President, Global Lead, Outcome Interventional Project Management

Mel has experienced a variety of roles within Project and Client management through her career with a strong focus on the late phase arena. She started her clinical and project management career at BI and became a Clinical Scientist primarily working in the cardiovascular and respiratory areas. At Covance in 2001 after several years of project and large program management she became a Director of Operations in Europe overseeing operational delivery of a group of key clients. In 2004 she became a Client Relationship Director overseeing Japanese clients globally within phase 111 and Late Phase drug development. In 2006 she became a Senior Director heading up the Respiratory and Cardiovascular groups within European Project Management within Covance. In 2008 she became Executive Director of a Global Strategic Alliance for all Late Phase projects within Covance overseeing a 10,000 patient CV Outcome study as part of the alliance portfolio.

In January 2010 she joined Quintiles to further focus her skills in the Late Phase and Observational research areas. The Global Outcome interventional group is currently responsible for operational delivery of several large CV outcome studies. Mel graduated from Southampton University and has a B.Sc. degree in Biological Sciences. She has a Diploma in Clinical Science from the University of Cardiff. She is CPMP qualified in project management and has a green belt in six sigma process management.
Today’s Webinar Audience

- Academia: 21.32%
- Biostatistician: 5.88%
- Clinical Operations: 36.76%
- Epidemiology: 3.68%
- Health Economics: 2.21%
- Market Access: 7.35%
- Medical Affairs: 0.74%
- Medical Affairs: 5.88%
- Other: 16.18%
- Risk Management: 0.74%
Polling Questions

• A small number of polling questions have been added to today’s webinar to make the session more interactive
Contents

Trends in demand for medical outcome trials

Operational strategies to maximize medical outcome trial success incorporating case studies
What your experience of Medical Outcome Trials?

• No experience
• One trial
• More than one trial
Trends in demand for medical outcome trials
Definition

• A medical outcome trial refers to a large-scale, long-duration clinical trial with hard clinical endpoints, including both morbidity and mortality, as outcomes.

• Medical outcome trials are important in establishing the long-term safety of agents used in preventative pharmacology, including type 2 diabetes, inflammatory disease (RA, OA) and asthma, and in demonstration of efficacy in cardiovascular disease and type 2 diabetes.

• Medical outcomes trials are often a requirement for regulatory approval and are an important mechanism for safety data capture post-approval.

• Note: Outcome Trials should not be confused with “Outcomes Research” which focuses on the effects of medical care on individuals and society, or with phase II/III safety and efficacy trials that measure outcomes using surrogate endpoints.

Ref: On the Need for Outcome Trials in Preventative Pharmacology: Lessons from the recent experience with adverse drug reactions. Stern, Diabetes Care 22(5) May 1999 [http://care.diabetesjournals.org/content/22/5/844.short](http://care.diabetesjournals.org/content/22/5/844.short)
Regulators may request medical outcome trials as a condition of product approval

Outcome trials may be mandated by regulators

Product with known safety risk

FDA Post-marketing Requirement

Clinical Trial

EMA Post-authorisation Safety Study

Clinical Trial

Study

Study

Section 505(o)(3)(A) states that postmarketing studies and clinical trials may be required for any or all of three purposes: 1. To assess a known serious risk related to the use of the drug; 2. To assess signals of serious risk related to the use of the drug; 3. To identify an unexpected serious risk when available data indicates the potential for a serious risk.

FDA section 505(o)3

Article 1(15) of the Directive 201/83/EC as any pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of the marketing authorisation, conducted with the aim of identifying or quantifying a safety hazard of an authorised medicinal product

EMA vol9a_09-2008
• “(The FDA has) determined that concerns about cardiovascular risk should be more thoroughly addressed during drug development”.

• “To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk”.

• “For new clinical studies ... sponsors should:
  > establish an independent cardiovascular endpoints committee
  > include patients at higher risk of cardiovascular events,
  > (design trials) to last more than the typical 3 to 6 months duration to obtain enough events and to provide data on longer-term cardiovascular risk (e.g., minimum 2 years)

Guidance for Industry: Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes, December 2008

• Respiratory:
  > http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM206722.pdf

• RA also covered.

• Anti Obesity drugs likely to follow suit
FDA requirements for Outcomes Trials on Cardiovascular Drugs

- None!
- However surrogate markers highly unlikely to be acceptable in key indications:
  - **Dislipidaemia**
    - ILLUMINATE, ENHANCE, dal-OUTCOMES all failed to meet primary endpoint despite favourable impact on lipid profile
  - **Anticoagulation, antiplatelet**
    - All recent factor Xa inhibitor and anti platelet drug development has been through phase III outcomes trials

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<th>Year</th>
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<th>Diabetes</th>
<th>Resp</th>
<th>GI</th>
<th>ID</th>
<th>MBC</th>
<th>Oncology</th>
<th>Womens Health</th>
<th>Blood</th>
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During what development phase have the Medical Outcome Trials that you have run taken place?

- Phase III
- Phase IV
- Phase III and IV
Medical outcome trials are used in both pre and post registration development to support efficacy and safety claims – 75% of all such trials begin pre-registration. Significant growth in post-approval medical outcome trials has led to 25% of all phase IV patients enrolled in medical outcome trials today.
Medical Outcome Trials fall at the explanatory end of the pragmatic-explanatory continuous design spectrum.

**Effectiveness**
Determine the effects of an intervention under the **usual conditions** in which it will be applied

More Representative

**Efficacy**
Determine the effects of an intervention under **ideal circumstances**

Less Representative

Costs

• Medical outcome trials can be expensive
  > Can be a major part of the overall cost of bringing a drug to market

• Sponsors must look at design and delivery approaches to minimize costs, and maximize value
Operational strategies to maximize medical outcome trial success incorporating case studies
From your experience, what are the most challenging aspects of Medical Outcome Trials?

- Protocol Design
- Site Selection and Start-up
- Site Monitoring
- Patient Enrollment and Retention
- Endpoint Adjudication and Data Management
Planning

• Detailed plans essential, and if done during the protocol development phase should not become rate limiting
  > Budgeting
  > Protocol development
  > Resource plans
  > Timelines
  > Site selection criteria and sources
  > Country and patient distribution – constraints and opportunities
  > Start up strategy
  > Monitoring strategy
  > Endpoint management
  > Recruitment modelling
## Protocol Design Considerations

<table>
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<tr>
<th>Category</th>
<th>Consideration</th>
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<tr>
<td><strong>Endpoint Selection</strong></td>
<td>• Hard endpoints vs. surrogates</td>
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<tr>
<td><strong>Treatment Options</strong></td>
<td>• Built on standard of care</td>
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| **Trial Duration**             | • Longer than phase II/III  
• Sufficient to accrue endpoints                                                 |
| **Inclusion/Exclusion Criteria** | • Potential for more representative patients likely to experience more events* |
| **Sample Size**                | • Typically 1000s of patients required for event determination                |
| **Patient Assessments and Frequency** | • Minimum sufficient to determine events and monitor patient safety       |
| **Safety Reporting**           | • May be reduced if safety database already well established (especially in phase IV trials) |

By analyzing 300 overlaid iterations, we can see the likelihood of possible study timeline results.
Recruitment Simulation – Recent ACS

Confidence Interval
If start up and enrollment go according to expectations, the enrollment target will be met (LPI Median, right; 50% confidence, below right). However, given variability in start up and recruitment rates, there is a higher confidence in a later LPI.

Simulation Results

<table>
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<tr>
<th>Metric</th>
<th>Start Date</th>
<th>End Date</th>
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<tr>
<td>FPFV is between</td>
<td>16-Sep-12</td>
<td>20-Oct-12</td>
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<tr>
<td>LPI 90% CI is between</td>
<td>27-Oct-13</td>
<td>22-Mar-14</td>
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<tr>
<td>LPI 50% CI is between</td>
<td>17-Nov-13</td>
<td>8-Feb-14</td>
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<tr>
<td>LPI Median is week of</td>
<td>15-Dec-13</td>
<td>21-Dec-13</td>
</tr>
</tbody>
</table>

Overall 75% Likelihood of LPI on this date OR EARLIER: 08-Feb-14
What monitoring strategies have you deployed for Medical Outcome Trials?

- Full on-site monitoring
- On-site and remote monitoring
- Full remote monitoring
Shift monitoring resources based on ‘risk’

Balanced relationship between on-site and centralized monitoring improves delivery & quality leading to better trial performance

Applying central monitoring based upon the following criteria:
1. Number of Subjects
2. Research experience of investigators and site resources
3. Electronic data capture (EDC)
4. Protocol complexity
5. Duration of study

This approach is designed to:
1. Increase site satisfaction, engagement and data quality;
2. prompt site adherence to the protocol
3. assist in timeliness of DE & queries
Flexible Monitoring Work Flow
iCRAs are Sites’ Main Point of Contact

On-site & Central Monitoring Visits

Regular & Ad hoc Contacts / Helpline

CTMS

Integrated Reporting

*Frequency of onsite/remote visits flexible; may drop after recruitment completes
The Effect of Drop-out on Outcomes Trials

*Drop out is the sum of withdrawal from randomized treatment and/or consent (% of initial randomized patients)*

- Withdrawal from randomized treatment
- May be a temporary suspension rather than permanent discontinuation
- Still allows patient to be followed for endpoint status
- Withdrawal of consent / failure to return → loss to follow-up
- Increasing impact from withdrawal of consent
- Vital status still may be collected in most countries, but not always possible

Hypothetical example

- A mortality study randomizes 2,000 subjects:
  - 1,000 to placebo
  - 1,000 to active treatment
- Assumptions:
  - True event rate (placebo-treated patients) = 20%
  - Active treatment event rate = 15% (i.e., a 25% relative risk reduction)
  - Assuming all patients continue treatment until study cessation or endpoint, \( p=0.004 \)
What would the impact on study results be for each scenario?

20% withdrawal from treatment
- Low
- Medium
- High
What would the impact on study results be for each scenario?

2% lost to follow-up

- Low
- Medium
- High
Hypothetical Scenarios

Scenario 1 – “Significant” loss of patient numbers due to withdrawal from treatment
- 20% of patients (N = 200) in each group dropped study drug but were followed up for vital status

Final analysis
- 800 patients/study arm compliant with treatment
- Placebo: 20% event rate
- Treatment: 16% event rate
  - 20% RRR; P = 0.02

Scenario 2 – “Slight” loss of patient numbers due to withdrawal but all withdrew consent, provide no data
- 2% of patients (N = 20) in each group dropped out and withdrew their consent for follow-up or failed to return

Final analysis
- 980 patients/study arm compliant with treatment
- Usual practice is to assume “worst case scenario”
- Placebo: 19.6% event rate
- Treatment: 16.7% event rate
  - 14.8: RRR; P = 0.10

Examples provided by Pr. R Scott Wright, Mayo Clinic
Regulatory Considerations

Thomas Marciniak. FDA Cardiovascular and Renal Drug Products Division Medical Team Leader:

“The rates of patients with unknown vital status greatly exceed the reported differences in mortality rates. We cannot have confidence that the claimed mortality benefits are real.”

Briefing materials for the Cardio-Renal Drugs Advisory Committee's May 23 2012 review of rivaroxaban

“While we are sympathetic to the difficulties of performing outcome trials in the modern era of increased patient awareness of medical treatments and mounting privacy concerns, if this trend continues we will not be able to interpret CV outcome trial results. This problem is the number one study conduct problem today threatening the integrity of CV outcome trials.”

Briefing materials for the Cardio-Renal Drugs Advisory Committee's July 28 2010 review of ticagrelor
Goals and Key Success Factors for Medical Outcome Trials

Goals

• Recruit sites with access to patients and referral partners
• Recruit patients as quickly as possible to meet endpoints as soon as possible
• Recruit patients that can be retained until sufficient endpoints are met

Key Success Factors

• Rising above the competition
• Motivated sites
  > Study support
  > Targeted site strategy
  > Effective tools
• Committed patients and care givers
  > Medication compliance
  > Endpoint reporting
  > Maintaining contact
Site Material Return on Investment

- Faster enrollment
- Time savings
- Cost savings
- Patient retention

Therapeutic Area: Cardiovascular
Acute Coronary Syndrome

Study: Global, Phase III, randomized, adult subjects, drug study

Sites/Patients: 500+ / 10,000+

Tools: Site materials

<table>
<thead>
<tr>
<th>Return on Investment</th>
<th>US</th>
<th>ROW</th>
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<tr>
<td>% Site with Site Materials</td>
<td>~80%</td>
<td>~80%</td>
</tr>
<tr>
<td>Site materials investment</td>
<td>$0.6m</td>
<td>$0.7m</td>
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<tr>
<td>Enrollment time saved (months)</td>
<td>2.09</td>
<td>1.53</td>
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<tr>
<td>Direct cost savings</td>
<td>$2.9m</td>
<td>$4.4m</td>
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<tr>
<td>ROI</td>
<td>3.8x</td>
<td>5.6x</td>
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Without site materials, 40+ and 30+ additional sites in the US and ROW respectively would have been needed to maintain the same enrollment performance.

Note: Savings includes costs of duration-based activities, but not potential savings of sponsor oversight or opportunity cost of faster marketing approval.
Patient Perspectives on Participation

**Motivators**

Benefit to participation
- Free medication and medical care (86%)
- Reimbursement for travel (82%)
- Contributing to medical research (73%)
- Comprehensive evaluation of CV risk factors (69%)
- Recommended by personal doctor (67%)

64% would not participate or considered it a drawback if their personal doctors expressed concerns

78% would like to be contacted if a study became available

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*iGuard.org 2009 (n=75)
iGuard.org 2011 (n=51)*
**Digital Strategy**
Driving Recruitment, Operations, Retention and Communications

**Investigators**
- Investigator Portal
  - Pre-ID (HRVD)
- Smartphone Protocol App

**Referring Physicians**
- Referral Website

**Patients and Care Givers**
- Recruitment Website (Prospective Patients)
- ICF Website (Consenting Patients)
- Study Website (Randomized Patients)

**Physician Outreach**
- Site referral tools
- Physician advertising

**Patient Outreach**
- Site recruitment tools
- Site advertising
- Regional advertising

**Quick Response (QR) Codes** on outreach tools will direct patients and physicians to the appropriate website in each country and track response by site (SmartPhone app)
Patient Perspectives on Retention

Actions rated as “extremely” or “very helpful” to staying in the trial

90% Improvement in heart disease risk factors
84% Email newsletters and updates
70% Emails from the site*
67% Extended/weekend clinic hours
53% Contact with trial participants
49% Phone calls from the site*
47% Non-monetary milestones rewards

Over 50% said that the following would be “very valuable” in managing their conditions

- Daily pill organizer
- Heart-healthy cookbook
- Heart-healthy diet tips
- Medical dictionary

Source: MediGuard.org 2011 (n=51)
Retention Begins at Enrollment

**Enrollment**
- Study education (ICF)
- Single consent to contact services
  - Study communications/reminders
  - Study withdraw
  - Lost to Follow-up

**Randomization**
- Study guide

**Treatment**
- Site/patient relationship
- Patient/care giver motivation
- Patient communications
  - Monthly calls/emails from sites
  - Automated visit and fasting reminders
  - Automated inquiries regarding events and hospitalization

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**Retention Strategies Reduce Dropout Rates**
An independent case study for a three-year CHD trial including 3,616 subjects and 117 sites in the US and Canada demonstrated the benefits of retention strategies:
- 5 sites with no retention program experienced 25% dropout
- 105 sites that relied on mailings experienced 20% dropout
- 7 sites with a dedicated retention strategy experienced 8% dropout
(Alliance Marketing Group, DIA Conference April 2003)
Summary

The outcome of outcomes studies

- Medical Outcome Trials answer critical research questions regarding product safety and efficacy, and represent some of the most costly and logistically challenging trials in the entire product lifecycle
- Done well, they can change the face of patient care
Upcoming Events

European Post-Approval Summit
11-12 September 2012
Zurich, Switzerland
www.europe.postapproval.org