Maximizing Value and Quality in Phase IV Trials

Webinar

Louise Parmenter
Ralph Moussalli
Your Presenters

**Louise Parmenter PhD**
Senior Director, Global Strategic Operations, Quintiles Outcome
Dr Louise Parmenter is a specialist in Real World and Late Phase research with over 20 years global operational and strategic experience, and is based in the UK. Her experience covers a breadth of observational and experimental approaches to develop evidence of clinical, economic and humanistic outcomes. Research objectives have spanned safety and comparative effectiveness for healthcare decision makers across regulators, payers and providers. In her current role, Louise is focused on the strategic development of Quintiles Real World and Late Phase services to meet customer needs in a rapidly changing market. Louise has a PhD in Neurophysiology, and a BSc in Physiology with Biochemistry from Southampton University, UK. She holds a keen interest in research approaches and is in the second year of an MSc in Epidemiology run by the London School of Hygiene and Tropical Medicine through the University of London International Programmes.

**Ralph Moussalli MSc**
VP, Regional Managing Director, Asia Pac, Quintiles Outcome
Ralph Moussalli is VP, Regional Managing Director for Asia Pac and Emerging Markets at Quintiles Outcome, and is based in Singapore. He is an international healthcare executive with over 23 years of professional experience in the healthcare industry. In his current role, Ralph has been focused on defining and implementing the business development and operational growth strategies for Asia Pac and the Emerging Markets, developing Asia Pac operational teams to support the scientific team and implement local, regional and global real World and Late Phase Research studies. Ralph holds a Masters in Human Nutrition from University of Montreal. He completed post-graduate courses in Drug Development and Management from McGill University and University of Montreal.
Today’s Webinar Audience

Biostatistician, 1%
Clinical Operations, 40%
Medical Affairs, 11%
Medical, 8%
Health Economics, 3%
Marketing, 3%
Epidemiology, 1%

Other, Director, VP, GM, 31%

China, 32%
South Korea, 13%
Singapore, 11%
US, 6%
Europe, 7%
Malaysia, 1%
Japan, 1%
India, 22%
Hongkong, 1%
Phase IV terminology and definitions
## Terminology

*You will hear phase IV studies defined by…*

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Regulatory Timing</strong></td>
<td>• Late Phase, IIIb, IV</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>• Experimental (Interventional) Trials &amp; Observational (Non-interventional) Studies and Patient Registries</td>
</tr>
<tr>
<td><strong>Research Objective</strong></td>
<td>• Benefit Risk evaluation, Proof of cost-effectiveness, Comparative (relative) effectiveness</td>
</tr>
<tr>
<td><strong>Research Setting</strong></td>
<td>• Real-world vs Controlled Trial Settings including “practical” and “pragmatic” trial approaches</td>
</tr>
<tr>
<td><strong>Study Direction</strong></td>
<td>• Retrospective, prospective, cross-sectional</td>
</tr>
<tr>
<td><strong>Data Source</strong></td>
<td>• Site based study, direct to patient, database analysis, chart review</td>
</tr>
</tbody>
</table>
Simple Summary of Phase IV Research

Design can be non-interventional/observational or interventional/experimental

Definitions and regulations for phase IV research vary by country and by study design

In general terms, phase IV research investigates approved products used in line with their approved labels
**CHINA**  
Drug Registration Regulation (No. 28), Chapter 3, Art. 31

*Phase IV*: This is the post-marketing study of the new drug, conducted by the applicant. The objective is to investigate the efficacy and adverse reactions under the conditions of wide use, and to evaluate the benefits and risks relationship when used by ordinary and special groups of patients and to improve dosage of the drug.

**INDIA**  
Ethical Guidelines for Biomedical Research on Human Participants dated 2006

*Phase IV* studies are designed to evaluate the marketed drug in specifically designed studies, which have inclusion/exclusion criteria, objectives and end points. The drug is used for the labeled indication in these studies.
Indonesia
Indonesian Good Clinical Practice
Decree Regarding Clinical Trial Procedure

Art. 1.18. Post-Marketing Clinical Trial is a clinical trial which uses study medication(s) that has been approved for marketing in Indonesia, including phase IV trials (new indication, new posology, new strength, and/or new dosage form are excluded from the post-marketing clinical trial).

Art. 2(3) The implementation of Clinical Trial in Indonesia: b. Those requiring to notify to the regulatory (Notification) for the postmarketing trial.
Regulatory Landscape

**Japan**
Good Post-Marketing Surveillance Practice (GVP) (Art. 2)

‘Post-manufacturing/marketing surveillance’ (PMS) indicates drug use results surveys or post-manufacturing/marketing clinical studies implemented by medicine marketing businesses or businesses with special foreign manufacturing approval (hereinafter collectively referred to as marketing businesses) to collect, obtain, verify or validate information on the quality, efficacy and safety of medicines.

**South Korea**
Regulation on Re-examination of New Medicinal Products (Art. 2)

“Post marketing surveillance” means a series of measures to collect, examine, and verify the safety and efficacy data of medicinal product, which is conducted by the Marketing Authorization Holder of which product is designated to be within the scope of PMS according to the Pharmaceutical Affairs Law. This surveillance is allowed to be done only during the designated period.
Terminology and Definitions

Take home messages

• Terminology and definitions vary but the principles underlying the conduct of phase IV apply across countries
• Know the terminology that applies to your country
• Keep up to date as regulations change
Phase IV market trends
Types of Study Run in Phase IV is Changing

Globally, the industry has shifted away from phase IV interventional trials to observational studies

> Increased pressures from providers and payers for ‘real-world’ data generated outside of a controlled trial environment.

> Technology advancements and EHR adoption have made observational studies more cost-effective

> Scientific methods for planning, analyzing and reporting observational studies have improved

Source: CT.gov, PAREXEL Biopharmaceutical R&D Statistical Sourcebook 2011-2012
Most Phase IV Studies are Local/Regional in Asia Pac

### APAC Clinical Trial Volume by Phase & Location in 2012

<table>
<thead>
<tr>
<th>Location</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>China + Hong Kong</strong></td>
<td>73</td>
<td>242</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>South Korea</strong></td>
<td>125</td>
<td>221</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Japan</strong></td>
<td>69</td>
<td>173</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>South-East Asia</strong></td>
<td>75</td>
<td>109</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Australia + New Zealand</strong></td>
<td>68</td>
<td>187</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>India</strong></td>
<td>55</td>
<td>62</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Taiwan</strong></td>
<td>44</td>
<td>95</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number of Clinical Trials

Source: BioPharm Clinical (Jan 2013) – Only drug, biological and genetic clinical trials with defined clinical phases are selected, excludes clinical trials that have been suspended, terminated or withdrawn.
Maximizing Value and Quality in Phase IV Research

Understanding Healthcare Stakeholder Needs, Infrastructure & Competitive Landscape

Maximizing Value & Minimizing Cost of Research Delivery

Optimizing your phase IV study portfolio

Choosing the Right Research Approaches

Real-World and Late Phase research is about delivering the right data in the right way, for the right stakeholder at the right time for optimal market success
Success Strategies in Phase IV Research

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Phase IV Research Provides Valuable Evidence For Healthcare Decision Makers

Different Stakeholders, Different Needs, Different Purposes

- Industry
  - Meet commitments
  - Add to the safety profile
  - Evaluate efficacy to improve patient outcomes
  - Prove value
  - Secure reimbursement
  - Enhance understanding of unmet patient needs
  - Explore new indications
  - Generate publications

- Regulators
  - Detect safety signals
  - Ensure long-term effectiveness

- Payers
  - Determine value and coverage
  - Monitor usage within criteria
  - Cost-effectiveness

- Physicians
  - Obtain locally relevant evidence
  - Advance science
  - Improve care
  - Ensure continued reimbursement
  - Generate publications

- Patients
  - My own health—what choices do I have?
  - What are the risks/benefits?
  - Which treatment will improve my quality of life?
  - Which treatment is safer, more convenient and affordable?
Success Strategies in Phase IV Research

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Choosing the Right Research Approaches

Optimizing your phase IV study portfolio

Real-World and Late Phase research is about delivering the right data in the right way, for the right stakeholder at the right time for optimal market success.
Phase IV Study Portfolio: Model 1

Country-level study planning, execution & analysis

= Phase IV study
Phase IV Study Portfolio: Model 2

Core Protocol

Region & country-level study planning, execution & analysis

= Phase IV study
Model Comparison

Region & country-level study planning, execution & analysis offers significant advantages

Benefits of Model 2

- Single versus multiple protocol design, statistical plan, monitoring plan, database programming and build – time and cost savings
- Sharing of expertise & best practice
- Sharing of lessons learned (especially for studies run in “waves”)
- Increased sample size for greater study power and precision
- Increased credibility, publication potential & impact
Real-World and Late Phase research is about delivering the right data in the right way, for the right stakeholder at the right time for optimal market success.
Phase IV Design Options

Interventional

Non-interventional

Retrospective EHR/Database

The Right Approach for the Right Question
## Interventional Phase IV Trials

### Features
- Randomized
- More real world in approach than phase II and III development trials (include practical & pragmatic approaches):
  - Community based physicians
  - Measure safety and effectiveness in terms of what matters to the patient (i.e., outcomes)
  - Broad patient population
  - Few interventions compared to standard of care

### Advantages
- Balance internal and external validity
- A more representative estimate of benefit/harm in typical patients compared to phase II and phase III trials
- Patient enrolment not dependent on prescribed treatment use, unlike observational studies

### Disadvantages
- Compared to a phase II/III RCT:
  - Real-world setting introduces variability
  - Effect size may be diluted
  - Physicians may not be routinely involved in research, need support
- Quite costly compared to prospective observational and database studies
Non-interventional Phase IV

Prospective Observational Cohort Studies & Patient Registries

<table>
<thead>
<tr>
<th>Features</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; Non-randomized</td>
<td>&gt; Examine longer-term outcomes in populations typically excluded from trials</td>
<td>&gt; Prone to bias and confounding</td>
</tr>
<tr>
<td>&gt; Non-interventional</td>
<td>&gt; Examine risks for uncommon harms &amp; factors that modify risk</td>
<td>&gt; Not feasible unless the treatment under observation is used in the care setting of interest. If not, the treatment may need to be provided in a clinical trial.</td>
</tr>
<tr>
<td>&gt; Monitor cohort(s) over time</td>
<td>&gt; More representative data on a range of outcomes</td>
<td>&gt; Optimal design, conduct and analysis critical for producing strong evidence</td>
</tr>
<tr>
<td>&gt; May focus on disease, product or exposure</td>
<td>&gt; More cost-effective than randomized trial designs</td>
<td></td>
</tr>
<tr>
<td>&gt; May be described as “Looking over the shoulder of the physician”</td>
<td>&gt; Assessment of actual use (including off-label) to identify potential new indications</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; Useful for studying rare exposures &amp; more than one outcome</td>
<td></td>
</tr>
</tbody>
</table>
## Retrospective Designs Using Routine Data

*Retrospective analysis of existing clinical or administrative data*

<table>
<thead>
<tr>
<th>Features</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| > Database epidemiological studies use routine data repositories  
> Used to determine the feasibility of, and to develop hypotheses for, prospective research designs  
> Used to quantify disease burden, evaluate treatment patterns and compare outcomes | > Assess benefits and harms across an extremely large population  
> Cost / time efficient compared to prospective, longitudinal research | > Underlying information is not collected in a systematic way  
> Data abstraction from paper records is resource intensive  
> Complete medical and clinical histories may not be available  
> Difficult to interpret missing data  
> Administrative databases and EHRs are not uniformly available across all countries. Chart reviews are an alternative option.  
> Privacy issues may create the need to aggregate data |
Success Strategies in Phase IV Research

Real-World and Late Phase research is about delivering the right data in the right way, for the right stakeholder at the right time for optimal market success.
Phase IV Operational Value and Quality Drivers

- Research Approach
- Protocol Design & Analysis
- Data Quality
- Site Monitoring
- Site Start-up
Phase IV Cost Continuum by Research Approach

*Phase IV trials reflect the widest cost spectrum of all trial phases*

For each research approach, costs vary due to your protocol design and operational delivery model.
## Protocol Design & Analyses

<table>
<thead>
<tr>
<th>Feature</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple endpoints (clinical, economic, patient reported); multiple data capture time-points; multiple analyses</td>
<td></td>
</tr>
<tr>
<td>Streamlined endpoints; few data capture time-points; single analysis;</td>
<td></td>
</tr>
<tr>
<td>Single endpoint; limited data capture time-points; single analysis</td>
<td></td>
</tr>
</tbody>
</table>

*Work backwards from your research question and collect only the data that you need*
Site Start-up

<table>
<thead>
<tr>
<th>Feature</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 1:1 Face-to-face site initiation</td>
<td></td>
</tr>
<tr>
<td>• Site initiation via investigator meeting</td>
<td></td>
</tr>
<tr>
<td>• Remote initiation with recorded training modules for new staff</td>
<td></td>
</tr>
<tr>
<td>through study life</td>
<td></td>
</tr>
</tbody>
</table>

A blended approach can be effective to ensure that site needs are balanced against study costs.
Quality Risk-Based Monitoring

- On-site; multiple visits
- Quality risk-based monitoring
- Full remote monitoring

Quality risk-based monitoring approaches can be highly effective in phase IV and are supported by regulatory guidance.
Quality Risk-Based Monitoring

- Quality Risk is determined at the study level: Therapeutic Area, Study Endpoints, Study Type, Study Phase, Study Complexity, Study Size
- Additional considerations: What data will be used for, Regulatory requirements, Sponsor SOPs, Study Budget
Regulatory Guidance

Regulators recognize and support quality risk-based monitoring

The U.S. FDA draft guidance and EMA reflection paper provides confidence that risk-based monitoring is an accepted method.

- Supports Risk-based Monitoring for improved quality and patient safety
- Keeps the focus on critical data

ICH E6 provides for flexibility in how trials are monitored, advising sponsors to consider “the objective, purpose, design, complexity, blinding, size, and endpoints of a trial” in determining the extent and nature of monitoring for a given trial.
### Efficient Site Management & Focus on Data Quality

> Examples of monitoring triggers

<table>
<thead>
<tr>
<th>Quality and Site Concerns</th>
<th>Increased Regular Site Contact</th>
<th>Remote Monitoring</th>
<th>On Site Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCP Non compliance/Major Protocol Deviations</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Suspicion of Issues with ICF or Process</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Suspicion of fraudulent activities</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>First SAE at Site</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Absence of AEs reported</td>
<td>Yes</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Sustained Absence of AEs reported (No AEs/SAEs after X time period)</td>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormally Elevated Number of Number of AEs/SAEs Reported (&gt;x in t)</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Signs of Lack of Site Responsiveness</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Sustained Lack of Site Responsiveness</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Abnormally Elevated Query Rates/Lack of Query Resolution</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Identified Data Anomalies</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Absence of Minimal Regulatory Documents at Site File</td>
<td></td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Important Changes to Site Team (PI)</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>
Quality Risk-Based Monitoring

Applying the integrated approach of **Quality Risk-Based Monitoring** in conjunction with procedures, such as investigators' training, and written guidance, can assure appropriate conduct of a post-approval study in accordance with ICH GCP and/or GPP guidelines.

Quality Risk-Based Monitoring enables focused attention of risk, while promoting efficient utilization of time, resources and budget.
Data Quality Challenges

Missing Source Data
Sites do not always record all data from routine practice into medical records
Sites may not understand importance of maintaining source data

Missing Data in CRF
Sites do not all follow same routine practice and therefore may not have same data available
Sites may need to enter data at multiple locations, and by multiple users if patients treated across different specialties
Sites may not have adequate staffing needed for data entry
Site omission to collect data if small target population with low study activity between visits
Participation is a burden to sites with too much data to collect and/or CRF not intuitive

Poor Quality Data
Erroneous data
Data not plausible
Unanswered queries
### Data Quality

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Risk Mitigation Plan - Keys to Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Missing Source Data</td>
<td>▪ <strong>Evaluation of availability of key data elements</strong> - at project planning phase</td>
</tr>
<tr>
<td>▪ Missing Data in CRF</td>
<td>- Informed by Feasibility Survey/Study</td>
</tr>
<tr>
<td>▪ Poor Quality Data</td>
<td>- Informed by Site Qualification Questionnaire</td>
</tr>
<tr>
<td></td>
<td>- Informed by current practice guidelines if available</td>
</tr>
<tr>
<td></td>
<td>- Get input from Advisors/KOLs/specialists organisations</td>
</tr>
</tbody>
</table>

**Keep it Simple**

- Focus on “must have” data in CRF
- Clear link from objectives to data collection to analysis
- Balance maximizing data collection with minimizing site & pt burden
- Do not make CRF complicated and cumbersome
- Provide sites with support tools; Pocket Guides, CRF Worksheets
- If during a period of time sites have limited resources - consider providing data entry support or sending an independent data abstractor to enter data
- Use e-CRF to leverage real time data cleaning capabilities
## Data Quality

<table>
<thead>
<tr>
<th>Challenges</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Missing Source Data</td>
<td><strong>Develop CRF Completion Guidelines (CCG)</strong></td>
</tr>
<tr>
<td>Missing Data in CRF</td>
<td>- CCG should explain how each field in the CRF should be completed and which fields need to be completed during each visit</td>
</tr>
<tr>
<td>Poor Quality Data</td>
<td>- Provide sites training on the CCG during the Site Initiation Visit and maintain a copy of the training record in the master file</td>
</tr>
<tr>
<td></td>
<td>- Provide sites with a copy of the CCG and maintain a copy in the master file</td>
</tr>
</tbody>
</table>
## Challenges

- Missing Source Data
- Missing Data in CRF
- Poor Quality Data

## Risk Mitigation Plan - Keys to Success

- **Develop Data Management Plan (DMP)**
  Outline plan for concurrent data review and cleaning to include:
  - If e-CRF – plan for real-time edit checks. Improve accuracy of data on entry.
  - If p-CRF – develop schedule to follow-up to ensure timely site entry of data. This is to allow timely follow-up of missing, incomplete or erroneous data and improve data accuracy.
  - Plan to review data & queries on an ongoing basis to identify error trends.
  - Plan for data consistency checks: Compare across sites and over time often uncovers systemic issues that would otherwise go unnoticed.
  - Identification of critical variables for review.
  - Ongoing monitoring of key SAE/AE occurrences.
  - Ongoing reporting to identify error trends.
### Data Quality

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<tr>
<td>▪ Missing Data in CRF</td>
<td></td>
</tr>
<tr>
<td>▪ Poor Quality Data</td>
<td></td>
</tr>
<tr>
<td>▪ Training</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>• Provide comprehensive training on data collection during the Site Initiation Visit including;</td>
<td></td>
</tr>
<tr>
<td>- What data is to be recorded in CRF and at what time points</td>
<td></td>
</tr>
<tr>
<td>- How to complete CRF (CCG &amp; if eCRF-an EDC User Manuel)</td>
<td></td>
</tr>
<tr>
<td>- What is considered as source data, and identify source data location(s)</td>
<td></td>
</tr>
<tr>
<td>- Data quality and managing queries</td>
<td></td>
</tr>
<tr>
<td>- How to request support</td>
<td></td>
</tr>
<tr>
<td>• During Site Monitoring Visits;</td>
<td></td>
</tr>
<tr>
<td>- Identify root cause of any data quality issues &amp; address on-site with follow-up as required</td>
<td></td>
</tr>
<tr>
<td>- Provide additional training during SMV</td>
<td></td>
</tr>
<tr>
<td>• Ensure escalation process for data quality issues within project team</td>
<td></td>
</tr>
<tr>
<td>• Provide sites with copies of any training slides/handouts</td>
<td></td>
</tr>
<tr>
<td>• Provide ongoing support &amp; training to sites through out the study</td>
<td></td>
</tr>
<tr>
<td>• Ensure all site staff sign &amp; date a training record and maintain copy in the master file</td>
<td></td>
</tr>
</tbody>
</table>
## Data Quality

<table>
<thead>
<tr>
<th>Challenges</th>
<th>Risk Mitigation Plan - Keys to Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Missing Source Data</td>
<td>▪ <strong>Develop Monitoring Plan using a Risk Based Monitoring Approach</strong></td>
</tr>
<tr>
<td>▪ Missing Data in CRF</td>
<td>– Outline what, when and how data will be monitored through-out the study</td>
</tr>
<tr>
<td>▪ Poor Quality Data</td>
<td>– Define how monitoring will be reported and develop templates for monitoring</td>
</tr>
<tr>
<td></td>
<td>– Define escalation process if data quality issues</td>
</tr>
<tr>
<td></td>
<td>– Define what standard procedures/guidelines will be followed</td>
</tr>
</tbody>
</table>

- Whether collecting data as part of a regulatory requirement or not, adherence to the core tenants of the ICH GCP and/or GPP Guidelines is a best practice that should be followed.

- To ensure the appropriate level of compliance and data integrity, evaluate on a per-study basis individual practices, national and local regulations & guidelines.
Notable Guides to Observational Study Quality

A rapidly developing area with many helpful resources now available globally

- AHRQ User’s Guide on Patient Registries
- ISPE Guidelines for Good Pharmacoepidemiology Practices (GPP)
- ENCePP Checklist for Study Protocols
- ENCePP Guide on Methodological Standards in Pharmacoepidemiology
- AHRQ User’s Guide to Designing Observational CER Protocols
- Strengthening the reporting of observational studies in epidemiology (STROBE) statement
- GRACE Validated Checklist for Assessing the Quality of Observational CER

All of these guides can be accessed freely via the internet
Additional Resources for Phase IV Research

www.ispor.org

www.pharmacoepi.org

www.diahome.org

www.quintiles.com
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Maximizing Value and Quality in Phase IV Trials is about Choosing the Right Approach for the Right Question
Q&A

Please send email to grp@quintiles.com for further questions