Operational and Regulatory Considerations for Running Effective Minimally Interventional Studies

Aurélie Vivet
Bridget O’Mahony, PhD
Your Presenters

**Aurélie Vivet**  
Associate Director, Regulatory Affairs, Real-World & Late Phase Research, Quintiles

Aurélie is based in St. Prex, Switzerland. She helps ensure compliance with global regulatory requirements for both pharmaceutical and medical device products applicable to observational studies and provides support to Data Protection requirements. Aurélie has more than seven years of experience with regulatory affairs in Europe, including the conduct of Post-Authorization Safety Studies. She also maintains the Late Phase Requirements international regulatory database with country-specific regulatory requirements pertaining to post-approval research.

**Bridget O’Mahony, PhD**  
Director, Clinical Project Management, Real-World & Late Phase Research, Quintiles

Bridget has over 14 years experience in clinical research, in both the pharmaceutical and contract research organisation environments. She is an experienced hands-on professional with extensive global experience in all operational aspects of clinical trial planning, execution and delivery in multiple therapeutic areas. Bridget has a wide range of therapeutic experience having worked in gastroenterology, oncology and neurology ranging from local UK based studies through to large global studies.

She is currently serving as Director of Clinical Project Management providing senior oversight for Real-World and Late Phase Studies. Bridget is a registered pharmacist and has a PhD in Pharmaceutical Sciences from the University of Strathclyde.
Agenda

• Definitions of observational/non-interventional studies
• Operational study considerations, challenges and solutions
• Regulatory framework for clinical trials vs observational/non-interventional studies
• Regulatory and operational case examples
• Q&A
Today’s Webinar Audience

- Academia
- Biostatistician
- Clinical Operations
- Epidemiology
- Health Economics/Health Outcomes
- 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
Regulatory Considerations
Clinical Studies Regulatory Framework

Classification criteria

Clinical Trials – interventional studies

- Definition, criteria, phases homogeneous between countries
- International references: ICH GCP

Observational / non-interventional studies

- Terminology varies depending on the study design
- Terminology not homogenised worldwide

Key criteria for observational / non-interventional studies

- There is no investigational medicinal product involved
- If a medicinal product is involved, the product has received marketing authorisation in the country where the study is conducted and is used in accordance with the marketing authorisation
- EU: Heterogeneity between Member States on interpretation of additional monitoring procedures e.g. questionnaires, biological samples etc.

The definition and criteria of “observational study” are not homogeneous between countries.
Polling Question

- What is your experience in conducting minimally interventional studies in the past 5 years?
  > No experience
  > Less than 2 studies
  > 3 or more studies
“Minimal Interventional”

Classification criteria

Key criteria for “minimal interventional”
- Medicinal product involved
- Medicinal product received the marketing authorisation
- Medicinal product is used in accordance with the marketing authorisation

The intervention can concern:
- Medicinal product: e.g. given free of charge by the Study Sponsor
- Study design: e.g. mandatory additional monitoring procedure outside standard of care

What is considered “non-interventional” in one country may be considered “interventional” in another country.
Regulatory Framework in the USA

Considerations for “minimal interventional” studies

United States of America

Studies conducted on Human subjects are covered by 45 CFR Part 46 (Protection of Human Subjects)

“intervention” is defined based on several criteria, including:

(i) **Minimal risk** means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Only IRB approval required if:
- Product has received Marketing Authorisation
- Product commercially available
- Product used in accordance with the Marketing Authorisation

Applies to “minimal interventional”
Non-interventional study (Art. 2c)

- The medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation
- The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study
- No additional diagnostic or monitoring procedures shall be applied to the patients
- Epidemiological methods shall be used for the analysis of collected data
Interventional vs Non-Interventional in EU

Unclear borderline

- Borderline is not clearly defined
- What is considered “non-interventional” in some EU Member States can be considered as “interventional” in other EU Member States
- Harmonization applies between EU member States
  - The same protocol must be submitted under the same regulation across the EU.
Regulatory Governance

EU

Interventional/Clinical trial

Clinical Trial Directive (2001/20/EC)

EudraLex Vol.10

Non-interventional trial

Definition as per Clinical Trial Directive (2001/20/EC)

Pharmacovigilance Directives (2001/83/EC and 2010/84/EU)

Good Pharmacovigilance Practices (GVP) Modules
Minimal Interventional

EU Considerations

EU Regulatory Framework:
→ CLINICAL TRIAL DIRECTIVE 2001/20/EC
→ EudraLex Volume 10

REGULATORY DOCUMENTS
REQUIREMENT

Simplified Clinical Trial Application

<table>
<thead>
<tr>
<th>Core Requirements</th>
<th>Local Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>-Covering letter</td>
<td>-Delegation of Authority letter</td>
</tr>
<tr>
<td>-List of NCAs</td>
<td>-Label (Annex 13)</td>
</tr>
<tr>
<td>-EudraCT Form</td>
<td>-Insurance certificate</td>
</tr>
<tr>
<td>-Protocol and synopsis</td>
<td>-Informed Consent Form</td>
</tr>
<tr>
<td>-SmPC</td>
<td>-CRF</td>
</tr>
<tr>
<td>-Simplified IMPD</td>
<td>-Site / PIs list / CVs / signature pages, contracts etc...</td>
</tr>
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</table>

REGULATORY SUBMISSIONS

Option 1: Clinical Trial Application submitted for approval in each Member State participating in the study (full CA and EC review for approval).

OR

Option 2: VHP (Voluntary Harmonisation Procedure)
→ VHP assessment for core requirements approval
→ National steps for local requirements approval
Future “Clinical Trial Directive/Regulation”

Change in definition and requirements of “clinical trial”

**Directive 2001/20/EC “Clinical Trial Directive”¹, Art. 2**
- ‘clinical trial’
- ‘non-interventional trial’

**New “Clinical Trial Directive”, proposal 2012/0192 (COD)² Art. 2**
- ‘clinical study’
- ‘clinical trial’
- ‘low-intervention clinical trial’
  - Products are authorised
  - Used in accordance with marketing authorisation / standard treatment
  - Additional diagnostic or monitoring procedures with no minimal risk or burden compared to normal practice
- ‘non-interventional trial’

Operational Considerations
Scenarios: “Minimally Interventional”

Minimally Interventional

Randomized

Patients randomized to TOI versus SOC in a real-world setting peri- or post-approval in a pragmatic / practical trial

Patients randomized to approved TOI, pre-launch with or without marketed product to assess effectiveness of marketed product on symptom control of adverse events related to approved treatment

Non-Randomized

Patients consent to receive an approved TOI, pre-launch, in an on-label clinical trial

Patients are prescribed TOI and entered into an observational study that involves additional patient interventions outside of standard care

TOI = Treatment of Interest  SOC = Standard of Care
Polling Question

- Does your organization plan to conduct minimally interventional studies
  - Yes
  - No
  - Not sure
What does success in Phase IV minimally interventional look like?

The Right Approach for the Right Question™

The Right Customer
- Medical Affairs, Clinical Dev., Marketing, HEOR, Epidemiology

The Right Question
- Regulatory, patient, payer, provider
- Local needs

The Right Research Design
- Endpoint selection
- PRO
- Patient sub-population analysis
- Site sampling for representativeness

The Right Delivery Approach
- Risk-based/Central monitoring
- Prescribers Vs investigator mgt.
- Right sites, right patients (real-world)
- Local Affiliate management

Right Strategy, Right Price
Decision Tree

- What is the study objective?
  > Registration study
  > on-registration study
- Who are the study result recipients?
- What is the study design?
  > Observational or interventional?
  > On-label or off-label?
  > Risk to patient?
- Adaptive/hybrid monitoring schematics?
  > 100% SDV?
  > Statistical sampling of SDV?
- Are the investigators research naïve or well-experienced?
- Types of safety data/endpoints to collect? PROs?
- How often & what method should be used to collect data?
  > Paper
  > EDC
- Targeted data management & cleaning?
- What is the study budget allowance?
## Operational Challenges & Solutions

### The Right Countries and Sites

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Solution</th>
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</thead>
<tbody>
<tr>
<td>Choice of Countries and Sites</td>
<td>• Choice of country participation must first be driven by study purpose (e.g. Payer needs)</td>
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<tr>
<td></td>
<td>• Choice of site must reflect real-word setting (consider physician type, health care environments and practice setting)</td>
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<td></td>
<td>• Secondary to this are feasibility considerations (recruitment rates, competitor studies, protocol acceptance)</td>
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<td></td>
<td>• Seek input from the local Sponsor team</td>
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<tr>
<td>Generalisability</td>
<td>• Define characteristics of care per country (existing data sources and/or survey)</td>
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<td></td>
<td>• Capture information on physicians that decline to participate</td>
</tr>
<tr>
<td></td>
<td>• Capture information on patients that decline to participate</td>
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</table>
# Operational Challenges & Solutions

*The Right Investigators and Patients*

<table>
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<tr>
<th>Challenge</th>
<th>Solution</th>
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<tbody>
<tr>
<td>Involvement of research naïve physicians</td>
<td>• Design study compatible with clinical care (minimise data capture, user friendly forms)</td>
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<tr>
<td></td>
<td>• Comprehensive training</td>
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<td>• On site initiation visits with some additional triggered visits</td>
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<td></td>
<td>• Reimburse all study treatments</td>
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<td></td>
<td>• KOL advocacy (steering group)</td>
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<td></td>
<td>• Publication</td>
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<tr>
<td>Involvement of heterogeneous patient population</td>
<td>• Clear patient consent forms</td>
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<tr>
<td></td>
<td>• Minimise patient burden</td>
</tr>
<tr>
<td></td>
<td>• Reimburse all study treatments</td>
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</table>
## Operational Challenges & Solutions

### The Right Research Design

<table>
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<th>Challenge</th>
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</thead>
</table>
| Protocol design                                                           | • Ensure that study endpoints are appropriate for a real-life setting  
|                                                                           | • Clear scientific rationale & explanation for design  
|                                                                           | • Insurance certificates are required  
|                                                                           | • Consider switch to local reimbursement when available  |
| Open-label approach may bias patient and physician response and behaviour | • Potential to introduce blind outcomes assessor, however adds logistical issues  |
| Selection of the right PRO instruments                                    | • Capture the exact message and support the intended endpoint  
|                                                                           | • Confirm target audience  
|                                                                           | • Minimise overlap across questionnaires  
|                                                                           | • Minimise patient burden  
|                                                                           | • Consider format (paper or electronic)  
|                                                                           | • Consider timing of administration  |
# Operational Challenges & Solutions

## The Right Delivery Approach - Patient Recruitment and Retention

<table>
<thead>
<tr>
<th>Challenge</th>
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</thead>
<tbody>
<tr>
<td>Slow patient recruitment rate</td>
<td>• Pre-trial feasibility study</td>
</tr>
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<td></td>
<td>• Site &amp; patient overage</td>
</tr>
<tr>
<td>Back-up sites</td>
<td>• Identify back-up site at the start to allow seamless study activation</td>
</tr>
<tr>
<td></td>
<td>should unforeseen recruitment barriers arise</td>
</tr>
<tr>
<td>Fast patient recruitment rate</td>
<td>• Assess site capabilities up-front</td>
</tr>
<tr>
<td></td>
<td>• Create IP distribution strategy</td>
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<tr>
<td></td>
<td>• Assess need for site or country recruitment cap and how this will be</td>
</tr>
<tr>
<td></td>
<td>implemented</td>
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<tr>
<td></td>
<td>• Create templates for site communication</td>
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<tr>
<td>Patient drop-out</td>
<td>• Manage through site motivation</td>
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<tr>
<td></td>
<td>• Collect patient contact details for direct follow-up</td>
</tr>
<tr>
<td></td>
<td>• SMS text messaging for enhanced patient communication</td>
</tr>
</tbody>
</table>
## Operational Challenges & Solutions

### The Right Delivery Approach - Patient Recruitment and Retention

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| CRF Design              | • Restrict data collection to high impact items  
• Streamline data collection while ensuring no influence on standard of care  
• Real time data entry edit checks  
• Maximise data quality with minimising site burden |
| Optimal Site Support    | • Central site management  
• One-stop- shop for sites  
• Single point of contact from site qualification to close-out  
• Consistent readily available resource to answer site questions |
| Rapid-Site Start-Up     | • Remote site qualification  
• Electronic Site Information Form - study specific questions are weighted and scored automatically  
• Once qualified CRA works with site to collect documents for regulatory submission |
## Operational Challenges & Solutions

The Right Delivery Approach - Patient Recruitment and Retention

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| Study and Data Quality                         | • Rigorous site training  
• Adequate site management & monitoring support  
• ICH GCP applies  
• Recommend use of an observational study data management platform |
| Data Analysis                                   | • Unbiased analysis of data  
• Achieve maximum representativeness and control bias |
| Study supply logistics                          | • Study drug is provided using market supplies with a study-specific labelling in accordance with local regulatory requirements  
• Study drug is provided FOC  
• Comparator treatments are provided FOC  
• Consider supply at end of study if reimbursement not available |

Only relevant where sponsor provides product free of charge (FOC)
Case Studies
Case Study: Non-Randomized Minimally Interventional Trial

Delivering real-world evidence between market approval and availability

**Challenge**

**Need for real-world evidence**
- Clinical effectiveness, Health related Quality of Life, Health economics-related outcomes, Patient adherence

**Need for patient access**
Product has received market approval but is not yet available due to lack of reimbursement

**Solution**

**Sponsor to provide drug free of charge in an open-label single arm trial until commercially available**
- Study to fall under the EU CT Directive

“Minimally Interventional” operational approaches:
- Simulate real-world conditions
- Cost efficient

**Result**

- Fulfilling an unmet medical need with early adoption of market authorized product
- Faster access to real-world data to support re-evaluation of reimbursement decisions and price negotiation
- Early publication from data collected to further strengthen value proposition

[Diagram showing Market Authorization, Market Availability, Market Access Discussions, and Real-world “minimally Interventional trial”]
Conclusions

The Right Approach for the Right Question™

Ensuring Success with your Minimally Interventional Studies

The Right Customer

The Right Question

The Right Research Design

The Right Delivery Approach
Upcoming Events

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

Topics include:

- DIABETES VALUE DEMONSTRATION
- ONCOLOGY VALUE DEMONSTRATION
- RARE DISEASE REGISTRIES
- EUROPEAN PHARMACOVIGILANCE LEGISLATION
- REGISTRIES 101
- MARKET ACCESS
- MAXIMIZING VALUE AND QUALITY IN PHASE IV

To register or view previous webinars please go to www.quintiles.com/real-world-late-phase-webinars
Thank you

Questions?