Quality in Post-Authorisation Safety Studies

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Post-authorisation safety studies (PASS): quale ruolo per gli Studi Osservazionali?
The aim of QUALITY MANAGEMENT in clinical research is:

i. To avoid bias of results by using an appropriate study design and an adequate data analysis

ii. To assure authenticity, completeness and validity of the data

iii. To assure the compliance to applicable regulations & rules
PASS studies: the regulatory definition

A post-authorisation safety study (PASS) is defined in Directive 2001/83/EC (DIR) Art 1(15) as any study relating to an authorised medicinal product conducted with the aim of:

I. identifying, characterising or quantifying a safety hazard,

II. confirming the safety profile of the medicinal product,

III. or of measuring the effectiveness of risk management measures.
PASS studies: the regulatory definition

the provisions of Directive 2001/20/EC and of Volume 10 of The Rules Governing Medicinal Products in the EU shall be followed.

the guidance reported in GVP Module VIII (Rev 1) shall be followed.
Objective ➔ Tool

Experimental

Observational
Clinical Epidemiology
- Epidemiology and Pharmacoepidemiology
- Post Authorization Safety Study (PASS) Registries

Outcomes Research
- Burden of Disease
- Health Related - Quality of Life
- Health Economics

Health Service Research
- Analysis of Health Care Processes
- Health Technology Assessment
- Monitoring of Clinical Guidelines

One Tool ➔ Many Applications!
Clinical Trial VS Observational Studies

Table 1: Main features of RCT and observational studies

<table>
<thead>
<tr>
<th>What?</th>
<th>RCT</th>
<th>ObS</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope</td>
<td>Analytical</td>
<td>Descriptive or analytical</td>
<td>ObS could not be performed on a specific health technology</td>
</tr>
<tr>
<td>Population</td>
<td>Selected</td>
<td>Unselected</td>
<td>Deeply controlled in RCT; real life setting for ObS</td>
</tr>
<tr>
<td>Site monitoring</td>
<td>Always and extensive</td>
<td>Seldom and light</td>
<td>GCP as a model, not as a constraint</td>
</tr>
<tr>
<td>Variables</td>
<td>All necessary</td>
<td>Nice versus need to have</td>
<td>ObS very often has many secondary objectives, mainly explorative</td>
</tr>
</tbody>
</table>
| Design           | Perspective              | Retrospective cross-  

...different confounders, different stakeholders, different constrains...

**Quest for Quality**

Good clinical research heavily depends on the quality of the data collected, particularly for clinical studies. Unfortunately it is less obvious how to assure good quality standards for real world data and, at the same time, maintain a reasonable level of acceptability in term of time and costs for their collection and management.

“Quest for Quality” Simoni L. & Fiori G., November 2012 –ICT, Adaptive Clinical Data Management, p.66
# Observational Studies: Regulatory Framework

<table>
<thead>
<tr>
<th>Topic</th>
<th>Rule</th>
<th>Comment</th>
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<tbody>
<tr>
<td>Safety</td>
<td>Directive 2010/84/EU</td>
<td>New NIS definition based on the methodological approach. Provide the definition of PASS study and define the regulatory oversight.</td>
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<td></td>
<td>Regulation 1235/2010</td>
<td></td>
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<td></td>
<td>Commission Impl. Regulation No 520/2012</td>
<td></td>
</tr>
<tr>
<td>Authorization</td>
<td>Ministerial Circular Letter n. 6, 2 sept 2002</td>
<td>First definition of Observational Study. Provide advices for the ethical review of non-interventional study protocol.</td>
</tr>
<tr>
<td>Process</td>
<td>T.U. Privacy, D.Lgs. 196/2003</td>
<td>Defining the management of data protection in case of different study conditions</td>
</tr>
<tr>
<td>Data Protection</td>
<td>General Authorization s release from 2008</td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td>EMA- Guideline on good pharmacovigilance practices (GVP)</td>
<td>First regulatory document interely dedicated to Observational Study on medicinal product.</td>
</tr>
<tr>
<td>Authorization</td>
<td>AIFA Resolution 20 March 2008</td>
<td></td>
</tr>
<tr>
<td>Study Conduction</td>
<td>GVP module VIII for PASS studies</td>
<td></td>
</tr>
</tbody>
</table>
...a guidelines proliferation....

...but which level of consensus?
How to manage the complexity and the variability of Observational Studies designs?

Study Case 1
- Local
- Sponsored
- Spontaneous
- Retrospective
- 20 sites
- 200 patients
- Pharmaco-economy objectives

Study Case 2
- International
- 5 countries involved
- Sponsored
- Mandatory
- Retrospective analysis from an international network DB + Perspective with PRO collection
- 200 sites
- 4000 patients
...it’s reasonable waiting a comprehensive guidance....

... to standardized objects so different as observational studies, aren’t we still try to fit the square peg in a round hole?
The MediNeos Experience: the hot topics on quality

- Study Design
- Informed Consent & Data Protection Management
- Site Monitoring
Study Design:
the quality starts from the beginning

- Good Research Question
- Feasible Measurable Outcome
- Clear Objectives
- Appropriate Design
- Adequate Sample Size
- Strong Statistical Analysis Plan

Feasible: F
Interesting: I
Novel: N
Ethical: E
Relevant: R

- Methodology (e.g. Cohort; Case-control; etc.)
- Type of Data Collection (e.g. Primary)
- Study Type (e.g. on the medicinal product)
- Target Population (inclusion/exclusion criteria)
- Duration
How to assure the quality of Study Design?

• By following the existing guidelines to draft protocols and to report the study results

As prescribed by the GVP Module VIII (Rev 1), relevant scientific guidance includes:

• the ENCePP Guide on Methodological Standards in Pharmacoepidemiology,
• the ENCePP Checklist for Study Protocols,
• the Guideline on Conduct of Pharmacovigilance for Medicines Used by the Paediatric Population for studies conducted in children,
• and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology (ISPE GPP)

3 CORE REQUIREMENTS for MANDATORY PASS
1. ENCePP Code of Conduct + Declaration of Interest
2. ENCePP Checklist for Study Protocols
3. Registration in EU PAS Register
How to assure the quality of Study Design?

• By following the existing guidelines to draft protocols and to report the study results

• By defining your own SOPs in order to be compliant to all applicable rules

• By evaluating your study design through the analysis of yours Lessons Learned
Informed Consent & Data Protection: differences from Clinical Trials

Informed Consent Form (ICF) collection in Observational Research has a different meaning than in Clinical Trial: the PASSIVE EXPOSURE make the difference.

Deviations observed in ICF collection in Observational Studies could impair mainly PATIENT DATA PROTECTION.

Be aware that as reported in General Practitioner Guidelines on Data Protection (24.07.2008):

- The PATIENT CODE IS AN IDENTIFIER, although indirect, of the patient.
- Therefore all data entered in a CRF/eCRF are PERSONAL AND SENSITIVE.
Informed Consent & Data Protection: the study timeframe make the difference

The **TIMEFRAME** of the study design make the difference: **PERSPECTIVE** (primary data collection) and **RETROSPECTIVE** (secondary usage of data) data collection follow different rules.

For **RETROSPECTIVE** studies you may not have to collect ICF & Data Protection consents....
...if **proper conditions** are met and if **proper authorizations** obtained..
Case 1: The study B is going to observe lung cancer patients. In order to acquire more data concerning the safety of the chemotherapy scheme, the study is designed to collect data both retrospectively and prospectively. Data from dead patients may be collected.

Should the ICF & Data Protection consents be collected?

YES for the patients observed prospectively.

Concerning the RETROSPECTIVE part:

- For dead patients, ICF & Data Protection consents may not to be collected (ref. General Authorization Data Protection Commissioner Provv. 406 del 13.12.2012 GU 3-4.01.13).
- If data are collected retrospectively from patients then observed prospectively, the ICF & Data Protection consents should be acquired prior collect the data.
- If GENETIC DATA are collected the Authorization of Data Protection Commissioner shall be requested.
Informed Consent & Data Protection: how to manage deviations?

In observational studies ICF & Data Protection management is strictly connected to the study design and to which data are going to be collected.

In addition, as the current clinical practice is followed, you may observe a huge variety of deviations.

The majority of the potential ICF & Data Protection Consent deviations may be identified prior data collection is started, because they deeply depend on the characteristics of your study.

From IDEAL world

To the REAL one!
Informed Consent & Data Protection: how to manage deviations?

DON’T let Monitoring SURPRISE you.

BUT identified potential DEVIATIONS in advance & PLAN... ...how to manage them!

From IDEAL world

To the REAL one!
Site Monitoring: differences from Clinical Trials

Study Features:
- N° sites involved (from 10 to >100);
- N° of patients observed per site (from 10 to 100);
- Duration of the study (from months to over 5-10 years)
- Study design (case-control, cross-sectional, etc..)
- Data Collection (primary or second usage of data)
- Inclusion & Exclusion criteria;
- Objectives (PASS, DUS, QoL, etc..)

Sites Features:
- Clinical charts (electronic or on paper);
- Data Writers (many and different);
- Current Clinical Practice at site

SITE MONITORING should be TAILORED on the study design and complexity
Site Monitoring: Remote VS On-Site

Tasks that can be managed by REMOTE MONITORING:

- Assist/motivate sites: recruitment and regulatory
- Identify potential impediments to quality performance and propose solutions
- Maintain site communication log
- Retrain if needed
- Distribute newsletters/site correspondence
- Physicians and staff
- Remote monitor
- Ensure timely CRF completion and query resolution
- Triage issues to project team and facilitate resolution
- Assist with collection safety information
- Track compliance
- Share ‘best practices’
- Identify potential requiring an on-site visit

ON-SITE MONITORING add:

- Source Data Verification;
- ICF & Privacy Form verification

...and the possibility to take a look on the real life of the Investigational Site.

A standard approach in Observational Studies is to combine ON-SITE visits with REMOTE MONITORING.
On-site vs Remote monitoring: the right balance ....

....depend on your STUDY ID....

....and on the “story” that study data are telling you!
Quality Bias in Monitoring Observational Studies

• In the STUDY PROTOCOL it's not consider the possibility that some data may not have a source document

• The SOURCE DATA VERIFICATION PLAN does not take into account variables important for statistical analyses

• REMOTE MONITORING FREQUENCY (or the total amount of calls) is set up without consider the data cleaning approach

• ISSUES MANAGEMENT & ESCALATION PROCESS is not set up, or not well documented between Sponsor & CRO

• The contents of REMOTE MONITORING calls are not tailored on the study phase/results
Conclusions

- The quality management of Non-Interventional PASS should take into consideration the **huge heterogeneity and complexity of the different study designs**.

- Therefore the quality management should start from an accurate project design phase followed by a risk assessment of the study protocol, of the CRF and of the Statistical Analysis Plan that should drive the study team into the definition of:
  - Site Management Plan
  - Monitoring Plan
  - Data Management Plan

- The risk assessment of the study characteristics should allow a management of quality tasks proportionate to what the study has been set up for.
Thank You for Your Attention!

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