EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

The importance of clarity in relationships and transparency: Lessons learnt from ENCePP

PML Workshop
Session 6: Building Collaboration

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Introduction

Number of Post-Authorisation Safety Studies requested by Regulatory Authorities is increasing, mainly due to:

Shift from the traditional, reactive PhV model to proactive model (Risk Management Plans)

Decreased time-to-market of key medicines (unmet medical needs)

Increased need for large scale PhEpi studies to investigate serious, rare and/or long-term safety issues, and benefit:risk

Introduction

Some Post Authorisation Safety Studies requested are excessively delayed[1] [or are never carried out]

Insufficient research centres and harmonisation between PhEpi/PhV data sources in EU, leading to fragmentation of research

➢Many PASS performed outside the EU – representativity of data with respect to the EU clinical setting?

[1]EMA review of post-authorisation studies with implications for ENCePP. Blake KV, Prilla S, Biscaro M, Guimier M, Accadebled S, Arlett P, Blackburn S, Persson I, Fitt H. Pharmacoepi Drug Saf 2011; (in press)

In this talk

- ENCePP: capacity building for independent, transparent, quality research
- EMA sponsored research
- IMI-PROTECT: improving methodologies

ENCePP - European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

- Collaborative project with academia led by EMA, bringing together the available expertise in the fields of pharmacovigilance (PhV) & pharmacoepidemiology (PhEpi) in a Network of Excellence

- Further strengthen the post-authorisation monitoring of medicinal products in Europe

- Facilitating conduct of post-authorisation safety and benefit risk studies (+ health outcomes)

Who are the ENCePP partners?

- public research centres – mostly university or hospital based;
- owners of healthcare databases and/or electronic registries;
- existing European networks covering certain rare diseases, therapeutic fields and adverse drug events of interest.
- for-profit organisations (CROs)
  - provided that they perform studies commissioned by third parties and their main focus is pharmacoepidemiology and pharmacovigilance research

ENCePP Database of Resources

Database describing resources in ENCePP and facilitating searches.

- offers information on the available sources of expertise and research experience across Europe
- for both study sponsors and researchers seeking to identify collaborations for the conduct of specific PhEpi and PhV studies in Europe
- freely available to the general public

ENCePP Database of Resources

- Fully searchable, it allows the identification of:
  - Research Centres (currently 89 in 17 countries)
  - Research Networks (currently 13)
  - Data sources (currently 17)

(http://www.encepp.eu/encepp/resourcesDatabase.jsp)

- linked to ENCePP e-register of studies

ENCePP Guiding Principles - key developments

- **Independence**

Roles and responsibilities of stakeholders

Freedom to publish results (–ve and +ve)

Code of Conduct

- **Standards**

Stimulate consideration of important methodological principles in design of studies

Checklist & Guide of Methodological Standards

- **Transparency**

Registration of studies

Publication of protocols and results

Resources Database & E-Register of Studies

ENCePP Code of Conduct: why?

- There is a need to have clarity of roles and responsibilities in studies.
- There are areas in PhEpi and PhV research which would benefit from a higher level of openness, communication and accountability.
- Transparency on roles and responsibilities and on the details of the design and the conduct of studies is a cornerstone in building trust and confidence.

Code of Conduct: Roles of investigator & funder

1. Registration of study & application for ENCePP Study Seal.

2. Final responsibility for study protocol.

3. Ultimately responsible for the study.

4. Right to independently publish study results.

Investigator **Funder**

Research contract

1. Requirement to follow the Code laid down in research contract.

2. Can be involved in design of protocol.

3. Will be informed of study progress; may be observer in Study Steering Group.

4. Right to review publications before submission & require deletion of confidential information.

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Methodological Standards

- **Promote quality** not uniformity; innovation and new methods welcomed.
- Ensure **consideration of important epidemiological principles** for designing a study.

- ENCePP Checklist of Standards

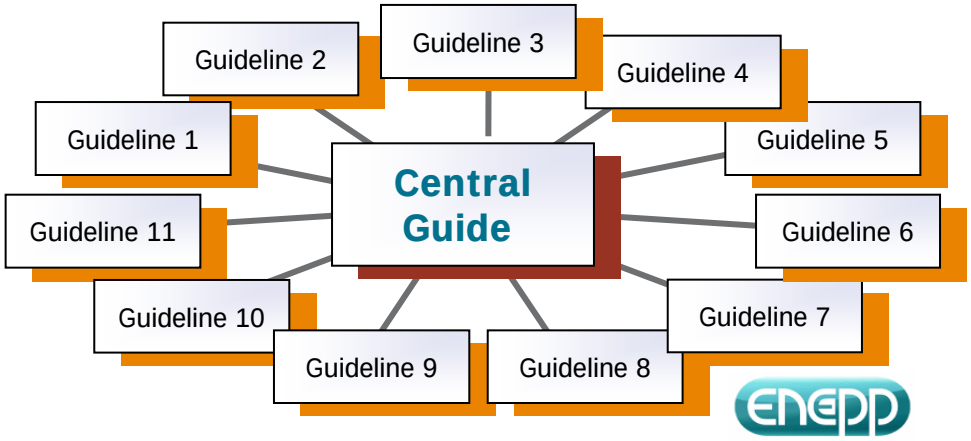
For an individual study ⇨ provides high level information on whether and where accepted standards and good practice are addressed in the study protocol.

- Guide on Methodological Research Standards

Single overview document

of internationally acknowledged

recommendations



Transparency requirements

Study timeline

Before

Registration of study

ENCePP study register

Declaration of interests

During

Documentation of relevant steps (incl. protocol updates)

Updates to entry in registry

Transparency

Afterwards

Publication of study protocol

Publication of results

Sharing of study data

Electronic (E-)Register of studies

➢ Publicly accessible resource for registration of PhEpi and PV studies that aims to:

- ✓ *Increase transparency*
- ✓ *Reduce publication bias (handles +ve and –ve results in same manner)*
- ✓ *Promote information exchange* ⇒
  - *Facilitate collaboration within the scientific community.*
  - *Facilitate optimal use of expertise and resources by reducing duplication*
- ✓ *Assures that information resulting from patient participation becomes part of the public record*

➢ Mandatory for 'ENCePP studies' – voluntary for any other

ENCePP Studies – CoRe requirements & Seal

1. Lead investigator belongs to an ENCePP ce
2. The CoRe requirements are met

- ENCePP Code of Conduct
  - ✓ Signed declaration & checklist
- Methodological standards for ENCePP protocols
  - ✓ signed checklist
- e-register of studies
  - ✓ registration prior to study start

ENCePP WG3 – Data sources

• EU inventory of data sources

- Expand the ENCePP Resources database with existing data sources.
- Stimulate and support initiatives to create new data sources in EU, including defining key elements in a guidance document.

• Methodological approaches for multi-source studies

- Develop operational approaches for organising and conducting multi-source studies through ENCePP (e.g. pooling data, use of common protocols, coding).

• ENCePP supports data privacy but seeks to facilitate use of health care data for the benefit of public health

- Compile existing practices in terms of national legislation to develop a common approach.
- Publication of a best practice guidance to facilitate multi-national studies in light of data privacy legislation.

EMA Funding of (ENCePP) Safety Studies

- Shift from traditional model of decision-making in PhV based on regulators placing obligations on the pharmaceutical industry and then regulators assessing the results of industry studies.
- New model has regulatory decision making based on the assessment of all available data including industry studies, academic studies, studies from public authorities and use of data from 'real-life' health outcomes.
- Complementary sources of data and methodological approaches are useful for the benefit–risk evaluation of medicines, incl. individual case safety reports, observational data, clinical trials and meta-analyses.

EMA Funding of (ENCePP) Safety Studies

- Small amount of funding (max 125,000 euros/study for commissioning safety studies
- Required deliverable: Application for ENCePP Study Sea

Carried out by ENCePP partners

ENCePP Studies

ENCePP: summary

- Facilitate conduct of post authorisation studies and collaboration between researchers.
- Ensure independence, transparency and standards, throughout the whole research process.
  - →Code of conduct to regulate interaction between study funder and researchers
  - →Checklist and guide of methodological standards
  - →E-register of studies to register studies and publish their results
- Capacity building for quality research.
- Contribute to public health.

PROTECT - To improve methods

To strengthen the monitoring of benefit-risk of medicines in Europe by developing innovative methods

to enhance early detection and assessment of adverse drug reactions from different data sources (clinical trials, spontaneous reporting and observational studies)

to enable the integration and presentation of data on benefits and risks

These methods will be tested in real-life situations.

PROTECT Consortium

Public

Regulators:
EMA (Co-ordinator)
DKMA (DK)
AEMPS (ES)
MHRA (UK)

Academic Institutions:
University of Munich
FICF (Barcelona)
INSERM (Paris)
Mario Negri Institute (Milan)
Poznan University of Medical Sciences
University of Groningen
University of Utrecht
Imperial College London
University of Newcastle Upon Tyne

SMEs:
Outcome Europe
PGRx

Others:
WHO UMC
GPRD
IAPO
CEIFE

Private

EFPIA companies:
GSK (Deputy Co-ordinator)
Sanofi- Aventis
Roche
Novartis
Pfizer
Amgen
Genzyme
Merck Serono
Bayer Schering
Astra Zeneca
Lundbeck
NovoNordisk
Takeda

WP 2: Framework for Phepi studies

Objectives:

To:

develop

test

disseminate

methodological standards for the:

design

conduct

analysis

of pharmacoepidemiological studies applicable to:

different safety issues

using different data sources

Work Package 3: Signal Detection

Objective:

To improve early and proactive signal detection from spontaneous reports, electronic health records, and clinical trials.

Work Package 4: Data collection from consumers

Objectives:

To assess the feasibility, efficiency and usefulness of modern methods of data collection including using web-based data collection and computerised, interactive voice responsive systems (IVRS) by telephone

Work Package 5: Benefit-Risk Integration and Representation

Objectives:

- To assess and test methodologies for the benefit-risk assessment of medicines
- To develop tools for the visualisation of benefits and risks of medicinal products

➔ Perspectives of patients, healthcare prescribers, regulatory agencies and drug manufacturers

➔ From pre-approval through lifecycle of products

EMA + European Commission DG Research – funding safety studies

- **List of priorities in drug safety research provided by EMA**
  - Scope: class issues or off-patent substances
  - Characterisation of safety profile(s)
  - Consider public health impact of research:
    - ✓ Usage of the drug class
    - ✓ Seriousness of the safety issue
    - ✓ Possibility of obtaining comparative safety data

EMA prioritisation of safety topics

- ✓ Identify current safety issues [discussed in the past 18 months] and ensure they are amenable to FP funding
- ✓ Discuss list of safety issues at PhVWP plenary
- ✓ Check proposed topics are not subject to current FP funding
- ✓ Adopt draft list of topics and prepare a 1-2 page fiche per topic
- ✓ Forward list + fiches to CHMP for comments and adopt final list
- ✓ Despatch Adopted list to DG Research

Topics for Safety Research proposed by EMA and included in FP-7

Call:	Consortium	Title	Co-ordinator	Drugs studied
2nd 2007	SOS	Cardiovascular and gastrointestinal safety of NSAIDs	Miriam CJM Sturkenboom, Erasmus Medical Centre	Traditional nonaspirin, nonsteroidal anti-inflammatory drugs *tNSAIDs) and cyclo-oxygenase II inhibitors (coxibs)
3rd 2008	ARITMO	Arrhythmogenic potential of drugs	Miriam CJM Sturkenboom, Erasmus Medical Centre	Antipsychotics (ATC N05A), anti-infectives (antibacterials (J01), antimicotics (J02) and antivirals (J05) and H1-antihistamines
4th 2009	ADDUCE	Attention Deficit Hyperactivity Disorder Drugs Use Chronic Effects	Ian Wong, School of Pharmacy, University of London	Methylphenidate
4th	EUROmediCAT	EUROmediCAT: Safety of Medication use in Pregnancy in Relation to Risk of Congenital Malformations	Helen Dolk, University of Ulster	New antiepileptics, insulin analogs, SSRI antidepressants, and antiasthmatics
4th	PHARMACHILD	Long-term PHARMacovigilance for Adverse effects in childhood arthritis	Nico Wulffraat, University Medical Centre Utrecht	Immune modulatory drugs
4th	STOP	Suicidality: Treatment Occurring in Paediatrics	Paramala J Santosh, University College London, Institute of Child Health	Risperidone in conduct disorder, fluoxetine in depression, and montelukast in bronchial asthma
Under negotiation				
5th 2010				Cancer risk and insulin analogues
				Safety of anti-diabetes drugs (cardio/cerebrovascular and pancreatitis/pancreatic cancer) such as iguanids, Sulfonamides, urea, Alpha_glucosidase inhibitors, Thiazolidinones, DPP-4, others
				Safety of asthma treatments (long acting ß-agonists)
				Long term risks (tumour progression and thromboembolic events) of Epoetins

Conclusions

- Important to build capacity for research through networking, transparency and standards

- Important to research new methods

- Important to ensure funding is available and well spent