EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

26 November 2013
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Workshop on methods for efficacy studies in the everyday medical practice

24 October 2013, 12:30-18:30 – Room 4A

25 October 2013, 08:30-15:30 – Room 4A

Day 1

Chair: Peter Arlett

Session 1		Speakers
12:30 – 13:00	Registration	
13:00 – 13:15	Welcome to participants	Guido Rasi
13:15 – 13:30	Tour de Table	All
13:30 – 14:00	Objectives of the workshop Presentation of working groups	Peter Arlett Xavier Kurz
Session 2	**Working Groups I**	
14:00 – 16:30	WG1: Pragmatic clinical trials – Room: 4A	
	WG2: Observational studies – Room: 4B	
	WG3: Registries – Room: 4C	
16:30 – 17:00	*Coffee break*	
Session 3	**Plenary session**	
17:00 – 18:30	Report from Working groups and discussion	WG Rapporteurs
18:30	*Close of session*	

Day 2

Chair: Michael Berntgen

Session 4	Plenary session	Speakers
08:30 – 09:00	Wrap-up of Day 1 and Introduction to Day 2	Xavier Kurz

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Session 5	Working Groups II	
09:00 – 12:00	WG4: Use of electronic health records in pragmatic trials- Room: 4A	
(including coffee break)	WG5: Methods to control for confounding - Room: 4C	
12:00 – 13:00	*Lunch break*	
Session 6	**Plenary session**	
13:00 – 14:30	Report from Working groups and discussion	WG Rapporteurs
14:30 – 15:30	Conclusions and next steps	Xavier Kurz
15:30	*Close of meeting*	

Annexes

- Background and objectives of workshop
- Questions to be addressed by each working group
- Composition of working groups

Backgroung and objectives of the workshop

Legal context

According to the new European pharmacovigilance legislation, post-authorisation efficacy studies (PAES) may be imposed by regulatory authorities to pharmaceutical companies:

- at the time of authorisation of a new product, where concerns related to some aspects of the efficacy of the medicinal product can be resolved only after marketing;
- at any time after product approval where there are indications that previous efficacy evaluations might have to be revised significantly.

The recitals of the new pharmacovigilance legislation indicate that PAES may be aimed at collecting data to enable the assessment of efficacy of medicinal products *in everyday medical practice.*

The new legislation also states that the European Commission may adopt supplementing measures in order to determine the situations in which post-authorisation efficacy studies may be required, and that the European Medicines Agency shall, in cooperation with competent authorities and other interested parties, draw up a scientific guidance on PAES.

Problem statement

The reference to everyday medical practice in the legislation builds the bridge to the conduct of efficacy studies outside the scope of a controlled clinical trial setting. While it is recognised that conventional interventional explanatory trials may not answer all questions related to efficacy in everyday medical practice, the experience of pragmatic trials and observational studies for measuring it is limited. Differing design options and analytical techniques need to be addressed with consideration of methodological aspects such as:

- most appropriate study design for the research question and hypotheses to be tested
- frequency of exposure as occurring without intervention in the study population
- endpoint(s) in terms of frequency, time to onset and measurement accuracy
- biases and confounding factors, measured and unmeasured, and their control
- inferences about effectiveness relating to particular interventions
- feasibility, efficiency and timelines
- definition and quality of data sources on exposure, outcomes and covariates in the context of the research question
- generalizability of findings derived from interventional and non-interventional studies.

The Agency considers that a review of current knowledge regarding use of interventional and non-interventional designs for measuring efficacy in the everyday medical practice is needed for the development of the scientific guidance.

Objectives of the workshop

The workshop brings together experts with the following objectives:

- To understand the strengths and weaknesses of differing design options to study efficacy in the conditions of the everyday medical practice, including pragmatic trials, observational studies with primary or secondary data collection.
- To express recommendations (appropriate for various types of research questions) on best use of available methods to account for bias and confounding in the context of efficacy studies in the everyday medical practice, including the level of evidence supporting each recommendation.
- To express recommendations (appropriate for various purposes) on the choice and measurement of exposure and outcomes in different types of trials/studies.
- To ascertain a future research agenda to improve methodology in this area.

Five main topics have been identified, acknowledging there is a degree of overlap. For each topic, a statement reflecting commonly held views and supported by one or two references (extracted from the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, http://www.encepp.eu) is put forward as a basis for questions to be answered by the working group. Each working group may discuss questions in a different order or discuss additional topics it considers important to address.

The workshop will not address the specific situations where PAES may be required by regulatory authorities.

Questions to be addressed by working group 1 - Pragmatic trials

Statement

While it is often considered that there is a continuum of design options between the explanatory and the pragmatic approaches of clinical trials,[1] which impact on the choice of subjects, intervention, measurement of outcomes and analysis of results, methodologies for conventional explanatory (Phase III) clinical trials are well codified. This is not the case for pragmatic trials and this affects their internal validity, use and acceptability.

Questions

1. In comparison to explanatory trials, for which research questions (related to efficacy/effectiveness) would pragmatic trials be more or less appropriate, e.g. for which types of interventions or clinical outcomes?
2. What are the key elements of pragmatic trials that should be collected and reported to be confident about their validity?
3. What advances need to be made in the design of pragmatic trials in order to be confident that the results are reliable?
4. What could be the role of cluster randomised trials for the measurement of effectiveness?

[1] Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, Tunis S, Bergel E, Harvey I, Magid DJ, Chalkidou K. A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. CMAJ. 2009; 180 (10):E47-57. http://www.cmaj.ca/content/180/10/E47.full.pdf

Questions to be addressed by working group 2 – Observational studies

Statement

There may be situations in the field of health care interventions where observational studies are needed because randomised trials are inappropriate, impossible or inadequate.[2] However, because of their observational nature and the potential for bias, it has been suggested that observational studies are only suitable for the study of adverse (non-predictable) effects of drugs and should not be used for measuring their intended effects.[3]

Questions

Note that methods to address confounding will be addressed in WG5.

1. What advances need to be made in the design of observational studies in order to be confident that the results are reliable, if the outcome is beneficial impact of treatments? Consider the following:
    - Primary or secondary data collection
    - Methods for patients' selection or restriction
    - Definition and data collection on exposure and outcomes (e.g. possibility of blinding of exposure/outcome assessment, validation of diagnosis)
    - Data analysis
    - Other aspects.
2. Taking your answer to the above question into consideration, can observational studies be suitable to study intended effects of drugs? Are they suitable to study beneficial unintended effects?
3. Are there minimal criteria for the study design that need to be met in order to address efficacy/effectiveness endpoints in observational studies?

[2] Black N. Why we need observational studies to evaluate effectiveness of health care. BMJ 1996;312(7040):1215-18. http://www.bmj.com/content/312/7040/1215?view=long&pmid=8634569
[3] Vandenbroucke P. When are observational studies as credible as randomised trials. Lancet 2004;363(9422):1728-31. http://www.ncbi.nlm.nih.gov/pubmed/15158638

Questions to be addressed by working group 3 – Registries

Statement

By collecting detailed information on patients diagnosed with a certain disease or treated with a certain drug in a defined setting, established registries provide an opportunity to assess patient outcomes, including effectiveness.[4] However, their recruitment is not always exhaustive, they may include patients already under treatment and a comparator group may not be available.

Questions

1. For which types of research questions are established registries particularly appropriate when studying efficacy? For which ones are they not appropriate?
2. What could be design options for studies on efficacy based on established registries?
3. What is the feasibility of setting up registries in different health care systems? What is the feasibility of merging several registries, and of merging registries with other datasets (e.g. with hospital/laboratory data)?
4. What measures would have the greatest impact in improving the quality of data, the validity of studies and the usefulness of results from registries?
5. Do established registries represent appropriate sources of patients for the conduct of clinical trials? Is randomisation within a registry a possible design option? In which situations is it possible and not possible?

[4] AHRQ Registries for Evaluating Patient Outcomes: A User's Guide. Second Edition. Chapter 13: Analysis and Interpretation of Registry Data To Evaluate Outcomes, 285-304. http://www.effectivehealthcare.ahrq.gov/ehc/products/74/531/Registries%202nd%20ed%20final%20to%20Eisenberg%209-15-10.pdf

Questions to be addressed by working group 4 – Use of electronic health records in pragmatic trials

Statement

Use of electronic health records is now current practice in the study of drug effects. They may also provide opportunities to conduct pragmatic trials.[5] However, challenges of randomisation within the database, methodological issues (eg. lack of data on diagnostic criteria and confounding variables) and consent issues need to be overcome.

Questions

1. Assuming that randomisation of treatment with follow-up using healthcare databases is possible, what are the main strengths and weaknesses of electronic health record databases for the conduct of clinical trials?
2. Randomisation within a database: what are methods currently available and their implication in terms of validity and feasibility? Are there any ways in which the trials could be carried out single or double blind?
3. How can use of electronic data be combined with information obtained directly from investigators and study subjects to collect missing data (e.g. diagnostic criteria, confounding variables)?
4. Are there any exposures or outcomes for which use of electronic health records is more/less appropriate to conduct pragmatic trials?
5. What advances need to be made in the electronic health records in order to be confident that the results of clinical trials are reliable, if the outcome is beneficial impact of treatments?

[5] Van Staa TP, Goldacre B, Gulliford M, Cassell J, Pirmohamed M, Taweel A, Delaney B, Smeeth L. Pragmatic randomized trials using routine electronic health records: putting them to the test. BMJ 2012;344:e55. http://www.bmj.com/content/344/bmj.e55.pdf%2Bhtml

Questions to be addressed by working group 5 – Methods to control for confounding

Statement

Several methods exist to control for confounding in the analysis of observational studies (e.g. stratification, matching, restriction, high dimensional propensity score, instrumental variables).[6,7] However, it is not possible to fully control for confounding by indication, and this undermines use of observational studies to investigate efficacy endpoints, especially for drugs recently introduced on the market and when study size is limited.

Questions

1. For each of the above methods to control for confounding, what are their strengths and weaknesses in studies with efficacy endpoints?
2. Are there any exposures (e.g. short term/long term) or outcomes (e.g. short or long latency, severe/not severe, frequent/not frequent, QoL) for which these methods would be more/less appropriate?
3. Do available methods allow to study intended effects with an observational design just after market authorisation or when study size is limited?
4. Is there any value of measuring residual confounding to try to estimate the minimum true effect size?
5. How should propensity score be used (e.g. stratification, matching, restriction, trimming) and are methods more appropriate to specific situations?

[6] Klungel OH, Martens EP, Psaty BM, Grobbee DE, Sullivan SD, Stricker BH, Leufkens HG, de Boer A. Methods to assess intended effects of drug treatment in observational studies are reviewed. J Clin Epidemiol. 2004;57(12):1223-31. http://www.ncbi.nlm.nih.gov/pubmed/15617947

[7] Schneeweiss S, Rassen JA, Glynn RJ, Avorn J, Mogun H, Brookhart MA. High-dimensional Propensity Score Adjustment in Studies of Treatment Effects Using Healthcare Claims Data. Epidemiol 2009;20(4):512-22. http://www.ncbi.nlm.nih.gov/pubmed/19487948

Composition of working groups

WG1. Pragmatic trials

Moderator: Spiros Vamvakas, EMA

Rapporteur: Sara Garner, NICE, London

Hans Hillege, University Medical Centre Groningen
Robert James Hemmings, MHRA
Sebastian Schneeweiss, Harvard Medical School, Boston
Tjeerd van Staa, LSHTM, London
Tom McDonald, University of Dundee
Mirjana Huic, Agency for Quality and Accreditation in Health Care and Social Welfare, Zagreb
Stephen Evans, LSHTM, London

Anne-Louise Svendsen, EBE
Boris Thurisch, EUCOPE
Chris Chinn, EFPIA
Guillermo Herrera, VE
Montse Soriano-Gabarró, AESGP
Nicolle Gato, EuropaBio
Dorothee Bartels, EFPIA

Michael Berntgen, EMA
Francesca Cerreta, EMA
Laura Fregonese, EMA

WG2. Observational studies

Moderator: Xavier Kurz, EMA

Rapporteur: Olaf Klungel, Utrecht University

Bert Leufkens, Utrecht University
Ian Douglas, LSHTM, London
Lucien Abenhaim, LA-SER, London
Nicholas Moore, University of Bordeaux
Stephen Evans, LSHTM, London

Patrice Verpillat, EFPIA
Michel Mikhail, EGA
Pam Bacon, EUCOPE
Laurence Baril, VE
Chrissie Fletcher, EuropaBio
Nadia Foskett, EBE

Corinne deVries, EMA
Efthymios Manolis, EMA
Jim Slattery, EMA
Marco Cavaleri, EMA
Irmgard Eichler, EMA

WG3. Registries

Moderator: Jordi Llinares Garcia, EMA

Rapporteur: Nancy Dreyer, Quintiles, Cambridge, USA

Angela Zink, Deutsches Rheuma-Forschungszentrum, Berlin

Elaine Gunn, UK Cystic Fibrosis Registry, London

Kathleen Bennett, Trinity College, Dublin

William Dixon, University of Manchester

Tomas Salmonson, Medical Products Agency, Sweden

Christine Luxemburger, VE

Michael Habs, EUCOPE

Niklas Hammar, EFPIA

Michael Busch Sorensen, EBE

Peter Arlett, EMA

Richard Vesely, EMA

Segundo Mariz, EMA

Gunter Egger, EMA

Stella Blackburn, EMA

WG4. Use of electronic health records for pragmatic trials

Moderator: Jim Slattery, EMA

Rapporteur: Tom McDonald, University of Dundee

Angela Zink, Deutsches Rheuma-Forschungszentrum,Berlin

Hans Hillege, University Medical Centre Groningen

Kathleen Bennet, Trinity College, Dublin

Mirjana Huic, Agency for Quality and Accreditation in Health Care and Social Welfare, Zagreb

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Niklas Hammar, EFPIA

Dorothee Bartels, EFPIA

Francesca Cerreta, EMA

Marisa Papaluca, EMA

Stylianos Tsigkos, EMA

Gunter Egger, EMA

WG5. Methods to control for confounding

Moderator: Corinne de Vries, EMA

Rapporteur: Sebastian Schneeweiss, Harvard Medical School, Boston

Lucien Abenhaim, LA-SER, London
Olaf Klungel, Utrecht University
William Dixon, University of Manchester
Stephen Evans, LSHTM, London
Rob Hemmings, MHRA
Irena Guzina, EUnetHTA observer

Chrissie Fletcher, EuropaBio
Christine Luxemburger, VE
Laurence Baril, VE
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