Looking beyond clinical trials data?

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Disclosures and slides availability

• Research grants
  – Theravance, Astellas, Targanta, Cerexa/Forest, AstraZeneca, Bayer, GSK, Trius, Rib-X, Eumedica, Debiopharm
  – Belgian Science Foundation (F.R.S.-FNRS), Ministry of Health (SPF), Walloon and Brussels Regions, European Union (FP7 programme)

• Speaking fees
  – Bayer, GSK, Sanofi, Johnson & Johnson, OM-Pharma

• Decision-making and consultation bodies
  – European Committee for Antimicrobial Susceptibility Testing [EUCAST] (General Assembly [2006 to now] and steering committee ([2008-2010]))
  – European Medicines Agency (external ad-hoc expert)
  – US National Institutes of Health (grant reviewing)
  – Drive-AB [Driving reinvestment in R&D and responsible use for antibiotics] (governance)

Slides: http://www.facm.ucl.ac.be → Lectures

All references are clickable (to PubMed or to the original texts)
How do I get a (useful) drug for my patients?

Because there is a patient to help!

And the patient has questions...

- Do I need **THIS** drug or **THAT** one?
- Which information should I get?
- And then, what can **this or that drug** bring to **this patient**?
Questions to you when selecting the best antibiotic for your patient?

Which source of information do you select preferentially?

1. The label (package insert), aka the registration data?

2. The published randomized controlled studies (primary data)?

3. The published independent reviews and meta-analyses?

4. The international (America, European…) guidelines?

5. The local guidelines (national, regional)?

6. Others sources?

Please, choose one! Key in the corresponding number …
An unusual source of information … used in Belgium (Flanders) …

Welcome

Welcome to the website of the Intego-project.

Intego has built a database that contains about 3 million diagnoses, 27 million laboratory results and 12 million prescriptions for medication. Our data are collected in general practices in Flanders.

As part of the Department of General Practice of the KU Leuven we facilitate research by providing researchers with registration data from general practices in Flanders.

Flanders is a region of about 6 millions inhabitants … and the database is now 20 years old

Last visited: 10 Oct 2016

The Intego database: background, methods and basic results of a Flemish general practice-based continuous morbidity registration project

Carla Truyers1, Geert Godeirs1, Harrie Dewitte1, Marjan vanden Akker2 and Frank Buntinx2

Let us apply that to treatment of acute bacterial skin and skin structure infection (ABSSSI)…

1. The emergence of MRSA…
   → what is the situation in your country? need of local databases!

2. Vancomycin is an old and "difficult" drug
   – IV only, at least twice daily, and 10 days or more…
   – monitoring is essential to avoid toxicity…
   – beware of MICs > 2 mg/L risk of local failures!

3. What about switching to linezolid!
   – drug interactions (MAO inhibition)
   – myelosuppression, lactic acidosis…

at least, two of your questions will not be answered by the "classical" clinical trials of the new antibiotic …
Why does Industry do "classic" clinical trials?

• A short answer: because it is the law!

• A more elaborate answer:
  – phase I → safety and pharmacokinetics
    → pharmacodynamics (if possible)
  – phase II → proof of concept
    → finding the useful dose
  – phase III → getting indication(s) and approval

• no major toxicity!
• could work …
• works in ideal conditions
• works in target population selected for registration
The regulatory requirements for registration are much demanding...

• For most indications, both FDA and EMA usually require two independent studies demonstrating efficacy and safety

✓ It is preferred that two major (pivotal) studies of efficacy are performed for each clinical indication sought… (EMA)

✓ … Two adequate and well-controlled trials generally are recommended to provide evidence of effectiveness … (FDA)

• General Considerations for Clinical Trials  (EMEA - March 1998 -- CPMP/ICH/291/95)

• Evaluation of medicinal products indicated for treatment of bacterial infections - Adopted guideline (EMA - 2011 -- CPMP/EWP/558/95 rev 2)

• Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment (FDA - CDER -- October 2013)
  http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071185
The regulatory requirements for registration are much demanding...

- Appropriate **comparators** should be utilized and adequate numbers of subjects included to achieve the study objectives
  - Comparisons may be made with placebo, no treatment, active controls or with different doses of the drug under investigation
  - The choice of the comparator depends, among other things, on the **objective of the trial**

- **The regimen selected [for comparison] should be considered one of the best available treatments based on** one or more of previous studies, medical opinion, indication specific treatment guidelines… and **anticipated prevalence of resistance to the comparative agent at the investigative sites** … (EMA)

- **For ABSSSI, there were no placebo-controlled trials reported in the historical literature**… (FDA)

- General Considerations for Clinical Trials  (EMEA - March 1998 -- CPMP/ICH/291/95)

- Evaluation of medicinal products indicated for treatment of bacterial infections - Adopted guideline (EMA - 2011 -- CPMP/EWP/558/95 rev 2)

- Guidance for Industry: Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment (FDA - CDER -- October 2013)
As a result...

Most classic clinical trials of novel antibiotics

– are non-inferiority trials

– explore a limited number of indications

– cover diseases that can be addressed/studied in a reasonable time span

– may not include enough patients with severe co-morbidities

– are limited in the detection of rare but severe adverse effects

15 Oct 2016

LATAM AI Forum, Cancún, Mexico
New approaches?

- Pharmacoepidemiological databases
- Registry studies
- Pharmacoeconomy-driven choices
- Structured Case reports
- Structured off- (beyond ?) label use
New approaches?

• Pharmacoepidemiological databases

Research on drug safety and effectiveness using pharmacoepidemiological databases

M. Andersen

From the Centre for Pharmacoepidemiology, Karolinska Institutet, Clinical Epidemiology Unit, Karolinska University Hospital Solna, Stockholm, Sweden

Journal of Internal Medicine, 2014, 275; 548–550 - PMID: 24635741

doi: 10.1111/j.1365-2958.2014.12235.x Journal of INTERNAL MEDICINE
New approaches?

• Pharmacoepidemiological databases
  – use of health care databases looking for
    • drug exposure
    • health outcomes
  – combining several databases to reach sufficient numbers
  – integrating simple RCTs into clinical care
  – using novel designs (e.g. self-controlled design)
  – developing approaches to detect and correct for confounders
How to choose a database?  
Functional and Substantive databases…

<table>
<thead>
<tr>
<th>Orientation</th>
<th>Description</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional</td>
<td>Facility</td>
<td>Hospital billing, nursing home stays, laboratory procedures</td>
</tr>
<tr>
<td></td>
<td>Provider</td>
<td>Physician practice data, pharmacy dispensing data</td>
</tr>
<tr>
<td></td>
<td>Sector</td>
<td>Private (for profit or nonprofit), government (federal, state, or local), mixed</td>
</tr>
<tr>
<td></td>
<td>Disease or organ</td>
<td>Cancer registry, kidney disease registry</td>
</tr>
<tr>
<td>Substantive</td>
<td>Financial</td>
<td>Reimbursement data, billing or charge data, copayment data</td>
</tr>
<tr>
<td></td>
<td>Utilization</td>
<td>Services provided, hospital admissions</td>
</tr>
<tr>
<td></td>
<td>Demographic</td>
<td>Medicare eligibility files, health plan enrollment data</td>
</tr>
<tr>
<td></td>
<td>Outcomes</td>
<td>Mortality data, adverse event and error reporting systems</td>
</tr>
</tbody>
</table>

Combining multiple healthcare databases for postmarketing drug and vaccine safety surveillance: why and how?

G. Trifiro1,2, P. M. Coloma1, P. R. Rijnbeek1, S. Romio1,3, B. Mosseveld1, D. Weibel1, J. Bonhoeffer4,5, M. Schuemie1,5, J. van der Lei1 & M. Sturkenboom1

From the 1Department of Medical Informatics, Erasmus Medical Center, Rotterdam, the Netherlands; 2Department of Clinical and Experimental Medicine, University of Messina, Messina; 3Department of Clinical and Preventive Medicine, Università Milano-Bicocca, Milan, Italy; 4Brighton Collaboration Foundation; 5University Children’s Hospital Basel, University of Basel, Basel, Switzerland; 6Janssen Research and Development LLC, Titusville, NJ, USA; and 7Observational Medical Outcomes Partnership, Foundation for the National Institutes of Health, Bethesda, MD, USA

Journal of Internal Medicine, 2014;275:551-561 - PMID: 24635221
Combining databases

Combining multiple healthcare databases for drug and vaccine safety surveillance: why and how

G. Trifirò1,2, P. M. Coloma1, P. R. Rijnbeek1, S. Romio1,3, B. Mosseveld1, D. Weibel1, M. Schuemie1,8, J. van der Lei1 & M. Strurkenboom1

From the 1Department of Medical Informatics, Erasmus Medical Center, Rotterdam, the Netherlands; 2Department of Experimental Medicine, University of Messina, Messina; 3Department of Clinical and Preventive Medicine, Italy; 4Brighton Collaboration Foundation; 5University Children’s Hospital Basel, University of Basel, Basel and Development LLC, Titusville, NJ, USA; and Observational Medical Outcomes Partnership, Foundation Health, Bethesda, MD, USA

OMOP: Observational Medical Outcomes Partnership (http://omop.fnih.org/)
US-FDA and Academia

EU-ADR: (Exploring and Understanding Adverse Drug Reactions by Integrative Mining of Clinical Records and Biomedical Knowledge, http://www.euadr-project.org/) financed by the EU (FP7 program)

CDM: common data model.

Journal of Internal Medicine, 2014;275:551-561 - PMID: 24635221

Fig. 1 Distributed analysis architecture in Mini-Sentinel and Observational Medical Outcomes Partnership as compared with Exploring and Understanding Adverse Drug Reactions (EU-ADR).
Combining multiple healthcare databases for postmarketing drug and vaccine safety surveillance: why and how?

Fig. 2 Distributed data processing in Exploring and Understanding Adverse Drug Reactions (EU-ADR) and other EU-funded projects.

LOCAL databases
- Prescriptions
  - Date
  - PatientID
  - Duration
  - ATC

SHARED
- Events
  - Date
  - PatientID
  - Event type

Population
- PatientID
- Birthdate
- Gender
- System entry date
- System exit date

Java application that can be configured using a scripting language.

Background incidence rates of events
Incidence rates of events during drug use
Patterns of drug use

Journal of Internal Medicine, 2014, 275; 551–561

doi: 10.1111/joim.12159

Review

Combining databases: EU-ADR information distribution
Integrating RCT and clinical care

Use of electronic healthcare records in large-scale simple randomized trials at the point of care for the documentation of value-based medicine

T.-P. van Staa, O. Klungel & L. Smeeth

From the ¹Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands; and ²London School of Hygiene and Tropical Medicine, London, UK

Journal of Internal Medicine, 2014; 275: 562–569 - PMID: 24635449
Integrating RCT and clinical care

Use of electronic healthcare records in large-scale simple randomized trials at the point of care for the documentation of value-based medicine

T.-P. van Staa\textsuperscript{1,2}, O. Klungel\textsuperscript{1} & L. Smeeth\textsuperscript{2}

Table 1 Example of trials using data from electronic healthcare records

eLUNG: the effectiveness of antibiotics compared to no antibiotics for exacerbations of chronic obstructive pulmonary disease: a feasibility study (ISRCTN72035428) [5]

<table>
<thead>
<tr>
<th>Research questions</th>
<th>Feasibility of trial; pilot for comparative effectiveness of antibiotics in patients with an exacerbation of chronic obstructive pulmonary disease and nonpurulent sputum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Randomization between antibiotic (whichever the general practitioner uses as first line) or usual care in 150 patients; nonblinded</td>
</tr>
<tr>
<td>Outcome measures</td>
<td>Recruitment rates and technical challenges; patient 4-week diary using the electronic EXACT-PRO tool; hospital admission over 3 months; long-term incidence of mortality (as measured in the CPRD or linked death certificates)</td>
</tr>
</tbody>
</table>
Integrating RCT and clinical care

Use of electronic healthcare records in large-scale simple randomized trials for the evaluation of value-based care

T.-P. van Staa¹,²,³
From the ¹Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands; ²London School of Hygiene and Tropical Medicine, London, UK; ³Division of Primary Care and Public Health, Brighton and Sussex Medical School, University of Brighton, Brighton, UK; ⁴Wolfson Centre for Personalised Medicine, Institute of Translational Medicine, University of Liverpool, Liverpool, UK

Pragmatic randomised trials using routine electronic health records: putting them to the test

What to prescribe for a patient in general practice when the choice of treatments has a limited evidence base? Tjeerd-Pieter van Staa and colleagues argue that using electronic health records to enter patients into randomised trials of treatments in real time could provide the answer

Tjeerd-Pieter van Staa head of research and honorary professor of epidemiology¹²³, Ben Goldacre research fellow³, Martin Gulliford professor of public health⁴, Jackie Cassell professor of primary care epidemiology⁵, Munir Pirmohamed NHS chair of pharmacogenetics⁶, Adel Taweel senior lecturer in software engineering⁴, Brendan Delaney Guy’s and St Thomas’ charity chair in primary care research⁴, Liam Smeth professor of clinical epidemiology³

¹General Practice Research Database (GPRD), Medicines and Healthcare products Regulatory Agency, 151 Buckingham Palace Road, London SW1W 9SZ, UK; ²Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands; ³London School of Hygiene and Tropical Medicine, London, UK; ⁴Department of Primary Care and Public Health Science, King’s College, London, UK; ⁵Division of Primary Care and Public Health, Brighton and Sussex Medical School, University of Brighton, Brighton, UK; ⁶Wolfson Centre for Personalised Medicine, Institute of Translational Medicine, University of Liverpool, Liverpool, UK
Novel designs: self-control methods

Use of self-controlled designs in pharmacoepidemiology

J. Hallas¹ & A. Pottegård²

From the ¹Department of Clinical Pharmacology, IST, University of Southern Denmark; and ²Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark

Journal of Internal Medicine, 2014, 275; 581–589 - PMID: 24635348
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Journal of Internal Medicine, 2014, 275; 581–589 - PMID: 24635348

Rx = NSAID prescription

reference point ▼

bleeding episode

Fig. 1 Schematic presentation of a case-crossover analysis. Each horizontal line represents a timeline illustrating the experience of one individual. The case-defining event is a bleeding episode, illustrated by a stylized droplet, and the prescription is a nonsteroidal anti-inflammatory drug. For each individual, three reference points in time are selected (illustrated by dark triangles). Three of the subjects are exposed at the time of their bleeding, illustrated by the black bar. Between zero and three of the reference points are exposed. A Mantel-Haenszel estimate of the association treating each individual as a separate stratum yields an OR of 4. The fourth and sixth individuals are unexposed on all occasions, and the fifth is exposed on all occasions. Neither of these individuals contribute to the analysis.
A large number of health care databases

<table>
<thead>
<tr>
<th>Public databases</th>
<th>Web site</th>
</tr>
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<tbody>
<tr>
<td><strong>US and Canada</strong></td>
<td></td>
</tr>
<tr>
<td>Healthcare Cost and Utilization Project (HCUP)</td>
<td><a href="http://www.hcup-us.ahrq.gov/databases.jsp">http://www.hcup-us.ahrq.gov/databases.jsp</a></td>
</tr>
<tr>
<td>HMO Research Network (HMORN)</td>
<td><a href="http://www.hmoresearchnetwork.org/">http://www.hmoresearchnetwork.org/</a></td>
</tr>
<tr>
<td>Medicare</td>
<td><a href="http://www.cms.hhs.gov/home/medicare.asp">http://www.cms.hhs.gov/home/medicare.asp</a></td>
</tr>
<tr>
<td>SEER-Medicare Linked Database</td>
<td><a href="http://healthservices.cancer.gov/seermedicare/overview/">http://healthservices.cancer.gov/seermedicare/overview/</a></td>
</tr>
<tr>
<td>Population Health Research Unit</td>
<td><a href="http://metadata.phru.dal.ca/">http://metadata.phru.dal.ca/</a></td>
</tr>
<tr>
<td>Saskatchewan Health Services Databases</td>
<td><a href="http://www.health.gov.sk.ca/">http://www.health.gov.sk.ca/</a></td>
</tr>
<tr>
<td><strong>Europe</strong></td>
<td></td>
</tr>
<tr>
<td>The General Practice Research Database (GPRD)</td>
<td><a href="http://www.gprd.com/">http://www.gprd.com/</a></td>
</tr>
<tr>
<td>Medicines Monitoring Unit (MEMO)</td>
<td><a href="http://www.dundee.ac.uk/memo/">http://www.dundee.ac.uk/memo/</a></td>
</tr>
<tr>
<td>PHARMO Record Linkage System</td>
<td><a href="http://www.pharmo.nl/">http://www.pharmo.nl/</a></td>
</tr>
<tr>
<td><strong>Private databases</strong></td>
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<tr>
<td><strong>US</strong></td>
<td></td>
</tr>
<tr>
<td>Boston Collaborative Drug Surveillance Program</td>
<td><a href="http://www.bcdsp.net/">http://www.bcdsp.net/</a></td>
</tr>
<tr>
<td>Healthcare</td>
<td><a href="http://www.healthcore.com/">http://www.healthcore.com/</a></td>
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<td>HMO Research Network (HMORN)</td>
<td><a href="http://www.hmoresearchnetwork.org/">http://www.hmoresearchnetwork.org/</a></td>
</tr>
<tr>
<td>Kaiser Permanente Medical Care Programs (KP-MCP)</td>
<td><a href="http://www.dor.kaiser.org/">http://www.dor.kaiser.org/</a></td>
</tr>
<tr>
<td>UnitedHealth Group</td>
<td><a href="http://www.unitedhealthgroup.com/">http://www.unitedhealthgroup.com/</a></td>
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</tbody>
</table>
# Strengths and limitations of health care databases

<table>
<thead>
<tr>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large clinical population in the real world</td>
<td>Concerns of accuracy and precision</td>
</tr>
<tr>
<td>Answer a variety of research questions at low cost in a relatively short time span</td>
<td>Misclassification of drug exposure and outcomes, diagnostic misclassification</td>
</tr>
<tr>
<td>Long-term follow-up</td>
<td>Available data limited to variables in the data source, missing data elements, unmeasured confounders</td>
</tr>
<tr>
<td>Appropriate to assess rare, long-term adverse events</td>
<td>Different data elements among data sources, e.g., administrative claims data and medical records</td>
</tr>
<tr>
<td>Data of routine clinical practice automatically stored</td>
<td>Data quality and integrity differ among health care databases</td>
</tr>
</tbody>
</table>

We now have guidelines for selecting good databases

PHARMACOEPIEMIOLOGY AND DRUG SAFETY 2012; 21: 1–10 PMID: 22069180
Published online 8 November 2011 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.2229

COMMENTARY

Guidelines for Good Database Selection and use in Pharmacoepidemiology Research†

Gillian C. Hall†, Brian Sauer2, Alison Bourke3, Jeffrey S. Brown4, Matthew W. Reynolds5 and Robert Lo Casale6

1 Grimsdyke House, London, UK
2 Salt Lake City VA IDEAS Centre & Division of Epidemiology, The University of Utah, Salt Lake City, UT, USA
3 CSD Medical Research, London, UK
4 Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, USA
5 United BioSource Corporation, Lexington, MA, USA
6 Department of Epidemiology, Merck & Co. Inc, West Point, PA, USA
We now have guidelines for selecting good databases

Guidelines for Good Database Selection in Pharmacoepidemiology Research

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6 Department of Epidemiology, Merck & Co. Inc., West Point, PA, USA

15 Oct 2016
LATAM AI Forum, Cancún, Mexico

CHECKLIST FOR INVESTIGATORS IN DATABASE RESEARCH

1 Database selection

Population covered: Does the resource include an appropriate population in terms of size, coverage and representativeness?
Capture of study variables: Are all exposures, outcomes, and other study variables captured in sufficient detail, without bias and accessible for research?
Continuous and consistent data capture: Are there any breaks or changes in data collection over time for either individual patients or the whole population during the study observation period? Are there any inconsistencies in provision of healthcare or capture of study variables across the database population?
Record duration and data latency: Is the average patient record duration, and the time between the occurrence of the exposure and data collection, sufficiently long for the study event?
Database expertise: Is the expertise required to use the resource available: in-house or elsewhere?

2 Use of multiple resources

Multiple resources linked to increase breadth of patient information: Can data resources be linked?
Multiple resources linked to increase numbers: Are the data sources and data systems compatible in metrics, policy and terminology?
Linkage: Is reliable person-matching possible for a sufficiently large proportion of the database population? Are experience and techniques available, and can duplicates be identified?
Data storage and analyses: In multi-institutional studies, should a central or distributed system be used?

3 Extraction and analysis of the study population

Specification of extraction: Are the following specified in detail: how to extract the study population and variables, code lists and non-coded systems, retrieval and merging of additional external data, output and final analysis?

4 Privacy and security

Compliance with privacy and security policy: Have all relevant local, regional and national policies been complied with?
Limited use of identifying information: Are all direct identifiers removed or masked? Whose responsibility is it to ensure privacy?
Secure data storage and transfer: Is there a formal data security policy, and has this been adhered to?
Review of policy and procedures: Are regular privacy reviews adhered to? Has the use of a new database, collection of additional patient or physician data, use of multiple resources, or narrative data impacted confidentiality?

5 Quality and validation procedures

Overall database: Have appropriate general quality checks been completed?
Study population: Which study-specific quality checks are needed: the extraction process, data merging, study variables, assumptions, etc.? Has the annotated programming code been reviewed by an independent programmer?
Testing: The checks can be external, logical or internal and should be cross-sectional, longitudinal and up to date.

6 Documentation

Format: Are rules of Guidelines for Good Pharmacoepidemiology Practices followed, including storage and indexing?
Specifications: Have extraction specification output, quality testing, merging resources, responsibility for privacy and annotated programming code for data extraction and final analysis been documented?
And read also this…

PHARMA COEPI DEMIOLOGY AND DRUG SAFETY 2016; 25: 2–10 PMID: 26537534
Published online 5 November 2015 in Wiley Online Library (wileyonlinelibrary.com) DOI: 10.1002/pds.3891

COMMENTARY

Guidelines for good pharmacoepidemiology practice (GPP)
Public Policy Committee, International Society of Pharmacoepidemiology†

The GPP addresses the following areas:
• protocol development,
• responsibilities, personnel, facilities, resource commitment, and contractors,
• study conduct,
• communication,
• adverse event reporting, and
• archiving
Pros and Cons to the use of databases

Pros

• rich resource for epidemiological research
• population based (potential large samples of patients and matched controls)
• amenable to other studies (cross-sectional, case–control, cohort)

Cons

• costs of access and their analysis
• validation issues
• generalizability of the data
• need of powerful computers, staff proficient in writing computer programs that facilitate analysis, and epidemiologists skilled in their use
• viability is dependent on their continued use

What about ethical problems?

PHARMA COEPIDEMIOLOGY AND DRUG SAFETY 2001; 10: 595–599  PMID: 11980246
Published online 25 October 2001 in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/pds.630

ORIGINAL REPORT

Ethical issues in pharmacoepidemiological research in Belgium

Alain G. Verstraete*1, Robert H. Vander Stichele2 and Luc H. J. Deliens3

1Laboratory of Clinical Biology, Ghent University Hospital, Gent, Belgium
2Scientific Association of General Practitioners, Sint-Hubertusstraat, 58, B-2600 Antwerp (Berchem), Belgium and Heymans Institute of Pharmacology, Ghent University, De Pintelaan 185, B-9000 Gent, Belgium
3Department of Medical Sociology, Free University of Brussels, Belgium and Center for Environmental Philosophy and Bioethics, Ghent University, Belgium
What about ethical problems?

**PHARMACOEPIDEMIOLOGY AND DRUG SAFETY** 2001; **10**: 595–599  **PMID: 11980246**

Published online 25 October 2001 in Wiley InterScience (www.interscience.wiley.com). **DOI**: 10.1002/pds.630

**ORIGINAl REPORT**

Ethical issues in pharmacoepidemiological research in Belgium

Alain G. Verstraete*1, Robert H.

1Laboratory of Clinical Biology, Ghent University, Belgium
2Scientific Association of General Practitioners, Belgium and Heymans Institute of Pharmacology, Belgium
3Department of Medical Sociology, Free University and Bioethics, Ghent University, Belgium

**KEY POINTS**

- In Belgium, all clinical research studies must be approved by an ethics committee
- A law on the protection of privacy, adapted to the European Directive 95/46/EC, is in force
- With some creativity, it was possible to meet the requirements and pharmacoepidemiological research has not really been impeded

*Pharmacoepidemiology and Drug Safety, 2001; 10: 595–599*
New approaches?

• Pharmacoepidemiological databases

• Registry studies

Prospective observational study of subjects, with certain shared characteristics, that collects ongoing and supporting data over time on well-defined outcomes of interest for analysis and reporting.


• Pharmacoeconomy

• Structured Case reports and Observational Studies

• Structured off- (beyond ?) label use
New approaches?

• What is Registry study?
  – registry studies are observational (vs clinical trials that are investigational → interventional).

  → Physician treat the condition however they (reasonably) want…
  → The sponsors remain passive observers (no intervention)…

• What do Registry studies measure?
  – registry studies effectiveness (vs clinical studies that measure efficacy).

  → effectiveness: how well a drug performs as intended in the "real world" and as used by a responsible professional (efficacy: how the drug performs in a controlled clinical trial)

adapted from NJ Stark, Clinical Device Group Inc
What are registry good at (vs clinical trials)?

• Obtain valid reimbursement data
  – comparative effectiveness data with suitable (local) competitors
    (not available from clinical trials)
  – impact (positive/negative) of local co-pay policies

• Post-approval effectiveness publications
  – convincing clinicians practicing in the local real world
    (patients with multiple confounding complications or healthcare attitudes)

• Finding the real incidence of adverse reactions
  – often required by the regulatory authorities
  – may reveal unsuspected or not-well appreciated toxicities …

• Rationalizing off-label use
  – raising hypotheses development for future studies
  – identifying new indications for future regulatory submissions.

some parts adapted from NJ Stark, Clinical Device Group Inc
Organization of Registry studies

• Post-approval FDA safety data
  – Centralized computerized information database for post-marketing drug safety surveillance (FDA Adverse Event Reporting System [FAERS]) *

* similar spontaneous reporting systems maintained by Australia, Canada, Europe, Japan, United Kingdom, and WHO (VigiBase);

From: *Post FDA-approval drug safety data: Why they are vital and how they can be made accessible, actionable, and predictable* Adverse events: redefining drug safety – White paper - [http://info.adverahealth.com/whitepaper-post-fda-approval](http://info.adverahealth.com/whitepaper-post-fda-approval)
FDA Registry studies: Results

- Post-approval FDA safety data:
  - Centralized computerized information database for post-marketing drug safety surveillance (FDA Adverse Event Reporting System [FAERS])

Table 1: Examples of effective FDA alerts, generated from Dusetzina et al. 2013.24

<table>
<thead>
<tr>
<th>Type of FDA Warning</th>
<th>Result Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommendations against co-prescribing due to drug-drug interactions.</td>
<td>Inappropriate co-prescribing decreases over time, but is sometimes low to begin (months to years delay).</td>
</tr>
<tr>
<td>Recommendations against use in patient subpopulation (various).</td>
<td>- Atypical antipsychotic use among elderly with dementia (substantial decreases).</td>
</tr>
</tbody>
</table>
| Recommendations against use in patient subpopulation (specific to anti-depressants). | - Substantial decreases in prescribing among children.  
- Shifts in market share.  
- Shift away from diagnoses from primary care physicians. |
| Serious Adverse Event Warnings Recommending Cautious Use of Product. | - Droperidol (significant decrease of use & increased use of ondansetron, a known substitute).  
- Rosiglitazone (significant decreases in use & significant increases in use of other anti-diabetes drugs). |

FDA Adverse Event Reporting System (FAERS)
A large number of registries (efficacy and safety)...

- **EMA** (for efficacy)
  - etanercept (Enbrel®) for the treatment of juvenile idiopathic arthritis
  - activated drotrecogin alpha (Xigris®) for sepsis patients with multiple organ dysfunction
  - Crohn's Therapy (Tool Registry [TREAT]) and infliximab (Remicade®)
  - Factor VIII products

- **FDA** (many registries)
  - The FDA uses (pre-requested) evidence from observational studies and registries to confirm safety, but rarely to confirm efficacy
  - When it does, it is more common in medical devices, procedures and in life threatening conditions, e.g., heart disease

- **Private organizations**
  - Blue Cross / Blue Shield ~100 million
  - Aetna ~20 million
  - United Healthcare ~70 million
  - WellPoint ~35 million
  - America’s Health Insurance Plans ~ 1,300 members (200 million)
  - HMO Research Network (HMORN) ~8 million

From Gemmen et al.: The Role of Patient Registries in Evidence Development: Similarities and Differences Between Europe and North America
Presented at the International Society of Pharmacoeconomic and Outcomes Research, Paris, France, 2009
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**AstraZeneca and WellPoint collaboration**
- linking patient administrative claims data, lab results, electronic medical record data to develop a longitudinal patient record.
- getting an insight to population health, unmet medical needs, the burden and cost of illness, treatment pathways, and the safety and value of specific therapeutic options
- existing products are being studied to help payers determine safety and value of drugs by combining real-world evidence and comparative effectiveness research.


15 Oct 2016

LATAM AI Forum, Cancún, Mexico
# Examples of drug-centered registries

## Patient-Centred Registries in Phase IV Drug Surveillance

### Table II. Examples of drug registries

<table>
<thead>
<tr>
<th>Nature</th>
<th>Principal outcome</th>
<th>Population size; duration of observation</th>
<th>Controls</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine&lt;sup&gt;[31,32]&lt;/sup&gt;</td>
<td>Agranulocytosis</td>
<td>Very large; ongoing</td>
<td>None</td>
<td>Established to ensure compliance with mandatory monitoring</td>
</tr>
<tr>
<td>Recombinant factor VIIa&lt;sup&gt;[19]&lt;/sup&gt;</td>
<td>Thrombosis</td>
<td>Moderate; limited to hospitalization</td>
<td>None</td>
<td>Established to determine the incidence of thrombotic episodes following administration; thrombosis was a theoretical risk based on the known mode of action.</td>
</tr>
<tr>
<td>Erythropoietin-α&lt;sup&gt;[33,34]&lt;/sup&gt;</td>
<td>PRCA</td>
<td>Large; 3 y post-enrollment</td>
<td>Eprex® vs other brands</td>
<td>Established to monitor the incidence of PRCA (compared with other brands) following the reintroduction of reconstituted subcutaneous formulation</td>
</tr>
<tr>
<td>Bosentan&lt;sup&gt;[20,21]&lt;/sup&gt;</td>
<td>Multiple</td>
<td>Small; ND</td>
<td>None</td>
<td>Established primarily to monitor the appropriateness of the use of bosentan</td>
</tr>
<tr>
<td>Infliximab&lt;sup&gt;[35]&lt;/sup&gt;</td>
<td>Multiple</td>
<td>Moderate; ongoing</td>
<td>Other therapies</td>
<td>Established to study the long-term safety of infliximab in Crohn’s disease patients</td>
</tr>
<tr>
<td>Biologicals&lt;sup&gt;[24,36,37]&lt;/sup&gt;</td>
<td>Multiple</td>
<td>Small; ongoing</td>
<td>None</td>
<td>Established to monitor the incidence of a range of significant adverse effects following use of these agents</td>
</tr>
</tbody>
</table>

ND = not determined; PRCA = pure red-cell aplasia.

An example of Registry Study in Infectious Diseases: the ceftaroline CAPTURE Study

Ceftaroline Fosamil for the Treatment of Community-Acquired Pneumonia: from FOCUS to CAPTURE
Joseph J. Carreno • Thomas P. Lodise

• Ceftaroline fosamil is anti-MRSA cephalosporin approved for treatment of CABP based on non-inferiority to ceftriaxone (FOCUS I and II studies).
  CABP caused by MRSA and ICU patients were excluded (because of the comparator)!

• CAPTURE *: 272 patients (1st year) and 528 patients (2d year) in registry
  – demonstrated similar cure rates to those seen in clinical trials across all range;
  – included older adults with more co-morbidities, more critically ill patients (ICU), and patients with renal insufficiency,
  – could include patients with MRSA pneumonia (n=39; 20 on monotherapy with 75% [n=15] success vs 47% [n=9] for combined therapy).

* Ceftaroline Assessment Program and Teflaro Utilization Registry

CAVEAT: while CAPTURE has provided valuable insights into ceftaroline use in special populations, including those with MRSA CABP, the data need to be interpreted with caution.
Clinical Registries: proven role in quality improvement


Adapted from: Califf et al. JACC 2002;40:1895–901
Bhatt et al. JACC 2015;68:2230-2245
Clinical Registries: proven role in quality improvement

New Drugs/Devices
- New Indications
- New Populations

Clinical Data & Outcomes

Risk Adjustment

Evidence

Clinical Registries

Measurement & Feedback

QA/PI Initiatives

Performance Indicators, Benchmarking

Guidelines

From: Laschinger J: Regulatory Pathways Devices vs. Drugs Are there roles for registries?
Adapted from: Califf et al. JACC 2002;40:1895–901
Bhatt et al. JACC 2015;68:2230-2245
New approaches?

- Pharmacoepidemiological databases
- Registry studies

- **Pharmacoeconomy-driven choices**

- Structured Case reports and Observational Studies
- Structured off- (beyond ?) label use
New approaches?

- Pharmacoepidemiological databases
- Registry studies

- **Pharmacoeconomy-driven choices**
  - Rational comparison of treatment alternatives for cost-effectiveness
  - Structured Case reports and Observational Studies
  - Structured off- (beyond ?) label use
New approaches?

- Pharmacoepidemiological databases
- Registry studies
- Pharmacoeconomy-driven choices
- **Structured Case reports and Observational Studies**
  - Low statistical value but often good at raising hypotheses for testing
- Structured off- (beyond ?) label use
An example of a short observational study

Use and toxicities of linezolid in severely-ill patients in two teaching hospitals: a retrospective pilot study revealing a large incidence of side effects

P. Papachristoforou¹, C. Briquet², F. Jacobs³, C. Yombi⁴, F. Van Bambeke¹, P. M. Tulkens¹
¹Université catholique de Louvain (Louvain Drug Research Institute); ²Cliniques universitaires St-Luc (Groupe de Gestion de l’Antibiothérapie); ³Cliniques universitaires de Bruxelles Erasme; ⁴Cliniques Universitaires St-Luc (Service de médecine interne); Brussels Belgium

15th Annual meeting of the International Society of Pharmacovigilance; Prague, Czech Republic, 27th-30th October 2015, Poster no. 166

Population:
• 40 treatments of > 7 days (all curative)
• 37/40 off-label (endocarditis, deep infected trauma, septicemia, catheter-related infection, tuberculosis)
• supported by microbiology (organism susceptible to linezolid)
• Rational: replacing vancomycin (24/40)

Untoward effects:
• attributable/likely attributable to linezolid: 9/40 and 22/40, respectively
• anemia (>20% decreased of red blood cell counts): 26%
• thrombocytopenia (>20% platelet decrease): 67%
• lactic acidosis: 8%
• drugs considered as contraindicated (monoamine oxidase inhibition): 74%
New approaches ?

- Pharmacoepidemiological databases
- Registry studies
- Pharmacoeconomy-driven choices
- Structured Case reports and Observational Studies

- Structured off- (beyond ?) label use
A few words about off-label use

✗ 70 percent of off-label drug use lacks scientific backing [1]

✓ but it may be essential in a series of situations where it is difficult to run large "classic" clinical trials (oncology, pediatrics, geriatrics, obstetrics…) [2]

☐ Drug manufacturers are prohibited from promoting a drug’s off-label uses, … but it may be discussed if seeking future regulatory approval.→ Company’s financial interest and lack of FDA approval must be disclosed [3]

Warning: this is the US law… Check the law of your country!

• Off-label use of prescription drugs is associated with adverse drug effects (ADEs), but electronic health records could be designed to enable postmarket surveillance of treatment indications and treatment outcomes [4]


Let us now rephrase the first set of questions …

Please, choose among the followings the source of information you will most trust to make a choice for your (specific) patient

1. Registration studies (including RCT)
2. Pharmacoepidemiological studies ("in my region/country")
3. Registry studies (on efficacy and/or side effects)
4. Pharmacoeconomic studies ("Can I treat for cheaper ?")
5. Observational Studies and case reports ("This could be my reality…")
6. Information about off- (beyond ?) label use

Please, make ONE choice (click only one number even if you would like to select more)
A increase in post-approval studies! Why?

• In the 1980s, FDA began to approve drugs with **post-approval research** being a required **condition of that approval**. EMA has followed…

For many drugs, this is now mandatory in exchange of accelerated approval…

• In the early 2000's, several approved drugs were withdrawn or severely limited because of **safety related issues**

Post-approval research may help in better mitigating these safety risks…

• Patient-centric studies are essential in **difficult-to-treat patients** (where classical RTCs are difficult to run but patients' communities can help)

Cystic fibrosis, cancer, multi-drug resistant tuberculosis…

• Post-approval studies can help in **reducing costs** of development by minimizing the number of pre-approval studies

Cost-containment has become a critical part of drug reimbursement schemes…
Nieuwe caerte van het Wonderbaer en de Goudrijcke Landt Guiana by Jodocus Hondius (1598) shows an enormous Lake Parime. Manoa, the fabulous city of gold is shown on the northeastern shore.

Where do we go from here?

*Nieuwe caerte van het Wonderbaer en de Goudrijcke Landt Guiana* by Jodocus Hondius (1598) shows an enormous Lake Parime. Manoa, the fabulous city of gold is shown on the northeastern shore.

But any post-marketing research on antibiotics would not have been possible without the bacteria!

Let us catch them

Slides: [http://www.facm.ucl.ac.be](http://www.facm.ucl.ac.be) ➔ Lectures

All references are clickable (to PubMed or to the original texts)