Looking beyond clinical trials data ?

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  - 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
  - Belgian Committee for Drug Reimbursement (*CRM/CTG*: 1998-2006)
  - 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 ?

the doctor's question

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 **<u>to this patient</u>** ?

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 data base is now 20 years old

https://intego.be/en/Welcome
Last visited: 10 Oct 2016


BMC Medical Informatics & Decision Making

RESEARCH ARTICLE Open Access

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

Carla Truyers[1*], Geert Goderis[1], Harrie Dewitte[1], Marjan vanden Akker[2] and Frank Buntinx[2]

Truyers et al. BMC Medical Informatics and Decision Making (2014), 14:48 – PMID: 24906941

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…

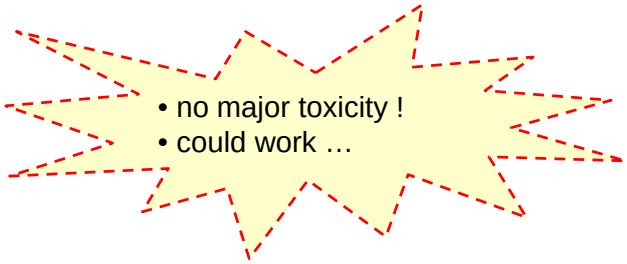
what is their true (local) incidence !

at least, two of your questions will not be answered by the "classical" clinical trials of the new antibiotic …

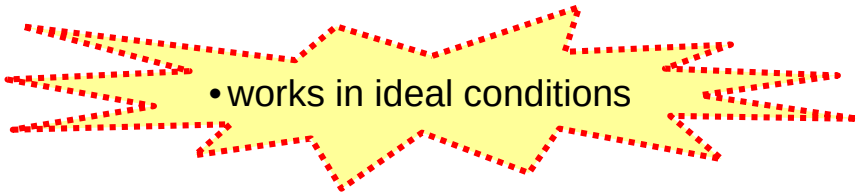
Why does Industry do "classic" clinical trials ?

- A short answer:

- 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

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) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002877.pdf
- Evaluation of medicinal products indicated for treatment of bacterial infections - Adopted guideline (EMA - 2011 -- CPMP/EWP/558/95 rev 2) http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500003417
- 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) http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002877.pdf
- Evaluation of medicinal products indicated for treatment of bacterial infections - Adopted guideline (EMA - 2011 -- CPMP/EWP/558/95 rev 2) http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500003417
- 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

As a result…

Most classic clinical trials of novel antibiotics

- are non-inferiority trials **the comparator must be active…**
- explore a limited number of indications **you cannot do all at the same time…**
- cover diseases that can be addressed/ studied in a reasonable time span **"popular" diseases with rapid outcome are favored…**
- may not include enough patients with severe co-morbidities **you cannot put the trial at risk of treatment-unrelated failures…**
- are limited in the detection of rare but severe adverse effects **it all depends on "n" *(< 0.1 % will be easily missed)***

New approaches ?

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

New approaches ?

- Pharmacoepidemiological databases

doi: 10.1111/joim.12235 Journal of INTERNAL MEDICINE

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

New approaches ?

- Pharmacoepidemiological databases
  - use of health care databases looking for
    - **drug exposure**
    - **health outcomes**

    examining the ratio
  - 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 1. Examples of Databases That Use the Functional and Substantive Organizational Framework[28]

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

Harpe SE. Pharmacotherapy. 2009; 29:138-53 - PMID: 19170584

Combining databases

Review doi: 10.1111/joim.12159 Journal of INTERNAL MEDICINE

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

G. Trifirò[1,2], P. M. Coloma[1], P. R. Rijnbeek[1], S. Romio[1,3], B. Mosseveld[1], D. Weibel[1], J. Bonhoeffer[4,5], M. Schuemie[1,6,7], J. van der Lei[1] & M. Sturkenboom[1]

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

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

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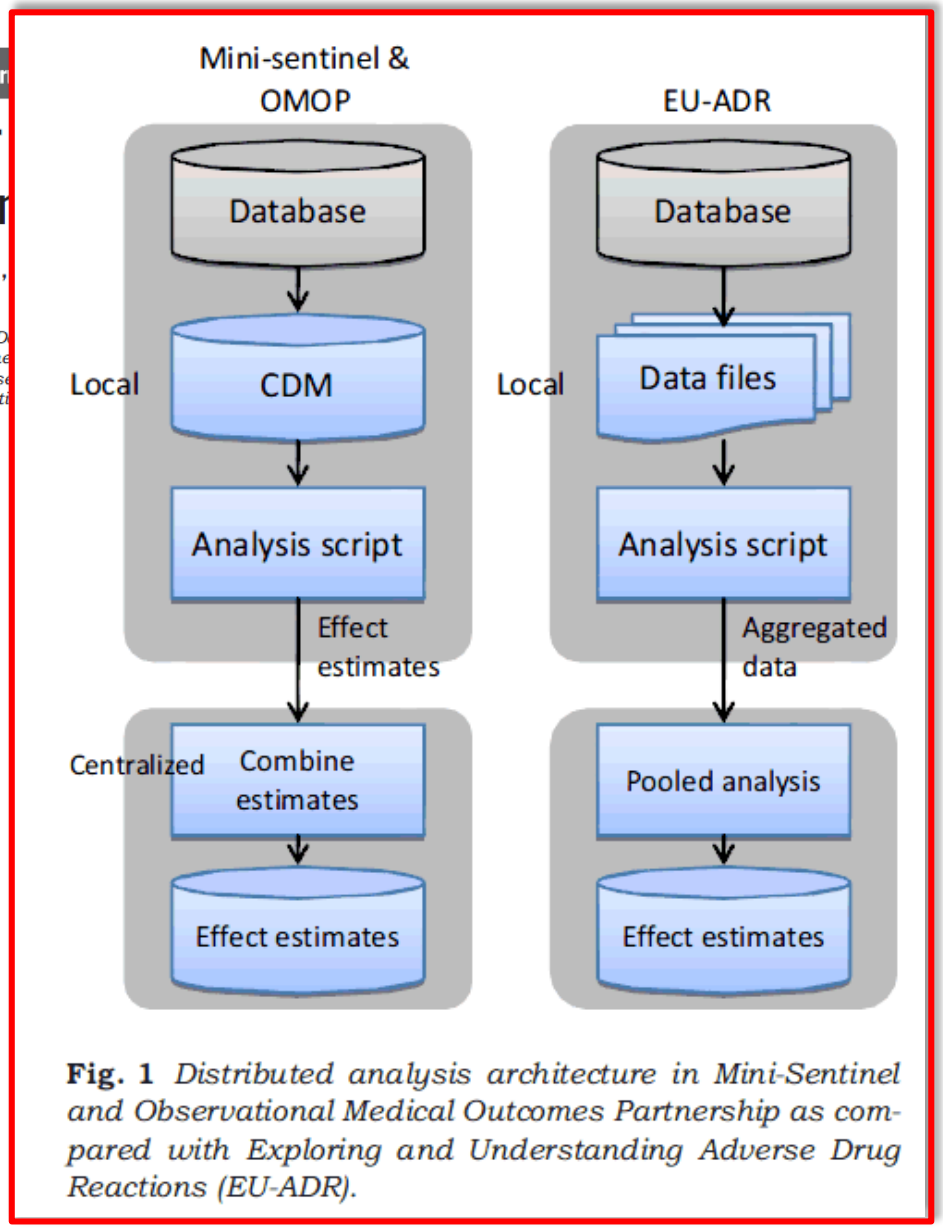

Fig. 1 *Distributed analysis architecture in Mini-Sentinel and Observational Medical Outcomes Partnership as compared with Exploring and Understanding Adverse Drug Reactions (EU-ADR).*

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.

Combining databases: EU-ADR information distribution

Review doi: 10.1111/joim.12159 Journal of INTERNAL MEDICINE

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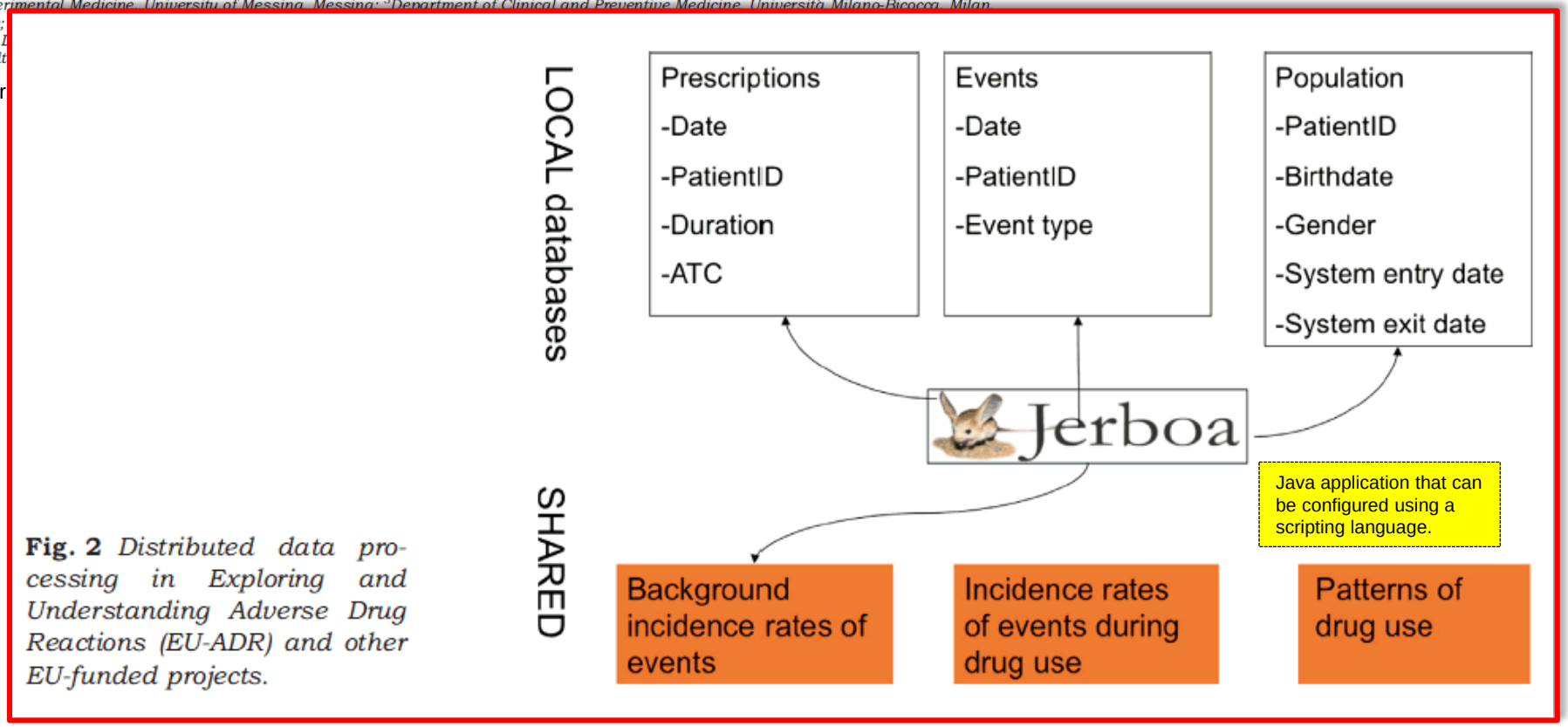

Fig. 2 *Distributed data processing in Exploring and Understanding Adverse Drug Reactions (EU-ADR) and other EU-funded projects.*

Integrating RCT and clinical care

Symposium

doi: 10.1111/joim.12211 Journal of INTERNAL MEDICINE

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[1,2], O. Klungel[1] & L. Smeeth[2]

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

Journal of Internal Medicine, 2014; 275: 562–569 - PMID: 24635449

Integrating RCT and clinical care

Symposium

doi: 10.1111/joim.12211 Journal of INTERNAL MEDICINE

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[1,2], O. Klungel[1] & L. Smeeth[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]

Research questions	Feasibility of trial; pilot for comparative effectiveness of antibiotics in patients with an exacerbation of chronic obstructive pulmonary disease and nonpurulent sputum
Intervention	Randomization between antibiotic (whichever the general practitioner uses as first line) or usual care in 150 patients; nonblinded
Outcome measures	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)

Integrating RCT and clinical care

Symposium

doi: 10.1111/joim.12211 Journal of INTERNAL MEDICINE

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From the [1]Utrecht Institu
Tropical Medicine, Londo

Journal of Internal Medic

BMJ 2012;344:e55 doi: 10.1136/bmj.e55 (Published 7 February 2012) PMID: 22315246

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 epidemiology*[1 2 3], Ben Goldacre *research fellow*[3], Martin Gulliford *professor of public health*[4], Jackie Cassell *professor of primary care epidemiology*[5], Munir Pirmohamed *NHS chair of pharmacogenetics*[6], Adel Taweel *senior lecturer in software engineering*[4], Brendan Delaney *Guy's and St Thomas' charity chair in primary care research*[4], Liam Smeeth *professor of clinical epidemiology*[3]

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

Novel designs: self-control methods

Review doi: 10.1111/joim.12186 Journal of INTERNAL MEDICINE

Use of self-controlled designs in pharmacoepidemiology

J. Hallas[1] & A. Pottegård[2]

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

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

Novel designs: self-control methods

Review doi: 10.1111/joim.12186 Journal of INTERNAL MEDICINE

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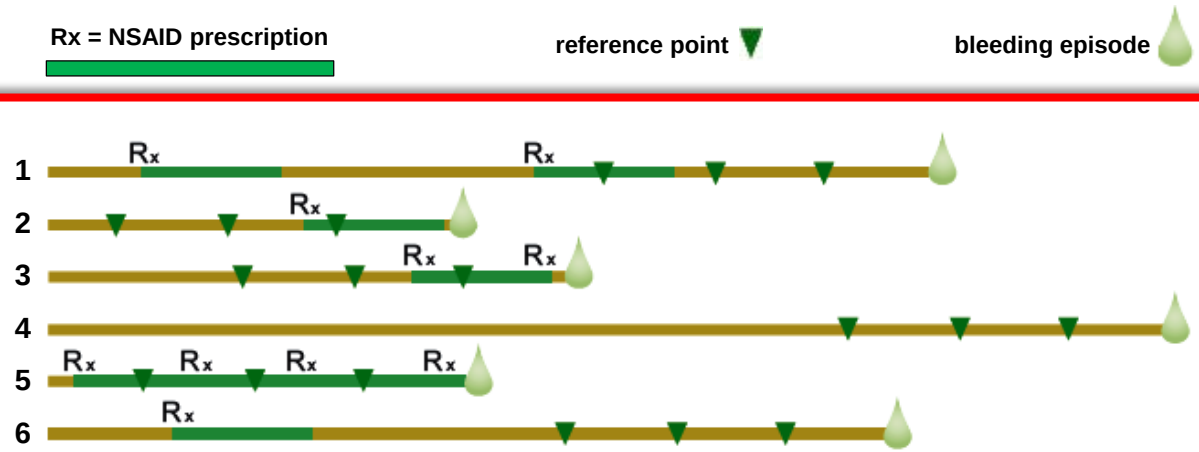

Fig. 1 *Schematic presentation of a case–crossover analysis. Each horizontal line represents a timeline illustrating the experience of one individual. The case-defining event is a bleeding episode, illustrated by a stylized droplet, and the prescription is a nonsteroidal anti-inflammatory drug. For each 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

Eur J Clin Pharmacol (2012) 68:123–129 PMID: 21808989

Table 1 Examples of health care databases

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

Strengths and limitations of health care databases

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

Takahashi et al. Eur J Clin Pharmacol (2012) 68:123–129 - PMID: 21808989

We now have guidelines for selecting good databases

PHARMACOEPIDEMIOLOGY 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[1]*, Brian Sauer[2], Alison Bourke[3], Jeffrey S. Brown[4], Matthew W. Reynolds[5] and Robert Lo Casale[6]

[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 guid

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2012; 2
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Guidelines for Good Database S
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[4] *Harvard Medical School and Harvard Pilgrim Health Care Inst*
[5] *United BioSource Corporation, Lexington, MA, USA*
[6] *Department of Epidemiology, Merck & Co. Inc, West Point, PA,*

do not read it all, but if you need them, here they are !

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?[4]
Specifics: 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…

PHARMACOEPIDEMIOLOGY 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

Adapted from Lawrenson *et al*. Journal of Public Health Medicine 1999; 21:299–304 - PMID: 10528957

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. Vander Stichele[2] and Luc H. J. Deliens[3]

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[2]*Scientific 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*
[3]*Department 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.

[1]*Laboratory of Clinical Biology, Ghent Un*
[2]*Scientific Association of General Practitio*
Belgium and Heymans Institute of Pharmac
[3]*Department of Medical Sociology, Free U*
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**
- Pharmacoeconomy
- Structured Case reports and Observational Studies
- Structured off- (beyond ?) label use

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

Gemmen EK, et al.: The Role of Patient Registries in Evidence Development: Similarities and Differences Between Europe and North America - International Society for Phamacoeconomics and Outcome Research -Workshop Paris 2009
https://www.ispor.org/sigs/presentations/Paris_25Oct2009Patient_Registry_EvidenceWorkshopinalslides.pdf

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
http://clinicaldevice.typepad.com/cdg_whitepapers/2011/07/registry-studies-why-and-how.html

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 …

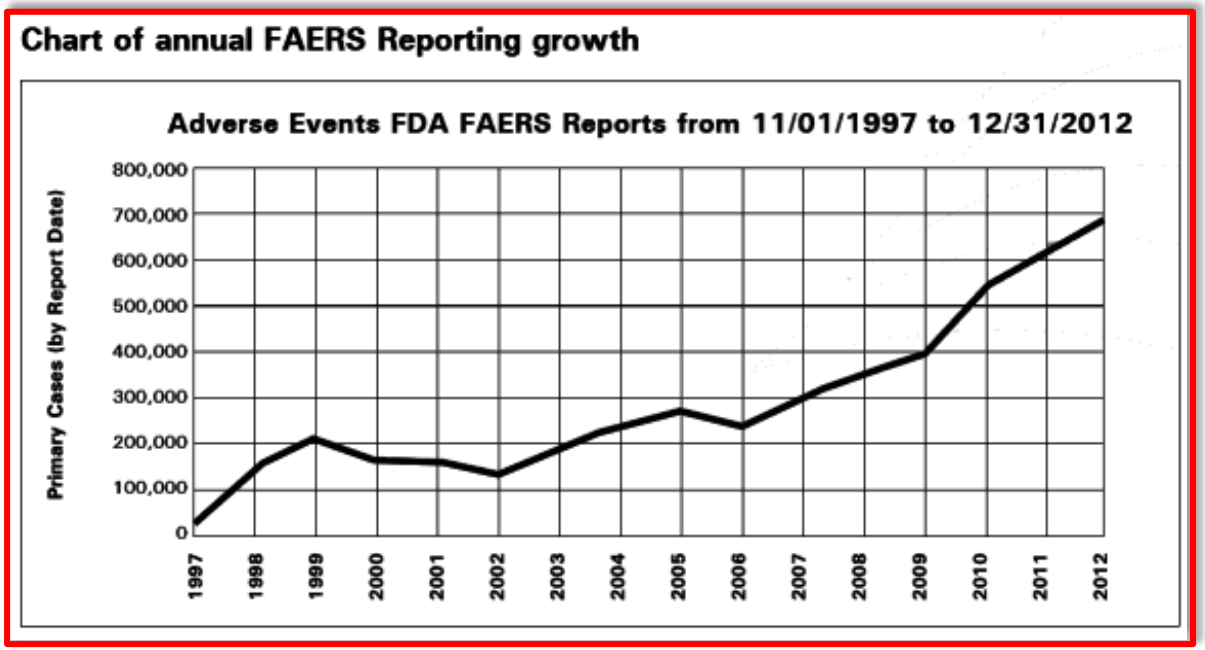
- **Rationalizing off-label use**
  - raising hypotheses development for future studies
  - identifying new indications for future regulatory submissions.

some parts adapted from NJ Stark, Clinical Device Group Inc
http://clinicaldevice.typepad.com/cdg_whitepapers/2011/07/registry-studies-why-and-how.html

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

FDA Registry studies: Results

- Post-approval
  - Centralized co
    drug safety su
    [FAERS])

Table 1: Examples of effective FDA alerts, generated from Dusetzina et al. 2013.[24]

Type of FDA Warning	Result Summary
Recommendations against co-prescribing due to drug-drug interactions.	Inappropriate co-prescribing decreases over time, but is sometimes low to begin (months to years delay).
Recommendations against use in patient subpopulation (various).	- Atypical antipsychotic use among elderly with dementia (substantial decreases).
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)
http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/

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
Available at https://www.ispor.org/sigs/presentations/Paris_25Oct2009Patient_Registry_EvidenceWorkshopinalslides.pdf

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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.

Lamberti & Getz: A Tufts Center for the Study of Drug Development White Paper (2015)
http://csdd.tufts.edu/files/uploads/CSSD_PhRMAWhitePaper_FINAL.pdf

Examples of drug-centered registries

Patient-Centred Registries in Phase IV Drug Surveillance

Table II. Examples of drug registries

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

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

Mc Neil et al. The Value of Patient-Centred Registries in Phase IV Drug Surveillance.
Pharm Med 2010;24:281-288
Available from http://link.springer.com/article/10.1007/BF03256826

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

Infect Dis Ther (2014) 3:123–132
DOI 10.1007/s40121-014-0036-8 PMID: 25193094

REVIEW

Ceftaroline Fosamil for the Treatment of Community-Acquired Pneumonia: from FOCUS to CAPTURE

Joseph J. Carreno · Thomas P. Lodise

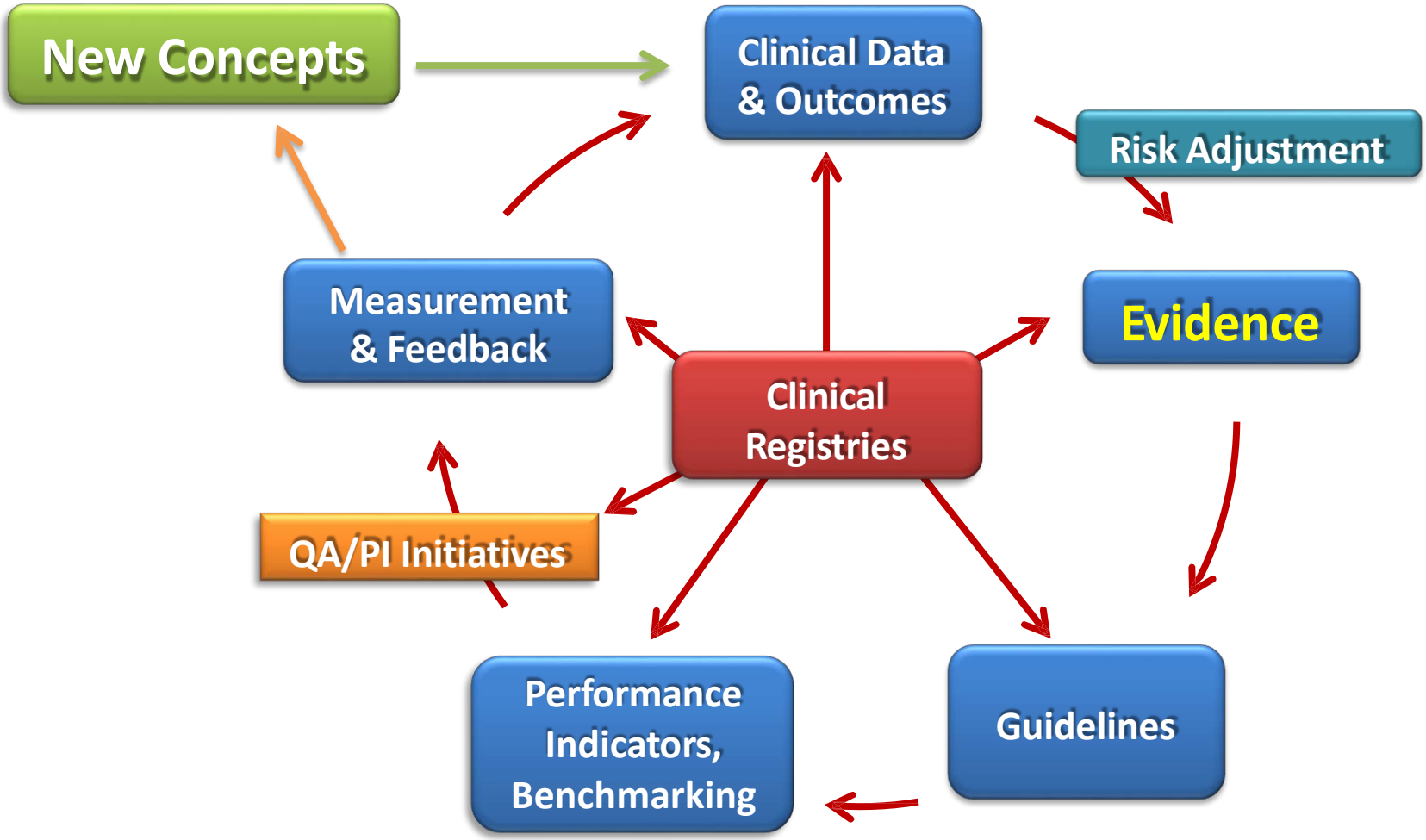
- Ceftaroline fosamil is anti-MRSA cephalosporin approved for treatment of CABP based on **non-inferiority to ceftriaxone** (FOCUS I and II studies).
  CABP caused by **MRSA and ICU patients were excluded** (because of the comparator) !

- **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).

* **C**eftaroline **A**ssessment **P**rogram and **T**eflaro **U**tilization **R**egistry

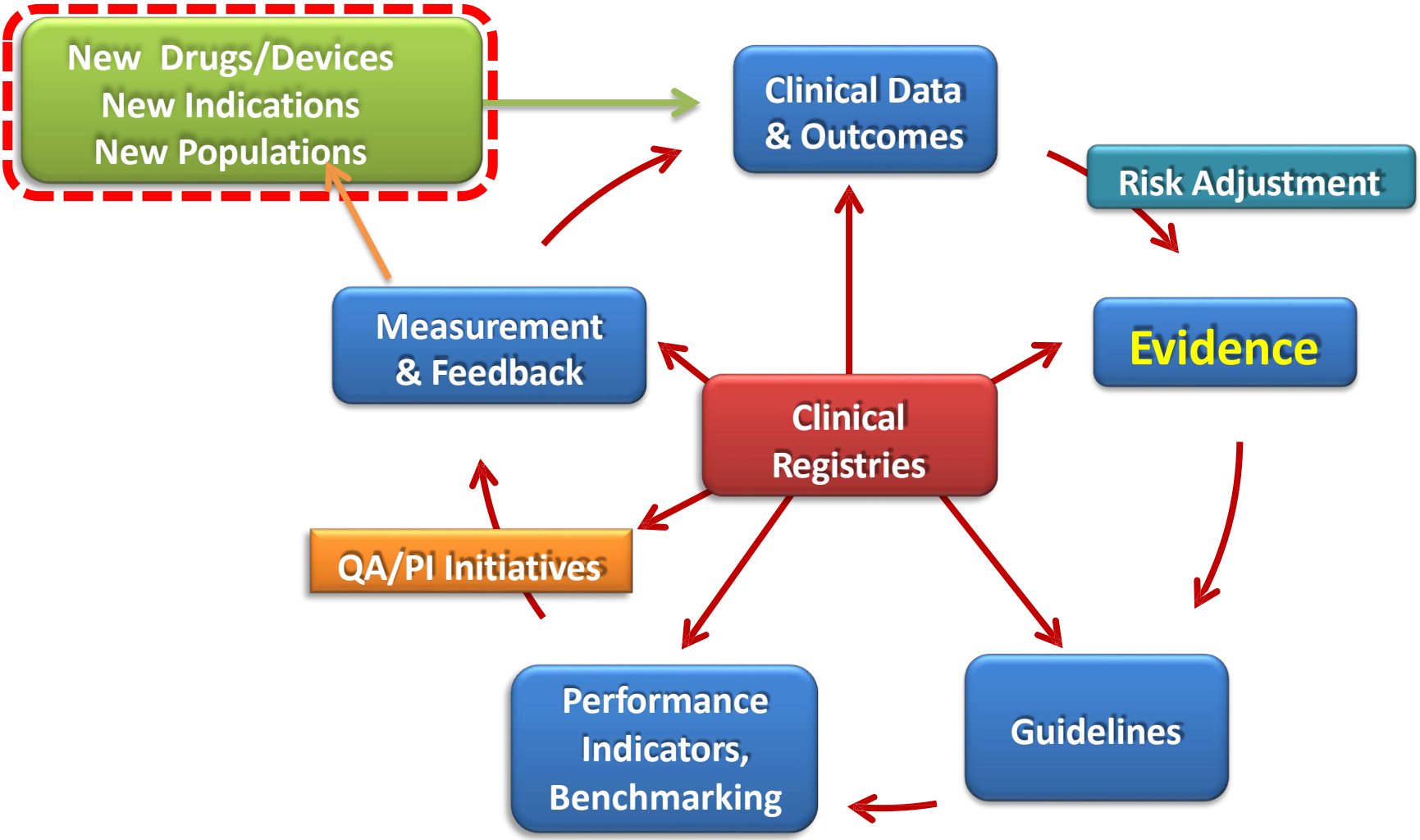
CAVEAT: while CAPTURE has provided valuable insights into ceftaroline use in special populations, including those with MRSA CABP, the data need to be interpreted with caution.

Clinical Registries: proven role in quality improvement



From: Laschinger J: Regulatory PathwaysDevices vs. Drugs Are there roles for registries?
https://www.ctti-clinicaltrials.org/files/session1-2_laschinger_regulatorypathways_regtrial_march30.pdf
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



From: Laschinger J: Regulatory PathwaysDevices vs. Drugs Are there roles for registries?
https://www.ctti-clinicaltrials.org/files/session1-2_laschinger_regulatorypathways_regtrial_march30.pdf
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

15TH ANNUAL MEETING

P 166

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

mailing address: tulkens@facm.ucl.ac.be

P. Papachristoforou[1], C. Briquet[2], F. Jacobs[3], C. Yombi[4], F. Van Bambeke[1], P. M.Tulkens[1]

[1]*Université catholique de Louvain* (Louvain Drug Research Institute); [2] *Cliniques universitaires St-Luc* (*Groupe de Gestion de l'Antibiothérapie*); [3]*Cliniques universitaires de Bruxelles Erasme*; [4]*Cliniques 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
Available from: http://www.facm.ucl.ac.be/posters/2015/15th-ISoP/Papachristoforou-et-al-ISoP-2015-poster-0166.pdf

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 <u>lacks scientific backing</u>** [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]

[1] Radley et al. Arch Intern Med. 2006;166:1021-1026 - PMID: 16682577
[2] Wittich et al. Mayo Clin Proc. 2012;87:982–990 - PMID: 22877654
[3] Dresser & Frader J Law Med Ethics. 2009;37:476–396 - PMID: 19723258
[4] Eguale et al. JAMA Intern Med. 2016;176:55-63 - PMID: 26523731

Adapted from: La Couture B:
"Primer: Introduction to the FDA Drug Approval Process and Off Label Use" - American Action Forum
(https://www.americanactionforum.org/research/primer-introduction-to-the-fda-drug-approval-process-and-off-labal-use/)

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…

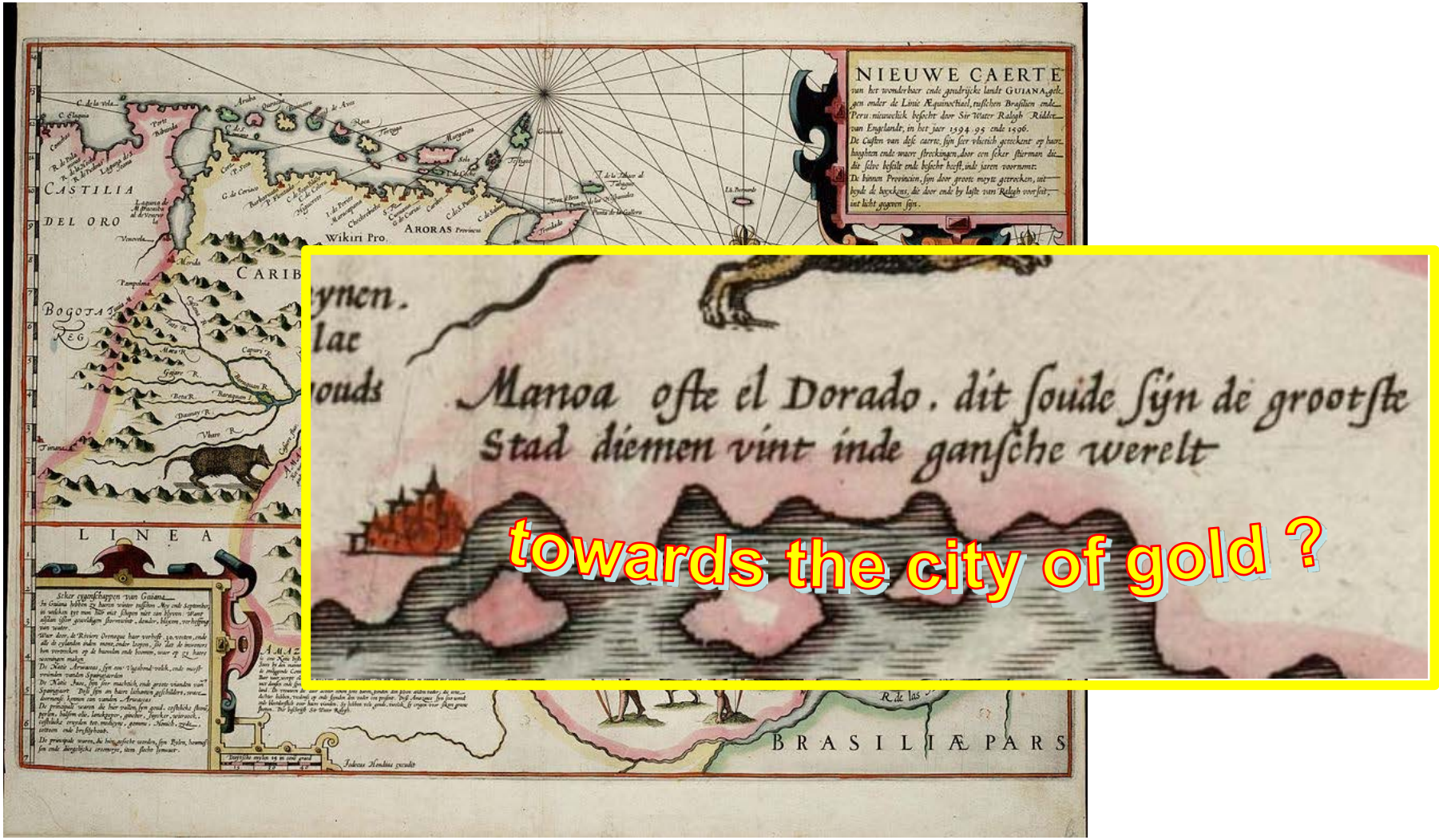
- Post-approval studies can help in **reducing costs** of development by minimizing the number of pre-approval studies

  Cost-containment has become a critical part of drug reimbursement schemes…

Where do we go from here ?

Nieuwe caerte van het Wonderbaer en de Goudrjcke Landt Guiana by Jodocus Hondius (1598) shows an enormous Lake Parime. Manoa, the fabulous city of gold is shown on the northeastern shore.
Original source: http://resolver.kb.nl/resolve?urn=urn:gvn:SURI01:KAARTENZL-104-05-04&size=large (public domain)

Where do we go from here ?



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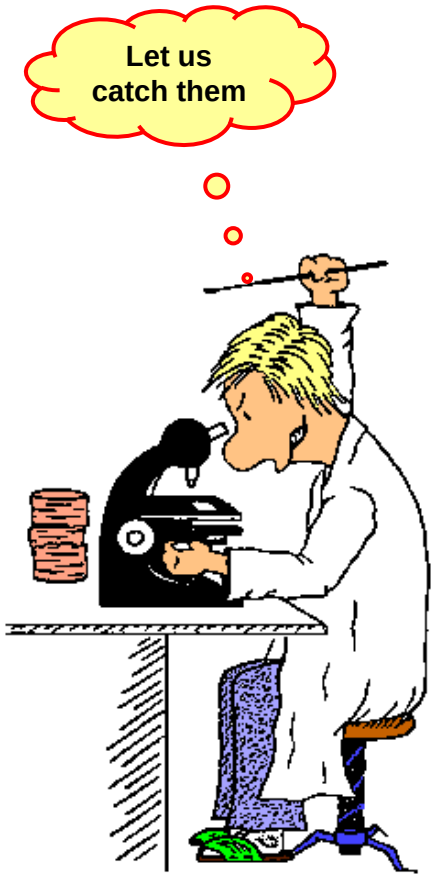
Original source: http://resolver.kb.nl/resolve?urn=urn:gvn:SURI01:KAARTENZL-104-05-04&size=large (public domain)

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



the bacteria !

Slides: http://www.facm.ucl.ac.be → Lectures
All references are clickable (to PubMed or to the original texts)