Pitfalls and challenges for biological registers in the next decade

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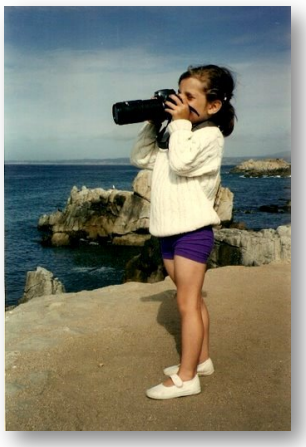

We are putting a lot of expectations on registers

…but you can't always anticipate what will happen…

In despite that just knowledge does not make mankind better…

Robert Schuman

Man is the only animal that
trips twice
Over the same stone

María Lorca-Susino

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…learning from our errors should help us develop better quality studies

EULAR points to consider when establishing, analysing and reporting safety data of biologics registers in rheumatology

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Ann Rheum Dis 2010;**69**:1596–1602

Registers Study Group → **Eular's Subcommittee on Registers**

Pitfall #1: We do not all speak the same language.

What is a registry or register?

- Definition
  - an official list or record
  - (in electronic devices) a location in a store of data, used for a specific purpose and with quick access time
  - written record, written account — a written document preserving knowledge of facts or events

The history of any scandinavian…

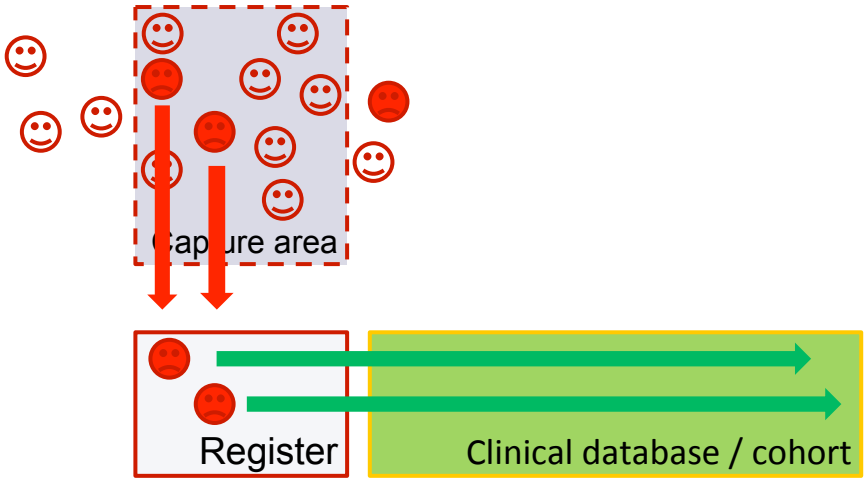


What is a register/registry epidemiologically speaking?

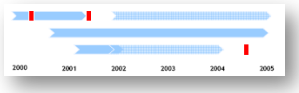
- A register is something between a **design** and a **tool**
  - The pure epidemiological design is a cohort / LOS
  - The pure tool is the database
- **Structure (prospective system)** that permits all cases within a pre-established capture area to be identified
  - **Capture area**:
    - Participant professionals that IDENTIFY + REGISTER
    - Delimited area
    - Well known referral pathways
    - Materials, ways
  - **Database -> lists of records**

- The entry of new cases (or registries) is not pre-planned

Visualizing a register



Types of registers



Type	Objective	Registries	Example
Disease registers	▪ To estimate disease incidence ▪ To describe incident cases	▪ Cases	NOAR
Drug registers	▪ To estimate incidence of AE (pharmacovigillance) ▪ To describe adverse events	▪ Treatment courses ▪ Adverse events	BSRBR RATIO
Clinical databases	▪ To select patients for studies ▪ To monitor indicators	▪ Patients, visits, treatments, prescriptions…	DANBIO
Repositories	▪ To select registries for studies	▪ Anything: patients, samples…	LFR & R
Registrations	▪ To contact all registered for whatever reason	▪ Persons	Lupus.ph

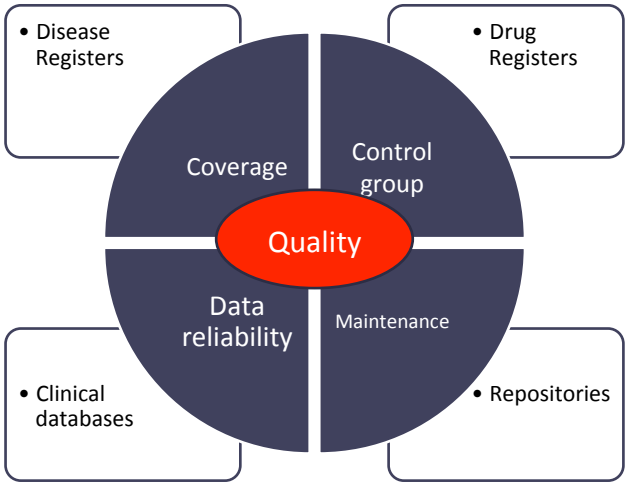
Regarding the design, your registry is closer to...

18. Regarding the design, your registry is closer to...

	Response Percent	Response Count
A true registry (new cases / events are added / notified when they appear / occur)	**62.5%**	**10**
A cohort (unselected cases, up to a total pre-specified number, are followed-up at pre-planned visits)	18.8%	3
A clinical database (selected cases are followed-up at the pace of clinical practice)	18.8%	3
answered question		16
skipped question		1

"Survey across registers; a structured inventory of characteristic features of established biologics registers". Eular Taskforce on Biologic Registers – Workshop at Zurich Jan, 17-18, 2011

Although they share challenges, different types of registers have different problems



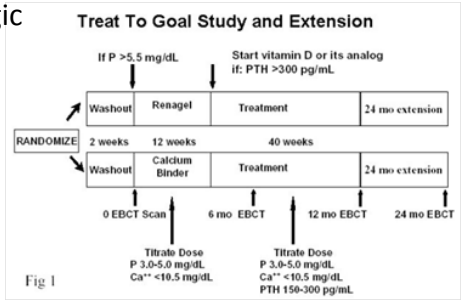
Pitfall #2: Efficacy is easy neither to collect nor to report in registers.

Retention rate vs endpoints

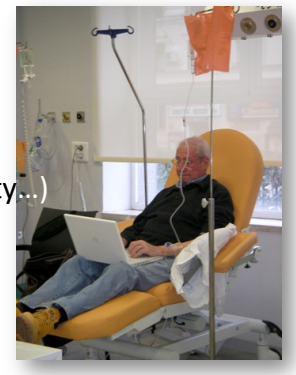
- Retention rates inform on **all patients** up to the point in time they were actually assessed.
- But what does retention mean?
  - It is not pure efficacy, but also includes safety and others
  - It changes with time periods due to expectations and practice
- Endpoint analysis only takes into account **some patients**: those who have a measure in the time point.
- There are ways to correct missing patients
  - Multiple imputation techniques
  - LUNDEX

How far are we informing on effectiveness?

- Do you think we are saying anything additional to trial extension studies?
  - *endpoints* at 1 year
  - Very seldom a control group is used (more often *before* and *after*)
  - Usually only the first biologic



Registers are open studies!



- Effectiveness may be driven by…
  - Patients' characteristics (baseline activity…)
  - Treatment choices
    - Concomitant DMARD
    - Type of drug
    - Dose
  - The time measurement is performed
    - i.e. IFX or RTX are measured before a new infusion, while others are measured at any point in time
  - Patient and doctor's expectations
  - …

Are we sure we are taking all this confounding into account?

Pitfall #3: We thought measuring safety was the easy part!

How do we report safety

- Incidence rate
  - Events / Denominator = patients*time exposed
- Rate comparison
  - Exposed rate / Controls rate (relative risk – Poisson)
  - Exposed rate / Expected rate in the general population
- Standardised Mortality Ratio
  - Mortality in exposed age and sex standardised / expected mortality

How do we screw-up safety

- Incidence rate
  - Events / Denominator = patients*time exposed
- Rate co
  - Exposed rate / Controls rate (relative risk – Poisson)
  - Exposed rate / Expected in the general population
- Standardised Mortality Rati
  - Mortality in exposed age an pected mortality

Different definitions
Unclear definitions

Different definitions
Unclear definitions

Comparable definition, collection and validation

Maybe there is no rate to compare to

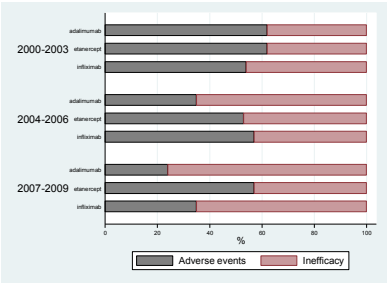
Just think about…

- A simple definition like serious infection is not so simple.
- Controls may not be that comparable…
  - Different time of follow-up
  - Data may not be as reliable
  - Patients may be really different
- Safety may be determined by
  - Population characteristics (baseline activity, comorbidity, age, diagnosis…)
  - or by treatment (concomitant, dose, steroids)
  - but… sometimes we report it without any adjustment whatsoever!

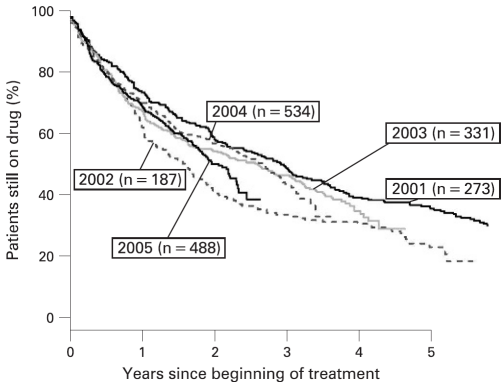
Pitfall #4: An RA is an RA.

Are the patients registered a stable population?

- Lower disease activity at first biologic, less co-Tx
- Higher expectations?



BIOBADASER. Manuscript under submission



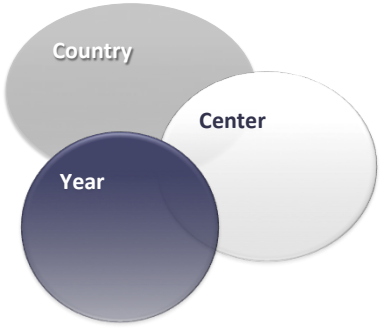
Hetland, ML et al. (2008). "Do changes in prescription practice in patients with RA treated with biological agents affect treatment response and adherence to therapy? Results from DANBIO." Ann Rheum Dis 67(7): 1023-6

Are the rheumatologists a stable population?

<< Somebody stop changing the criteria, please!! >>

The decision to start one treatment or another...

- Is not at random
- It may depend on
  - availability
    - market
    - center
  - indication
  - familiarity
  - prejudices



Without clear information on methods it is impossible to understand whether different results between studies are due to true differences or to the methodology

Pitfall #5: Probably we behaved as new rich men when it came to add data fields into our databases.

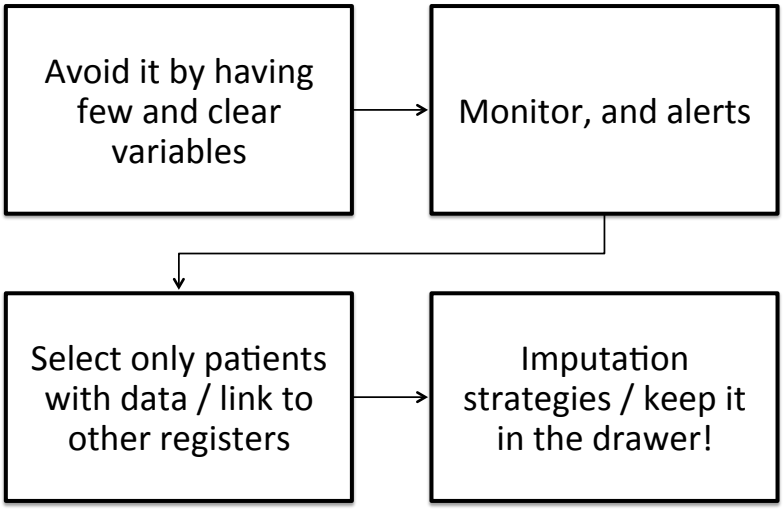
Reliability *versus* size

Wide

Long

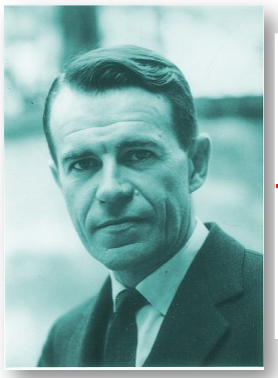
- Most people will encourage you to collect as many data as possible
- How many data are you able to collect without making errors, forgetting, etc?
- Would you rather monitor/clean 500 variables in 200 patients or 50 variables in 2000 patients?
  - It depends on your objective:
    - For effectiveness you do not need many patients, but you need many confounding variables
    - For safety, specially rare events, you need a lot of patients
  - It depends on your money
  - It depends on your trust

How to deal with unreliable / missing data



Biologics registers 2011

CHALLENGE #1: COLLABORATION



Carlo Maria Cipolla
(1922-2000)

- + You harm yourself in order to benefit others: You are **GOOD**	**+ +** You benefit yourself and others: You are **INTELLIGENT**
You harm yourself in order to harm others: You are **STUPID** **- -**	You benefit yourself but harming others: You are **BAD** **+ -**

What would you definitely have done otherwise if you were to do it all over again?

Reinforce participation	A good web-based platform (interactive, interface…)	A (better) control group	Include not just one drug
Regular checking	Better coding (comorbidities, AEs, DMARDs, steroids)	Blood samples collected at baseline	Regular members-meeting
	Patients introducing side effects into the registry	**Automated quality control mechanisms**	

"Survey across registers; a structured inventory of characteristic features of established biologics registers". Eular Taskforce on Biologic Registers – Workshop at Zurich Jan, 17-18, 2011