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- Honorary Rheumatology Consultant at Central Manchester Foundation Trust

GaBI Scientific Meetings

ROUNDTABLE ON REGISTRIES
Practical Considerations for Registries – making them work

26 January 2017, Pullman London St Pancras, London, UK

Practical experience with a pharmaco-vigilance register for biologicals/ biosimilars – the BSRBR-RA*, a Manchester case study

Professor Kimme Hyrich, MD, PhD, FRCPC, UK

26 January 2017

GaBi
GENERICS AND BIOSIMILARS INITIATIVE
Building trust in cost-effective treatments

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Bringing medicines to life

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BSRBR
The British Society for Rheumatology Biologics Registers
Rheumatoid Arthritis

Practical experience with a pharmacovigilance register for biologicals/biosimilars

The BSRBR-RA, a Manchester case study

Professor Kimme Hyrich
The University of Manchester

MANCHESTER 1824
The University of Manchester

ARTHRITIS RESEARCH UK

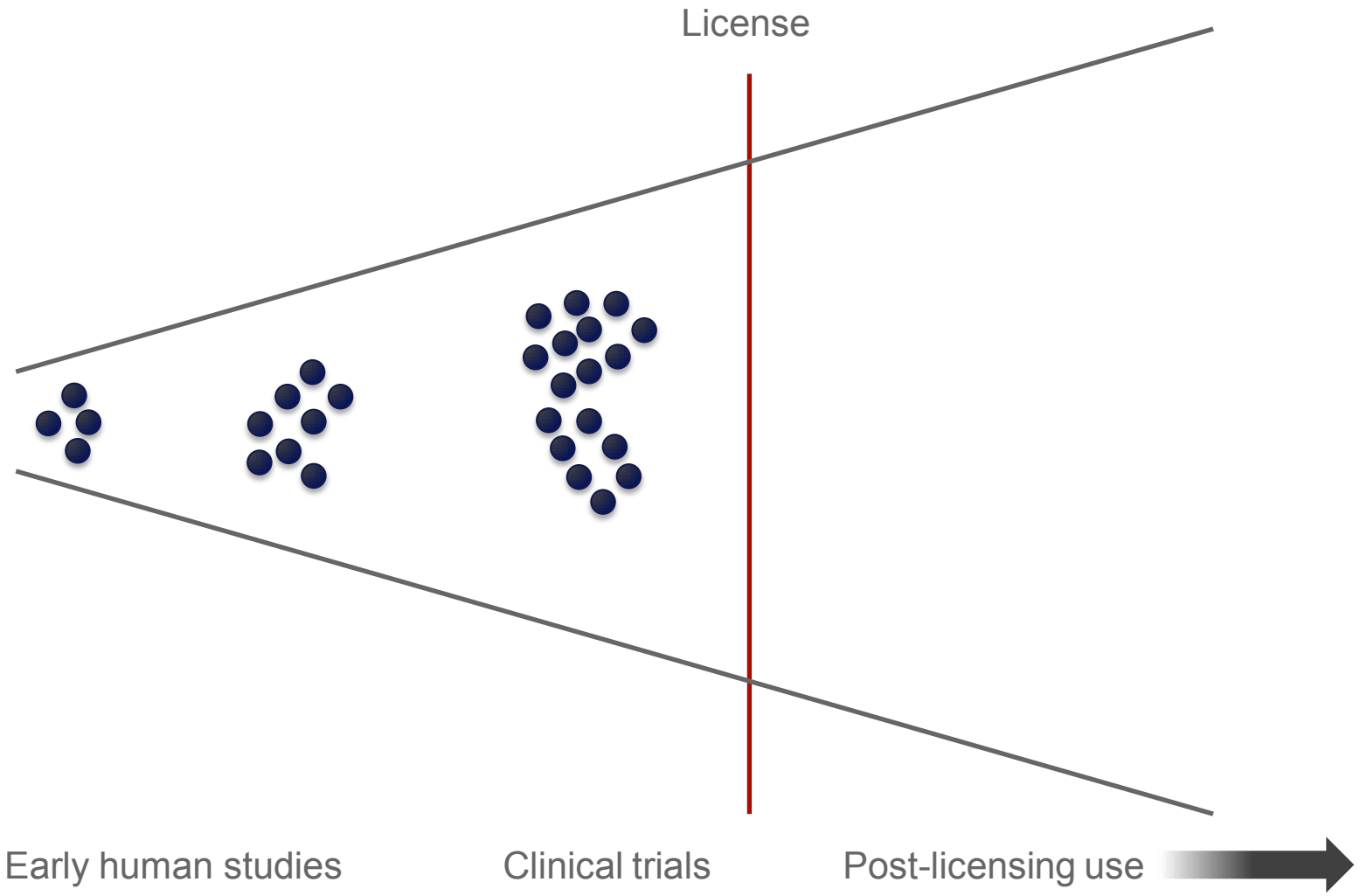
BSRBR

The British Society for Rheumatology Biologics Registers

Rheumatoid Arthritis

- Commenced 2001
- Observational prospective cohort study
- Initially a study of original anti-TNF therapies but has expanded to include rituximab, certolizumab, tocilizumab and most recently biosimilars

Exposure: From Bench to Bedside



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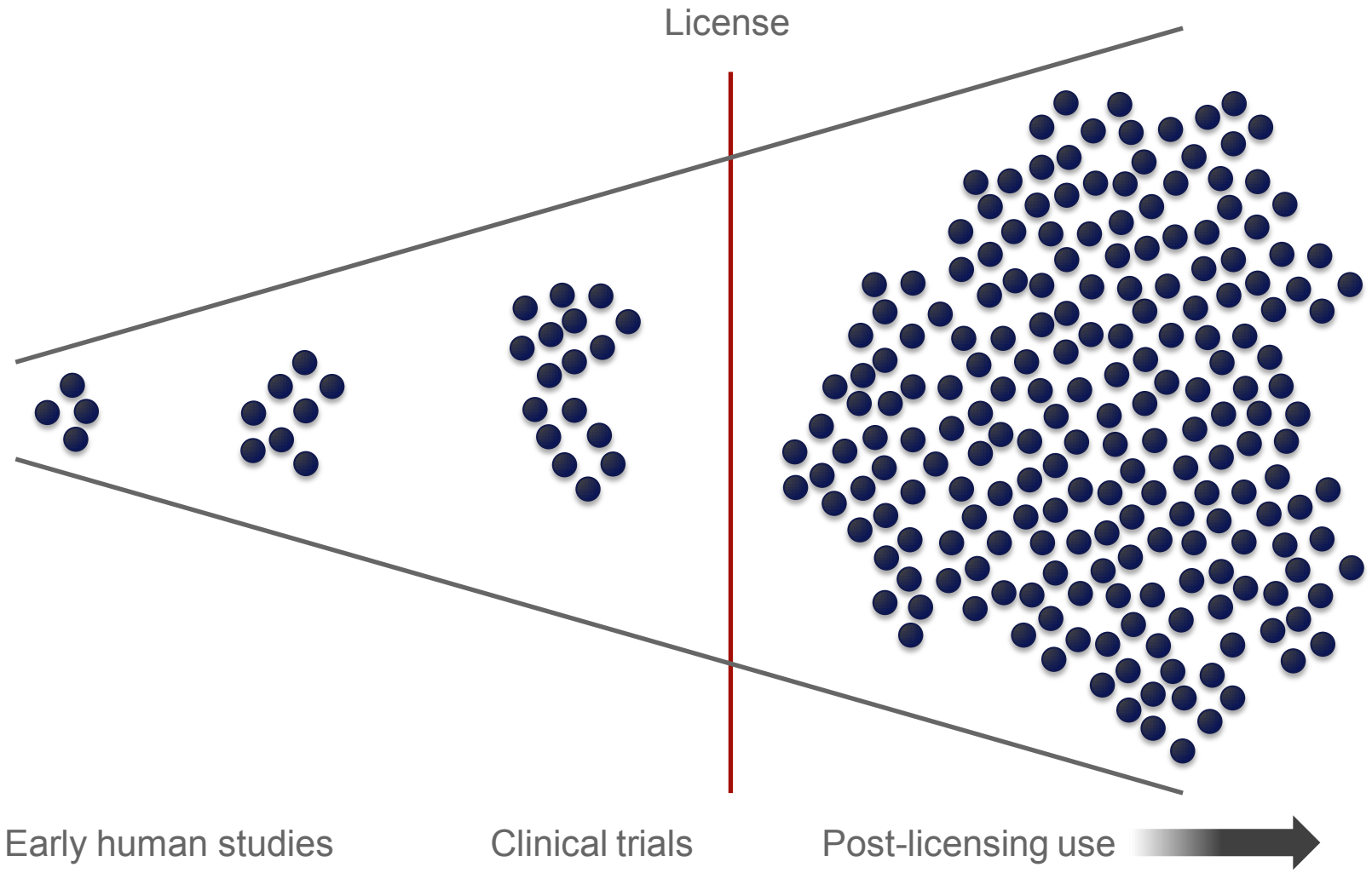
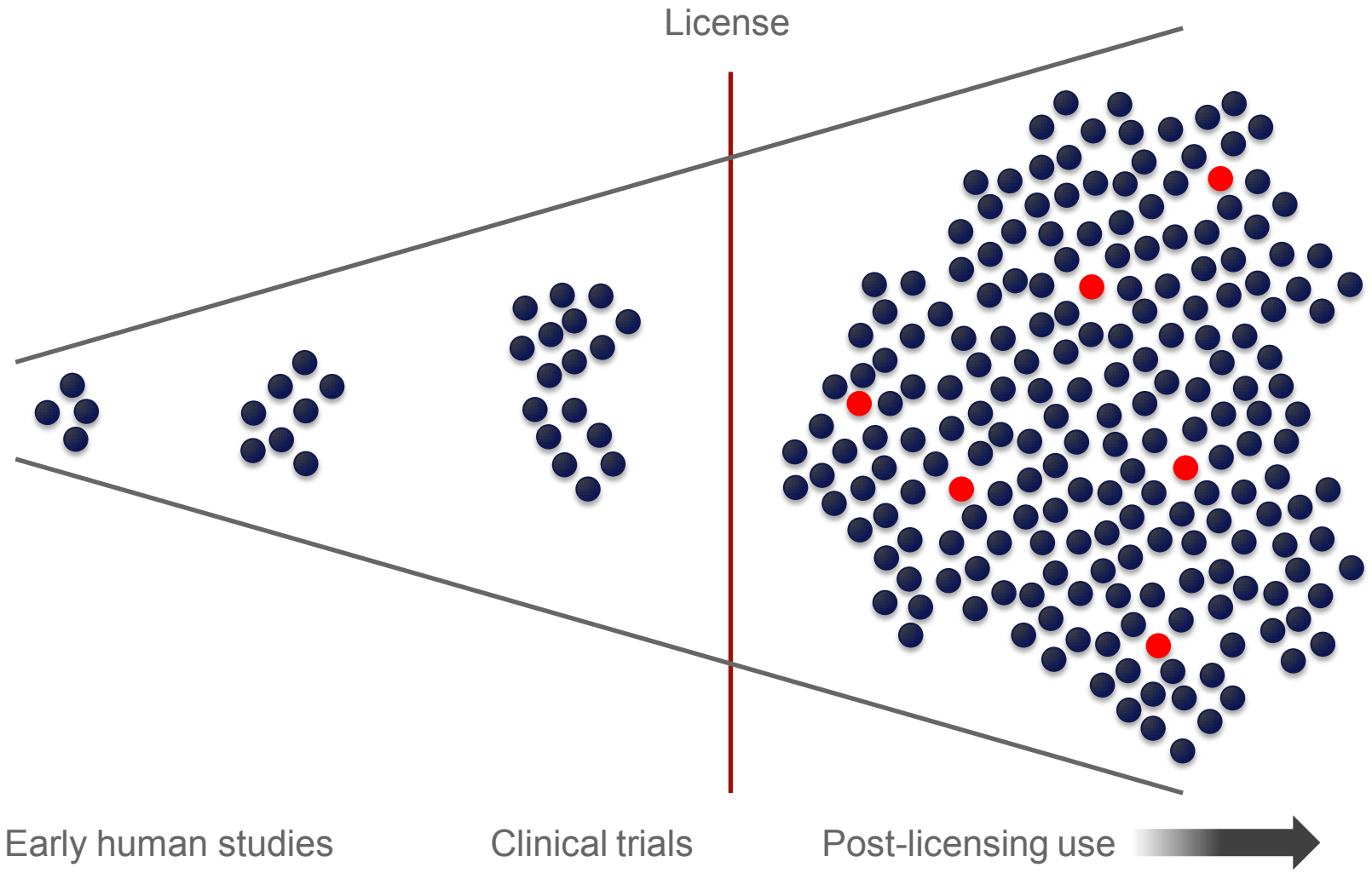
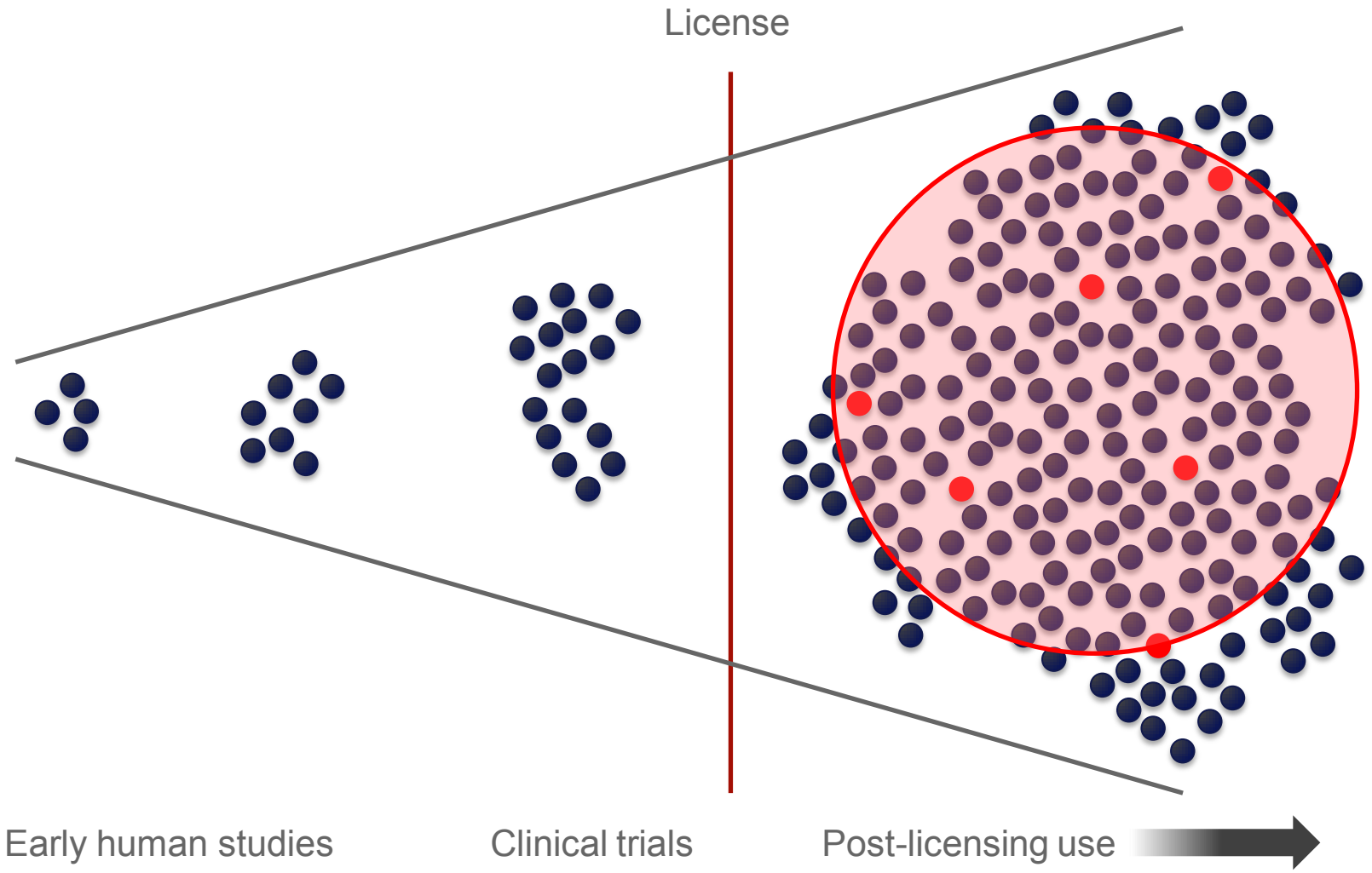


Spontaneous Pharmacovigilance



Observational Patient Registers



Clinical Trials vs. Observational Studies

Trials

Ideal, “designed” setting

Observational Studies

Real-world

Observational Patient Registers

Increased external validity

- Increased sample size
- Wider variety of patients
- Longer follow-up, even after drug is stopped

- But, treatment decisions no longer randomised.

- Careful consideration must be taken if comparing outcomes between treatments.


BSRBR
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Rheumatology
Biologics Registers
Rheumatoid Arthritis

A New Way of Conducting Drug Safety Research

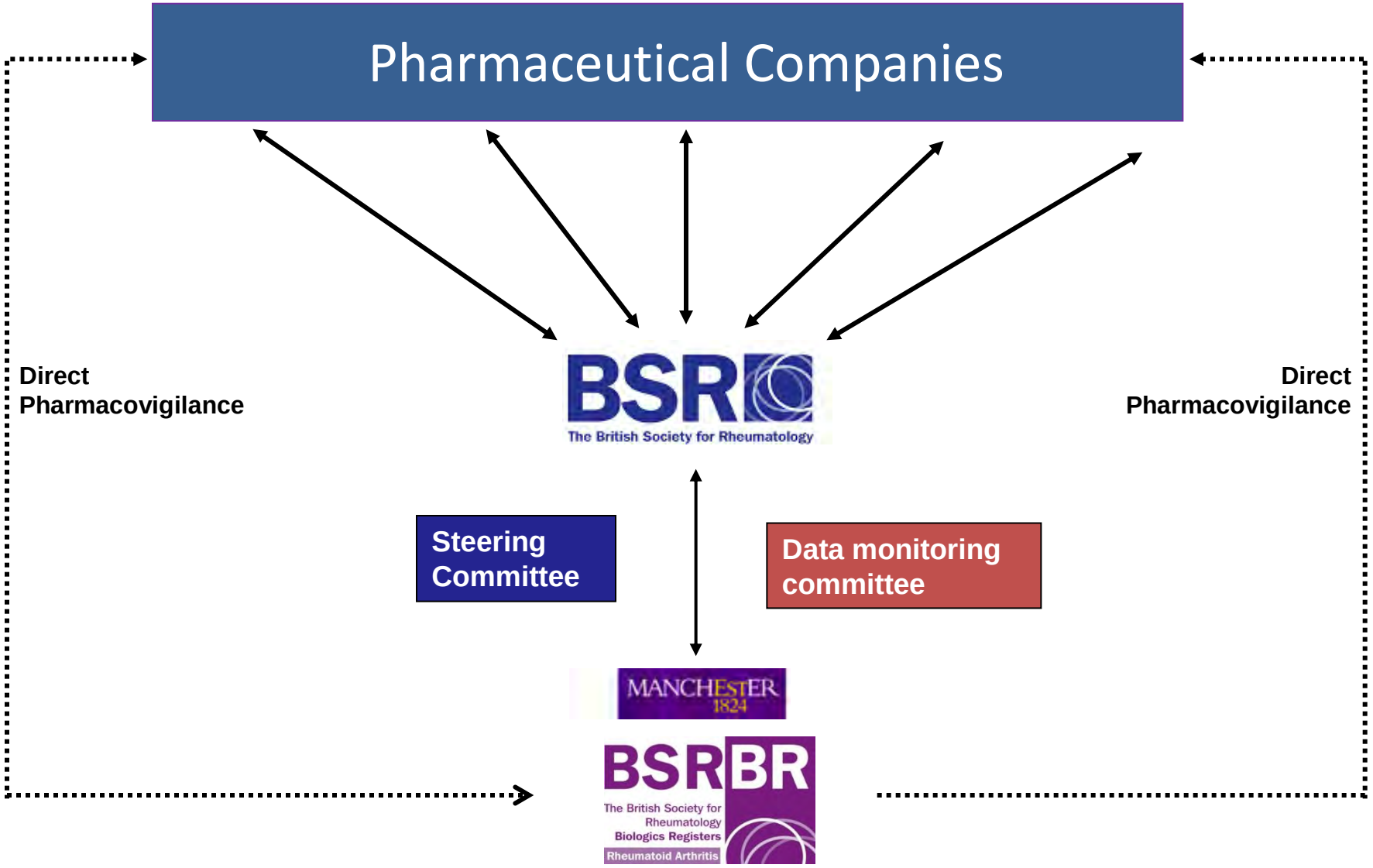
- Context:
  - All pharma companies must continue to monitor the effectiveness and safety of their drugs after they are licensed.
  - The BSRBR represented a new way of adding to these data.
  - An independent academic institution would gather safety data independently to the pharma companies and share anonymous safety data with pharma as part of a risk management plan.

A New Way of Conducting Drug Safety Research

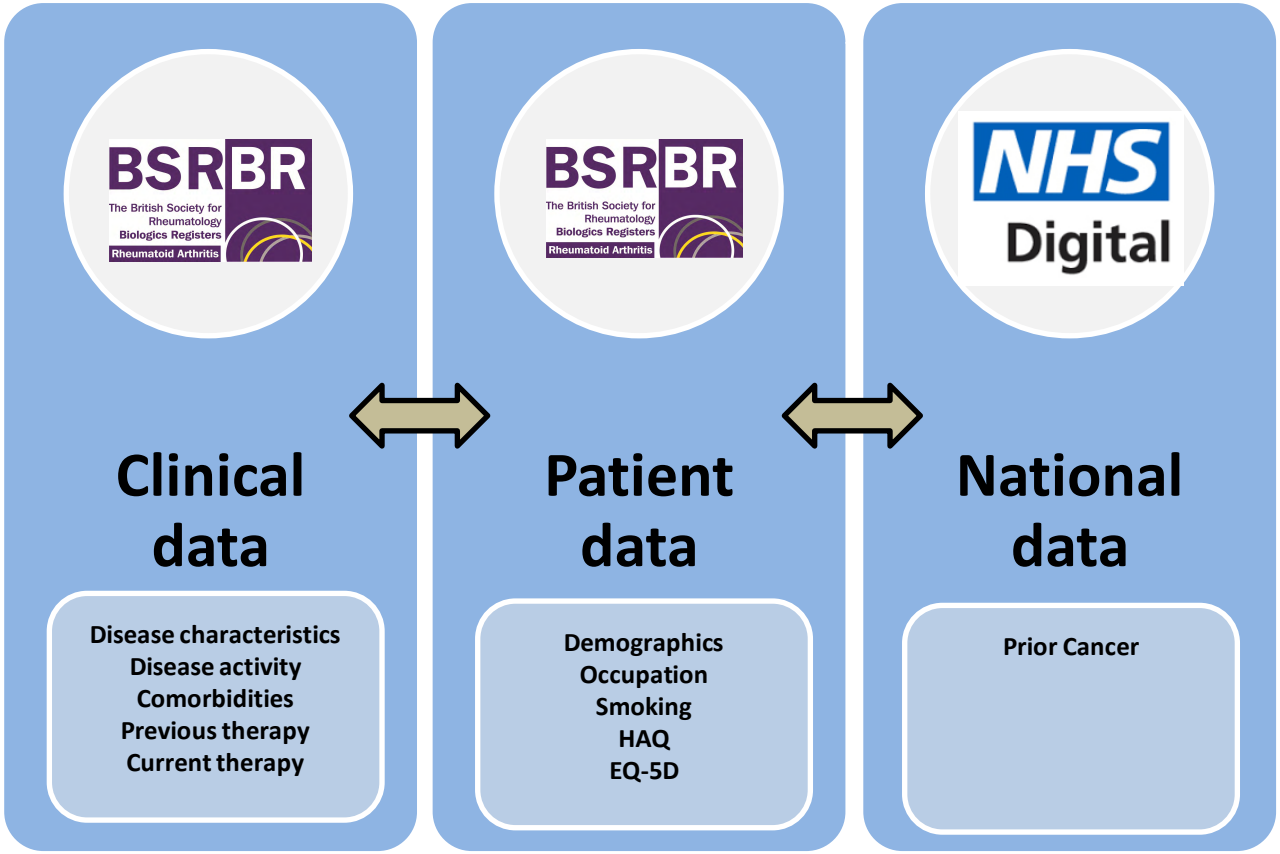
- **Pharmacoepidemiology:**
  - The BSR would oversee the register. They would conduct negotiations with pharma and also allow academics to analyse the data independent of pharma to address questions about “real-world” safety and effectiveness.

- **Pharmacovigilance:**
  - The University would be required to report serious adverse events (SAEs) (with no patient or doctor identifiers) and 6-monthly aggregated reports to pharma to help them monitor the safety of their new products.

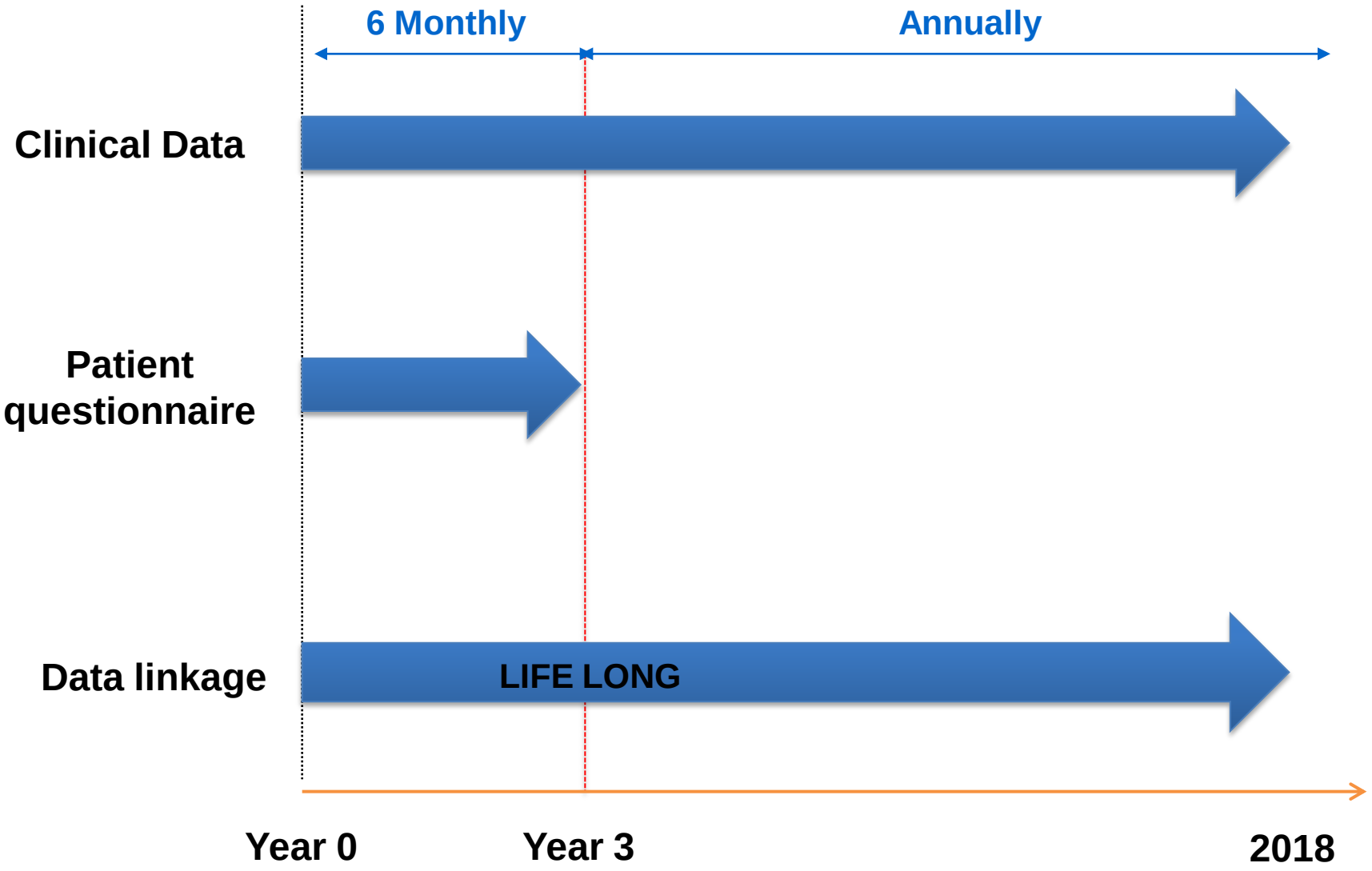
BSRBR-RA Funding and Stakeholders



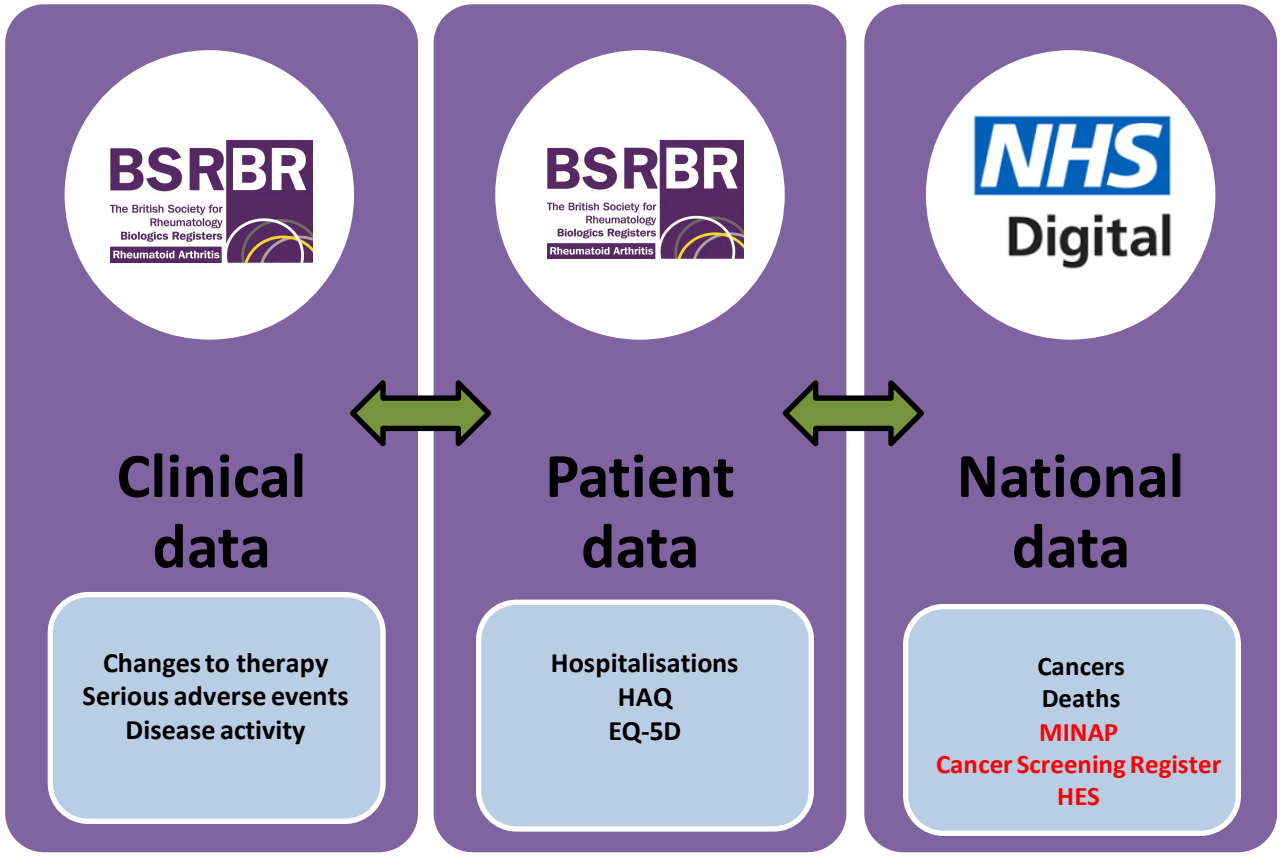
Baseline data collection (At start of biologic)



Follow-up

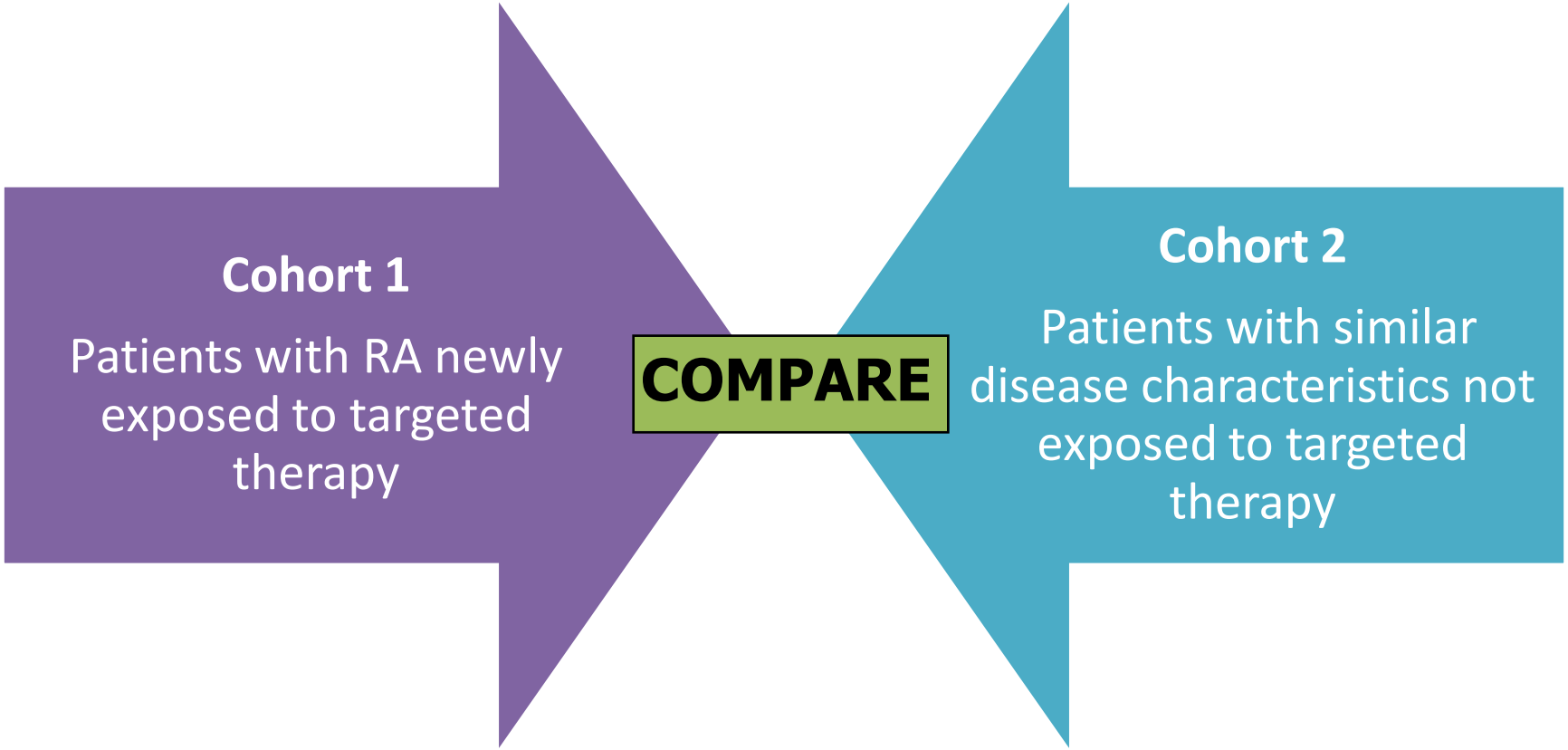

6 Monthly
Annually
Clinical Data
Patient questionnaire
Data linkage
LIFE LONG
Year 0
Year 3
2018

Follow-up data collection

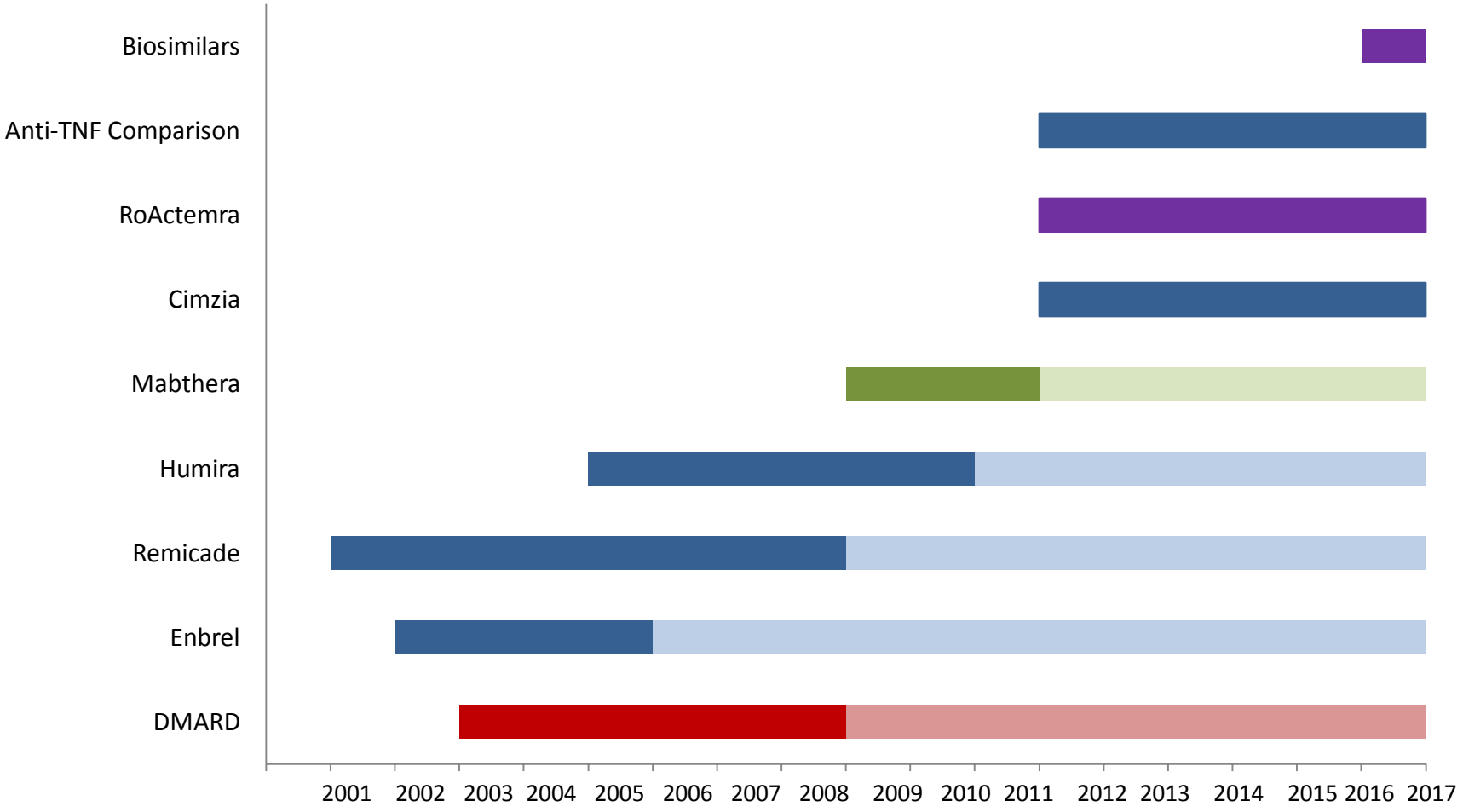


Events of Special Interest Forms

Comparative Effectiveness Study Design



BSRBR-RA cohort recruitment/follow-up



BSRBR-RA cohort recruitment (to November 2016)

Cohort	Registrations	Ever Treated
Enbrel	6489	10651
Remicade	4909	6139
Humira	5396	9079
Mabthera	1651	5479
Cimzia	1306	1691
RoActemra	1225	2373
Biosimilars	379	432
Total Treatment Courses	21355	35844

How are the data collected?


UNIT
1
0000335
-
0002205
UNIT
2
0001206
-
0004410
UNIT
3
UNIT
4
UNIT
5

Why are we so “old-fashioned”??

- In an ideal world: data captured in the medical record would automatically travel through to a national biologics register for analysis.

- But:
  - Study pre-dated widespread use of online data capture
  - Currently no universal rheumatology EMR
  - No national database of biologic prescribing
    - secondary care, injectables

- Currently, in the UK, no other way of capturing biologic exposure data or RA disease outcome data other than direct report

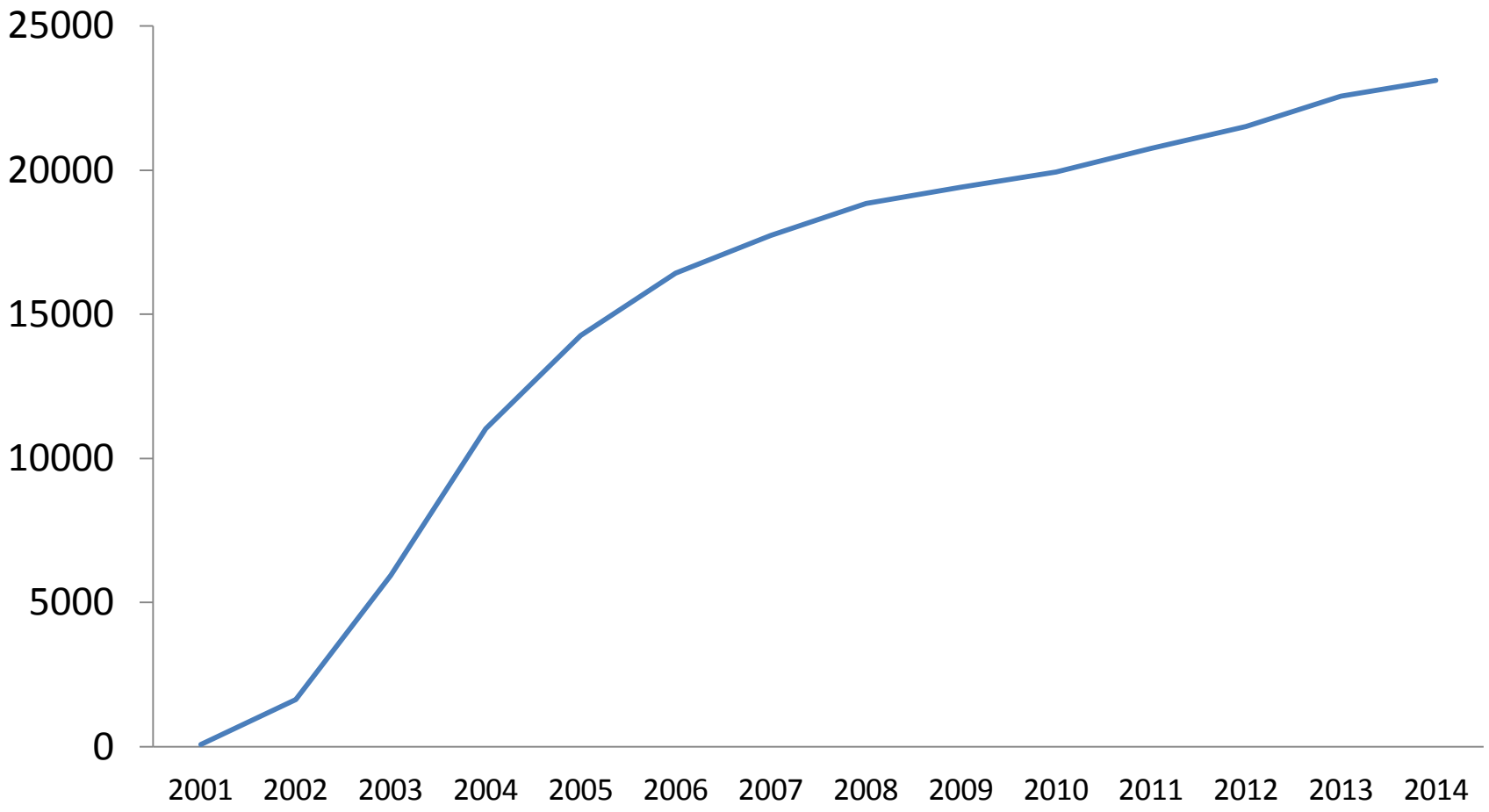
Example Biologics Registers In Europe

Country	Acronym	Year started
Switzerland	SCQM	1997
Finland	ROB-FIN	1999
Sweden	ARTIS	1999
Denmark	DANBIO	2000
Norway	NOR-DMARD	2000
Spain	BIOBADASER	2000
Germany	RABBIT	2001
United Kingdom	BSRBR-RA, BSRBR-AS	2001
Czech Republic	ATTRA	2002
Hungary	HU-REGAR	2003
Netherlands	DREAM	2003
France	RATIO,AIR, ORA and REGATE	2004
Russia	BIOROSS	2005
Italy	GISEA	2008
Portugal	Reuma.pt	2008
Slovenia	BioRx.si	2008

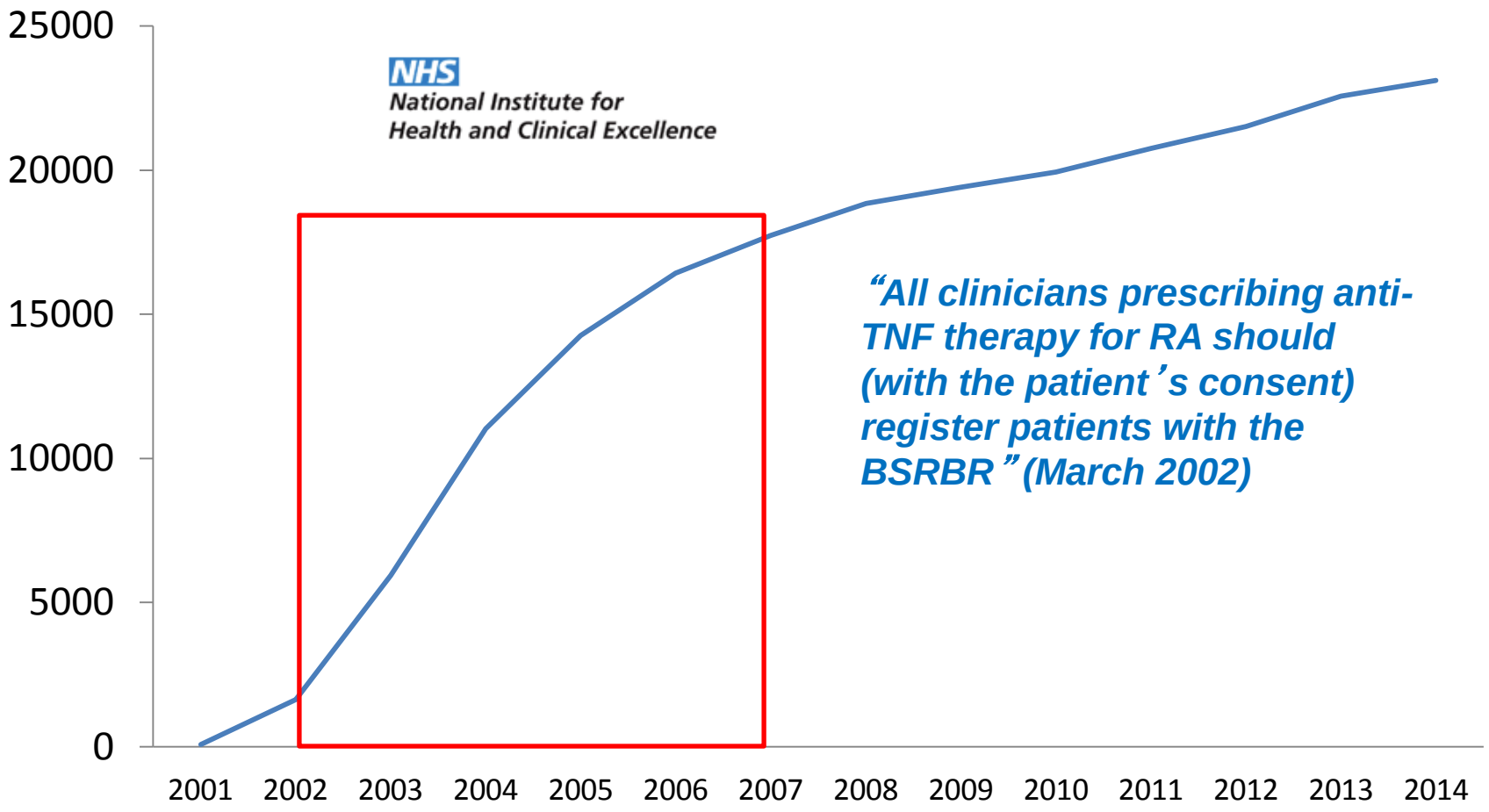
Differences in European Registers

Traditional Cohort Model	Embedded in EMR
Example: UK, Germany, Czech Rep	Example: Sweden, Denmark, Swiss
Pros: Extensive patient level data Less missing data	Pros: Potential for larger sample sizes Patients must opt-out not opt-in
Cons: Hard work at local level May require patient consent	Cons: Risk of missing data Less “event” details

BSRBR-RA Recruitment



BSRBR-RA Recruitment



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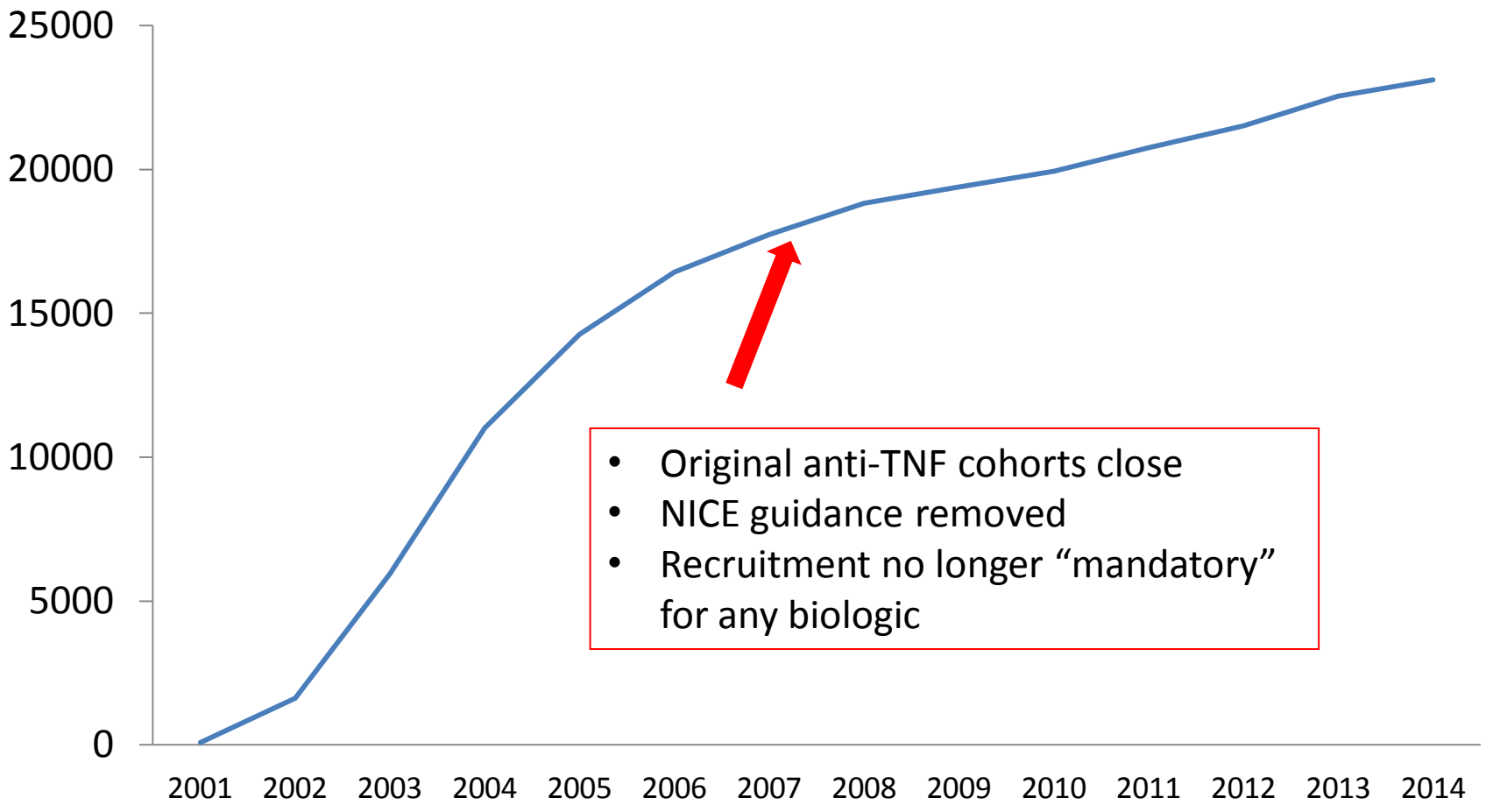

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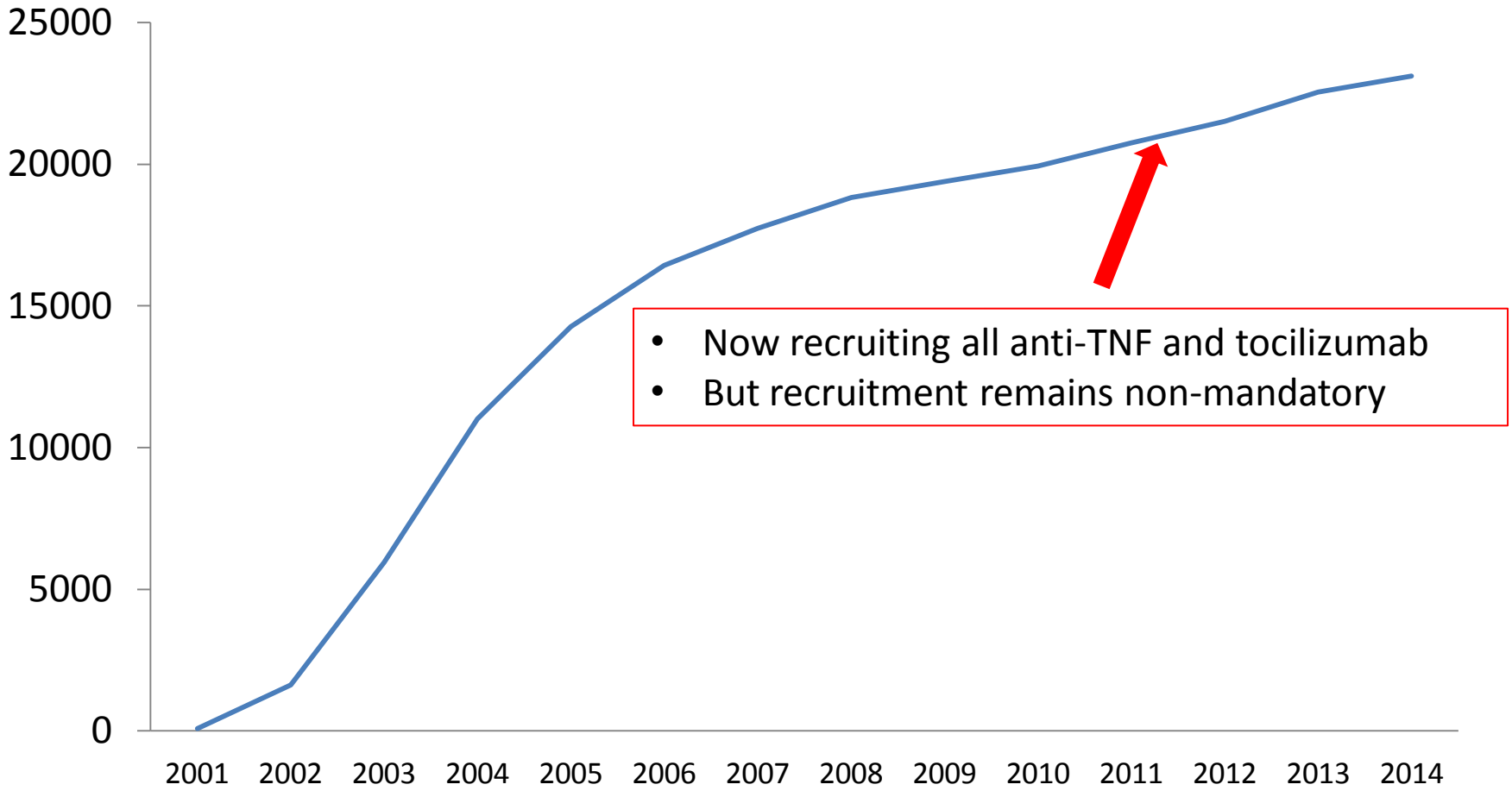
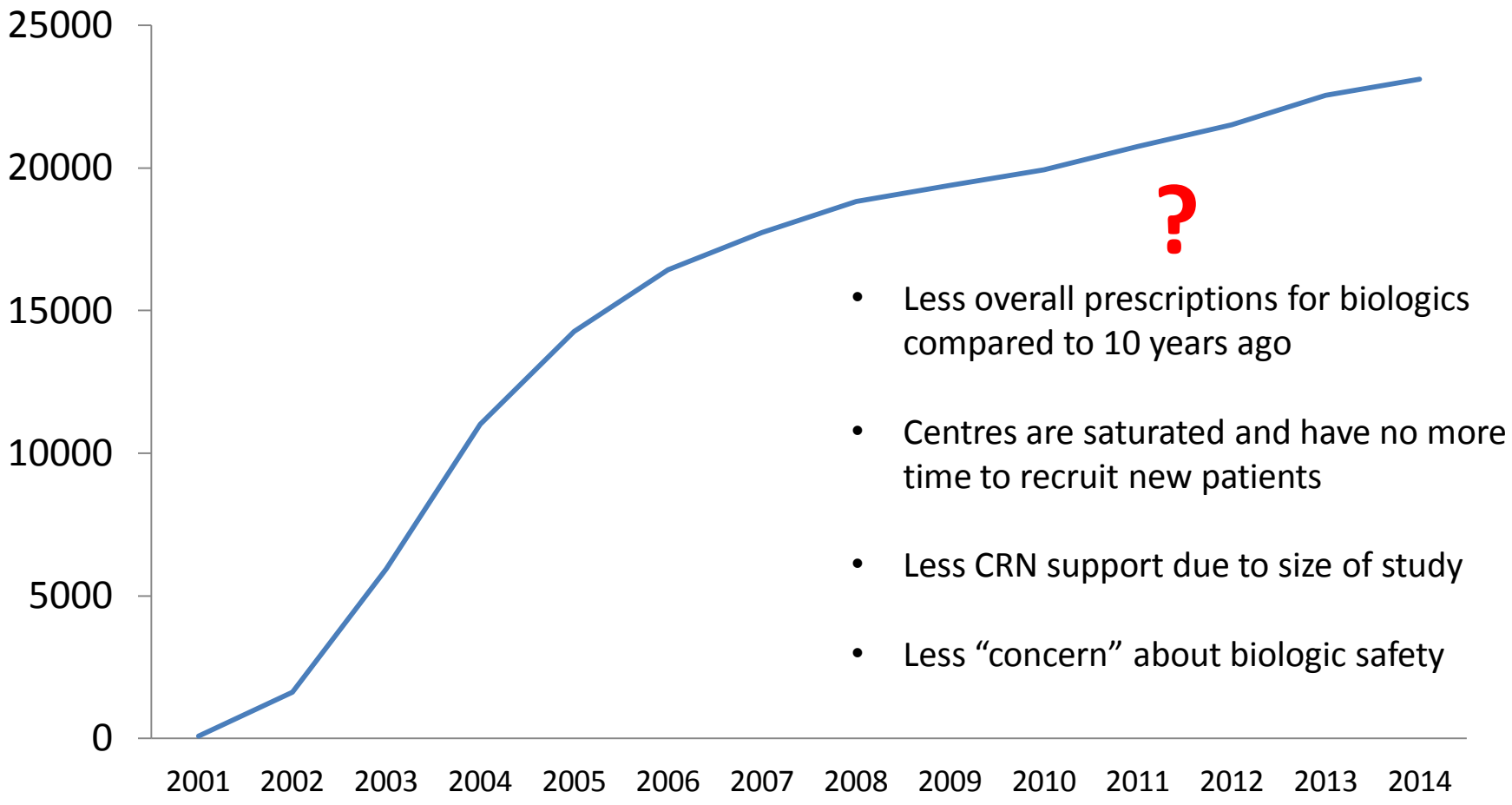


BSRBR-RA Recruitment



BSRBR

The British Society for Rheumatology Biologics Registers

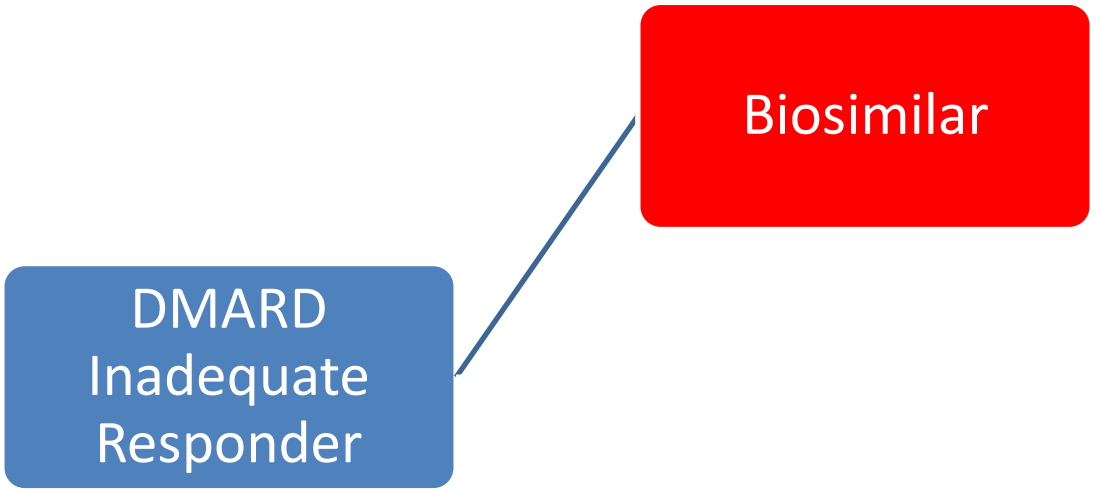
Rheumatoid Arthritis

A new era for rheumatology with the launch of the first biosimilar product.

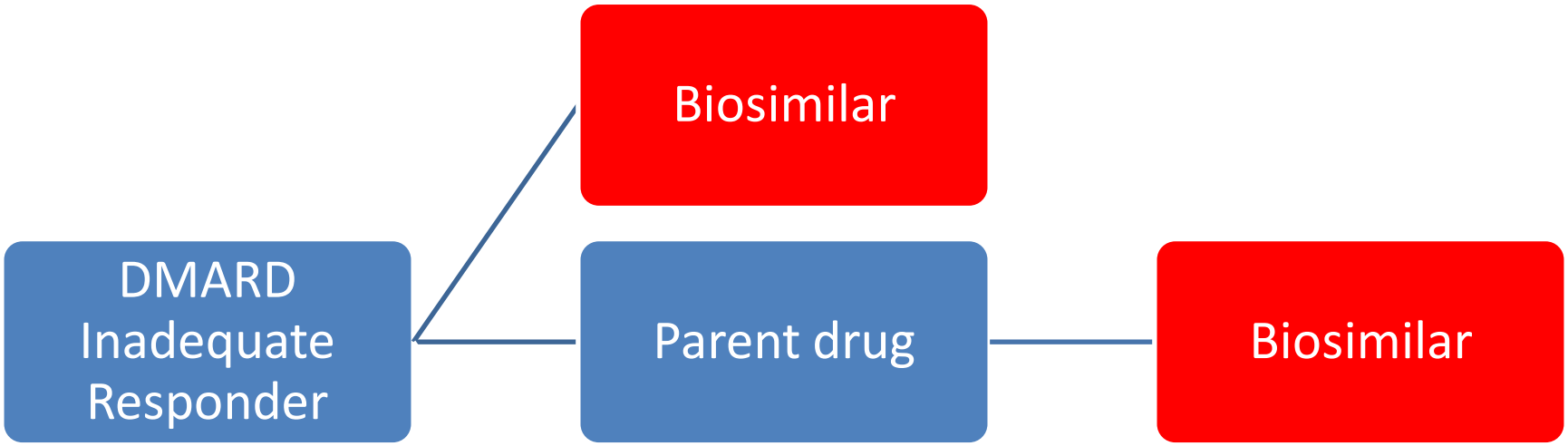
Biosimilars and the BSRBR-RA

DMARD Inadequate Responder

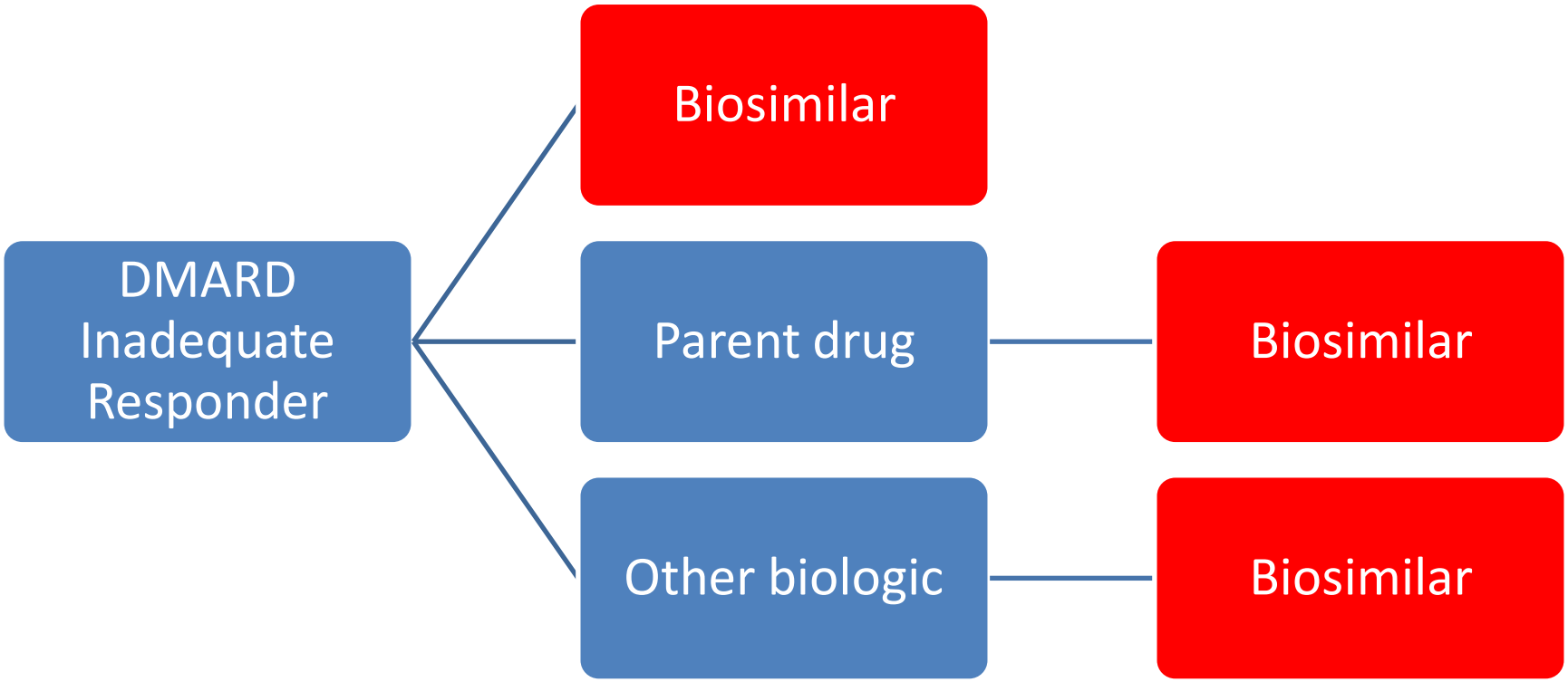
Biosimilars and the BSRBR-RA



Biosimilars and the BSRBR-RA



Biosimilars and the BSRBR-RA



Important to capture all exposures – regardless of point in pathway

Challenges in Capturing "Real-World" Biosimilar Exposure and Outcome Data

1. **Expected number of treated patients in currently unknown**

- May be small with increasing choice of therapies
- May be large if preferred treatment option

Centres must be supported in identifying and consenting patients and capturing data

Challenges in Capturing "Real-World" Biosimilar Exposure and Outcome Data

2. Patients receiving biosimilars must be identifiable

- Need to capture drugs based on trade names not generic names
- Batch numbers on drug packaging will identify the drug.
- Drug packaging is available in hospital (infusion therapy) but may not be if drug home delivered
- **This is true not only for our study, but also for the treating clinical team**

Challenges in Capturing "Real-World" Biosimilar Exposure and Outcome Data

3. **Exact date of "switch" must be available ideally with disease activity data captured at same time**

   – Will allow researchers to look at outcomes before and after change in therapy

   – But, exact date of switch may be unknown if drug is simply delivered to patient when current parent drug prescription nears its end

Challenges in Capturing "Real-World" Biosimilar Exposure and Outcome Data

4. **Loss of effectiveness should be captured in addition to side effects**

   - Frequency of capture of disease activity scores in an observational register can make differentiation between primary and secondary "failure" difficult
   - May need to capture more frequent data
   - But, our experience now shows that DAS28 is not measured routinely at the point of switching, especially if switching is automatic or independent of the hospital.

Challenges in Capturing "Real-World" Biosimilar Exposure and Outcome Data

5. What is the appropriate comparison?

- Patients starting the parent drug?
- Same patient's previous experience on parent drug?

- Will differ based on whether patients are starting a biosimilar de novo or switching from the parent drug

Summary

- Registers are a valuable source of “real-world” outcome data
- May be even more important for biosimilars given limited number of patients exposed at time of drug license
- Challenges in collecting and interpreting data
- Data collection must be supported
  - physicians, nurses, patients, trusts, drug companies, NHS

Acknowledgements

- UK Consultant Rheumatologists and Specialist Nurses
- NIHR Comprehensive Local Research Networks
- BSRBR Control Centre Consortium
- British Society for Rheumatology
- Arthritis Research UK Centre for Epidemiology, Manchester
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