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SCIENCE MEDICINES HEALTH

Epidemiology as an enabler for Health

Tenth Stakeholder forum on the Pharmacovigilance legislation
21st September 2016
European Medicines Agency London

Presenter: Dr Alison Cave
Pharmacovigilance and Epidemiology Department, EMA

Disclaimer

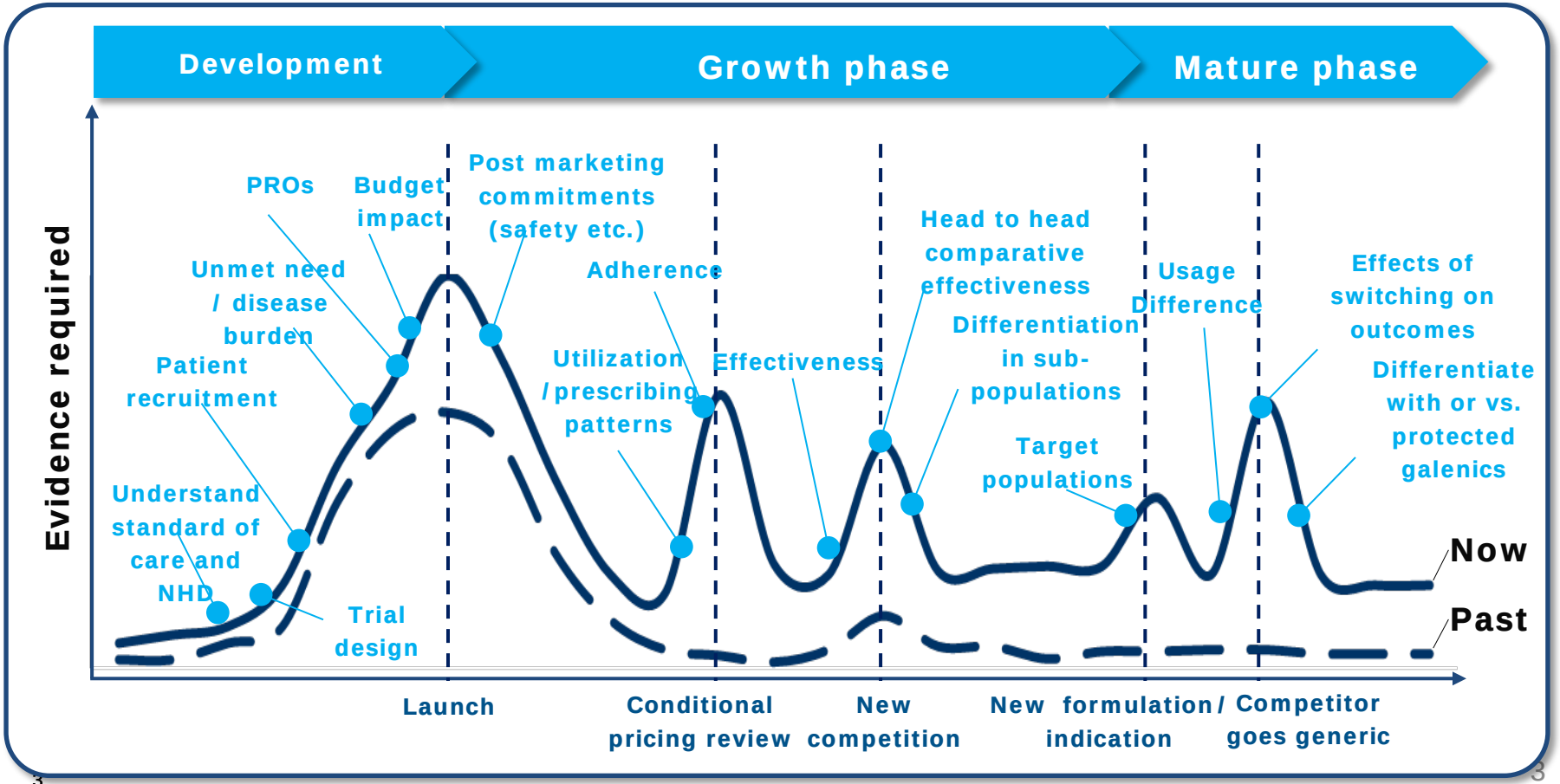
I am a full time employee of the European Medicines Agency

Epidemiology as an enabler for health

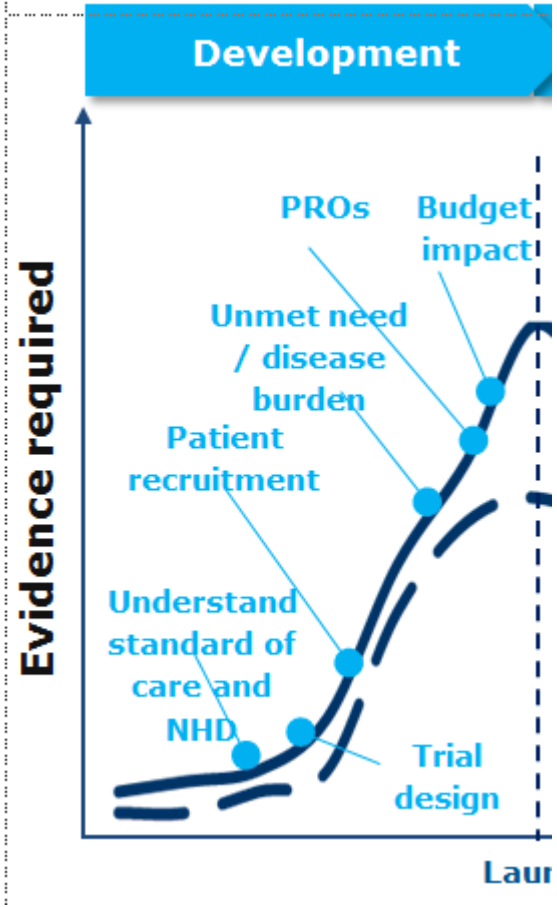
In this talk:

- What are the data needs across the life of a product?
- Data subtypes
- Power of data integration to drive innovation
- Initiatives to build capacity
- Key messages

What are the data needs across the life of a product?



Source: IMI GetReal



Medicines Development

- Population-based databases to characterize frequency and distribution of disease
- Identify the population to be treated
- Identify whether the disease effects high risk populations e.g. paediatrics
- Identify unmet medical need
- Identifying prevalence of disease (orphan medicines)
- Current standard of care
- Clinical trial recruitment
- Real World clinical trials

Salford Lung Study – Real World Trial

ORIGINAL ARTICLE

Effectiveness of Fluticasone Furoate–Vilanterol for COPD in Clinical Practice

Jørgen Vestbo, D.M.Sc., David Leather, M.B., Ch.B., Nawar Diar Bakerly, M.D., John New, M.B., B.S., J. Martin Gibson, Ph.D., Sheila McCorkindale, M.B., Ch.B., Susan Collier, M.B., Ch.B., Jodie Crawford, M.Sc., Lucy Frith, M.Sc., Catherine Harvey, D.Phil., Henrik Svedsater, Ph.D., and Ashley Woodcock, M.D., for the Salford Lung Study Investigators*

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2012; **21**: 261–268
Published online 3 November 2011 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.2243

ORIGINAL REPORT

Health problems most commonly diagnosed among young female patients during visits to general practitioners and gynecologists in France before the initiation of the human papillomavirus vaccination program

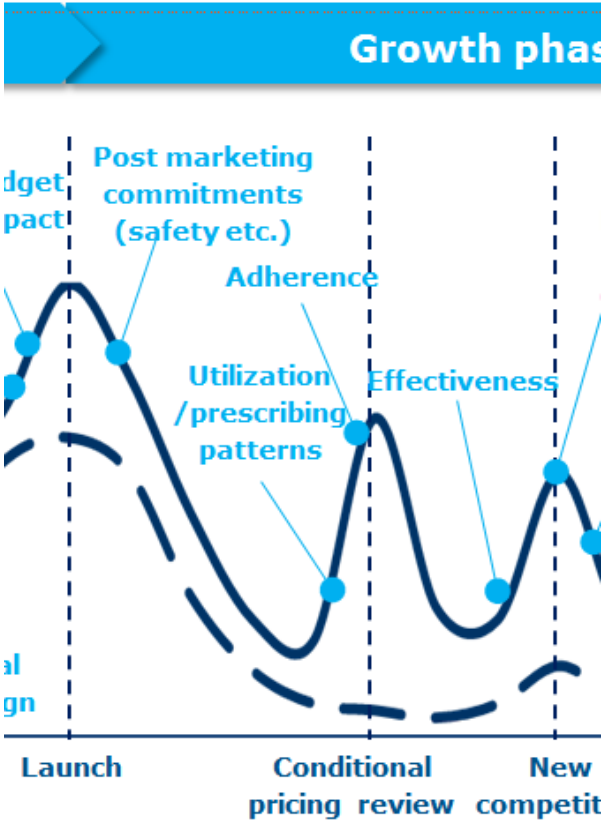
Eric Van Ganse[1]*, Laurent Letrilliart[2], Hélène Borne[3], Francois Morand[4], Matthieu Robain[4] and Claire Anne Siegrist[5]

Published in final edited form as:
Lancet. 2009 December 19; 374(9707): 2115–2122. doi:10.1016/S0140-6736(09)61877-8.

Disease Epidemiology

Importance of background rates of disease in assessment of vaccine safety during mass immunisation with pandemic H1N1 influenza vaccines

Steven Black, Juhani Eskola, Claire-Anne Siegrist, Neal Halsey, Noni MacDonald, Barbara Law, Elizabeth Miller, Nick Andrews, Julia Stowe, Daniel Salmon, Kirsten Vannice, Hector S Izurieta, Aysha Akhtar, Mike Gold, Gabriel Oselka, Patrick Zuber, Dina Pfeifer, and Claudia Vellozzi



At and Following Authorisation

- The EU Risk Management Plan is key to driving proactivity and promoting better targetted studies
  - Safety Specification – important known and potential risks + missing information
  - Pharmacovigilance Plan – routine PhV + additional studies
  - +/- Risk Minimisation Plan – including effectiveness measures
- Future – Benefit risk management plans

At and Following Authorisation

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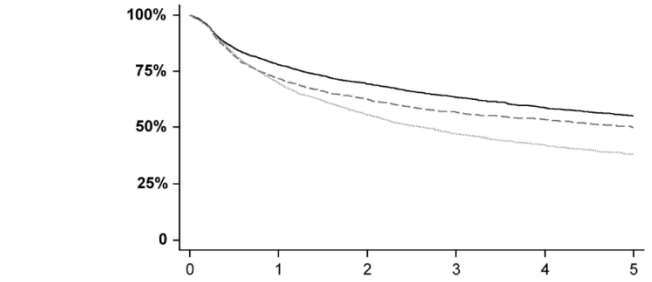
Journal of Obesity
Volume 2011, Article ID 459263, 7 pages
doi:10.1155/2011/459263

Research Article

Usage, Risk, and Benefit of Weight-Loss Drug

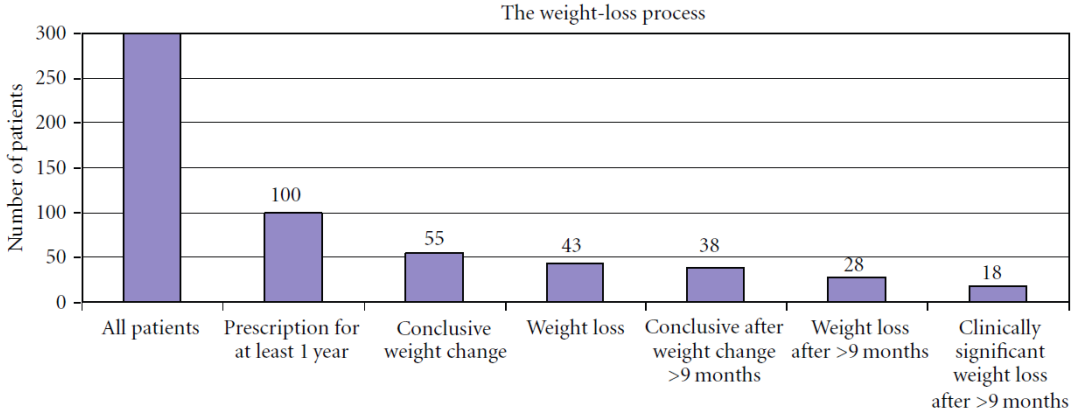
Tomas Forslund,[1] Pauline Raaschou,[2] Paul Hjemdahl,[2] Ingvar Krakau,[3] and Björn Wettermark[4]



Number at Risk (Discontinuations)

Etanercept	3892	(823)	2677	(266)	1924	(151)	1446	(94)	1027	(57)	712
Adalimumab	2349	(632)	1462	(169)	1034	(88)	766	(41)	577	(33)	418
Infliximab	2898	(824)	1730	(320)	1110	(157)	791	(74)	587	(53)	415

Adj. Hazard Ratios (95%CI)	0-1y	>1-1.9y	2-5y	0-5y
-Adalimumab vs Etanercept	1.37 (1.23-1.52)	1.18 (.97-1.44)	1.00 (.84-1.20)	**1.26 (1.16-1.37)**
-Infliximab vs Etanercept	1.48 (1.34-1.64)	2.02 (1.70-2.40)	1.70 (1.46-1.99)	**1.63 (1.51-1.77)**
-Infliximab vs Adalimumab	1.10 (.99-1.23)	1.65 (1.36-2.00)	1.67 (1.40-2.00)	**1.28 (1.18-1.40)**



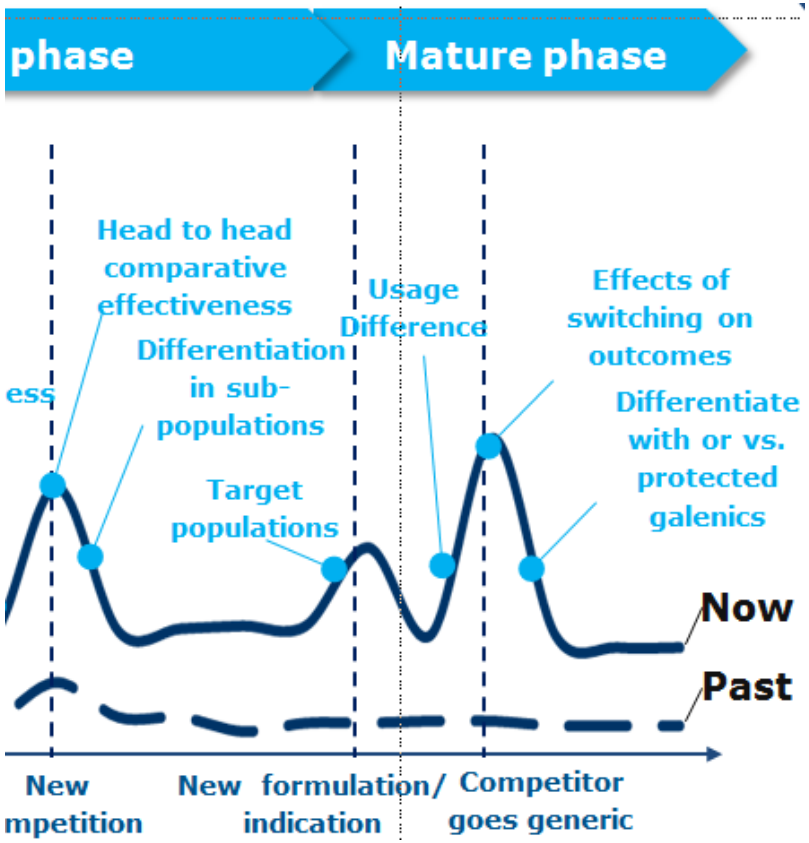
Clinical and epidemiological research

OPEN ACCESS

EXTENDED REPORT

Drug survival on TNF inhibitors in patients with rheumatoid arthritis comparison of adalimumab, etanercept and infliximab

M Neovius,[1] E V Arkema,[1] H Olsson,[1] J K Eriksson,[1] L E Kristensen,[2] J F Simard,[1] J Askling,[1,3] for the ARTIS Study Group



Post-authorisation safety

- The entire evidence hierarchy
- Detecting signals (new or changing safety issues)
- Confirming signals e.g: observed vs. expected; impact / burden
- Continuous safety monitoring in real world
- Formal association studies in case control, cohort, etc
- Assessing rare, delayed or chronic exposure adverse reactions
- Effectiveness studies
- Health outcome and HTA studies

Post-authorisation safety

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The New England Journal of Medicine

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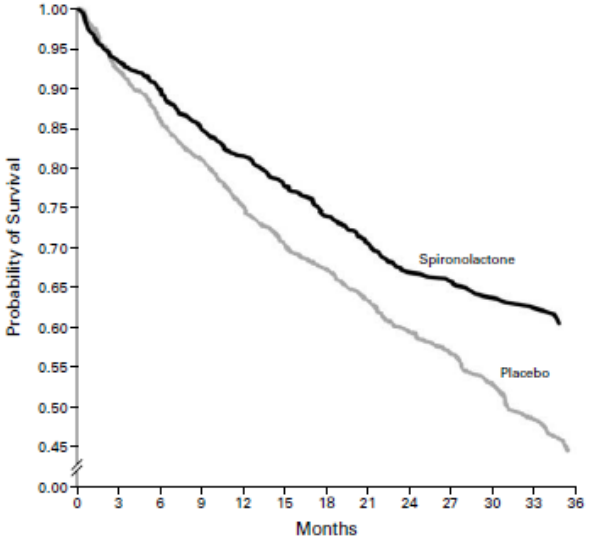
VOLUME 341 SEPTEMBER 2, 1999 NUMBER 10

THE EFFECT OF SPIRONOLACTONE ON MORBIDITY AND MORTALITY IN PATIENTS WITH SEVERE HEART FAILURE

BERTRAM PITT, M.D., FAIEZ ZANNAD, M.D., WILLEM J. REMME, M.D., ROBERT CODY, M.D., ALAIN CASTAIGNE, M.D., ALFONSO PEREZ, M.D., JOLIE PALENSKY, M.S., AND JANET WITTES, PH.D., FOR THE RANDOMIZED ALDACTONE EVALUATION STUDY INVESTIGATORS*



No. at Risk													
Placebo	841	775	723	678	628	592	565	483	379	280	179	92	36
Spironolactone	822	766	739	698	669	639	608	526	419	316	193	122	43

Figure 1. Kaplan–Meier Analysis of the Probability of Survival among Patients in the Placebo Group and Patients in the Spironolactone Group.
The risk of death was 30 percent lower among patients in the spironolactone group than among patients in the placebo group (P<0.001).

RALES: RCT 25mg spironolactone + usual treatment *v* placebo + usual treatment

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Rates of Hyperkalemia after Publication of the Randomized Aldactone Evaluation Study

David N. Juurlink, M.D., Ph.D., Muhammad M. Mamdani, Pharm.D., M.P.H., Douglas S. Lee, M.D., Alexander Kopp, B.A., Peter C. Austin, Ph.D., Andreas Laupacis, M.D., and Donald A. Redelmeier, M.D.

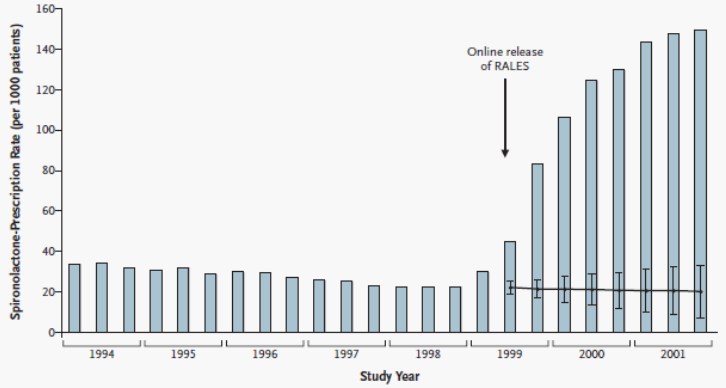


Figure 1. Rate of Prescriptions for Spironolactone among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.

Each bar shows the observed spironolactone-prescription rate per 1000 patients during one four-month interval. The line beginning in the second interval of 1999 shows projected prescription rates derived from interventional autoregressive integrated moving-average (ARIMA) models, with I bars representing the 95 percent confidence intervals.

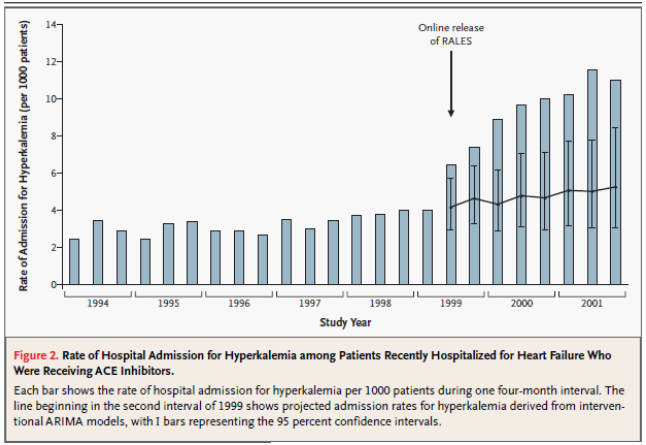


Figure 2. Rate of Hospital Admission for Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.

Each bar shows the rate of hospital admission for hyperkalemia per 1000 patients during one four-month interval. The line beginning in the second interval of 1999 shows projected admission rates for hyperkalemia derived from interventional ARIMA models, with I bars representing the 95 percent confidence intervals.

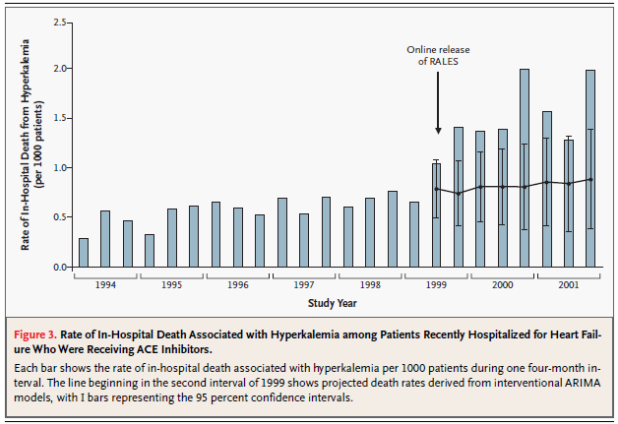


Figure 3. Rate of In-Hospital Death Associated with Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.

Each bar shows the rate of in-hospital death associated with hyperkalemia per 1000 patients during one four-month interval. The line beginning in the second interval of 1999 shows projected death rates derived from interventional ARIMA models, with I bars representing the 95 percent confidence intervals.

Post-RALES: Spironolactone use & outcomes in community practice, Ontario, Canada

What are the available datasources?

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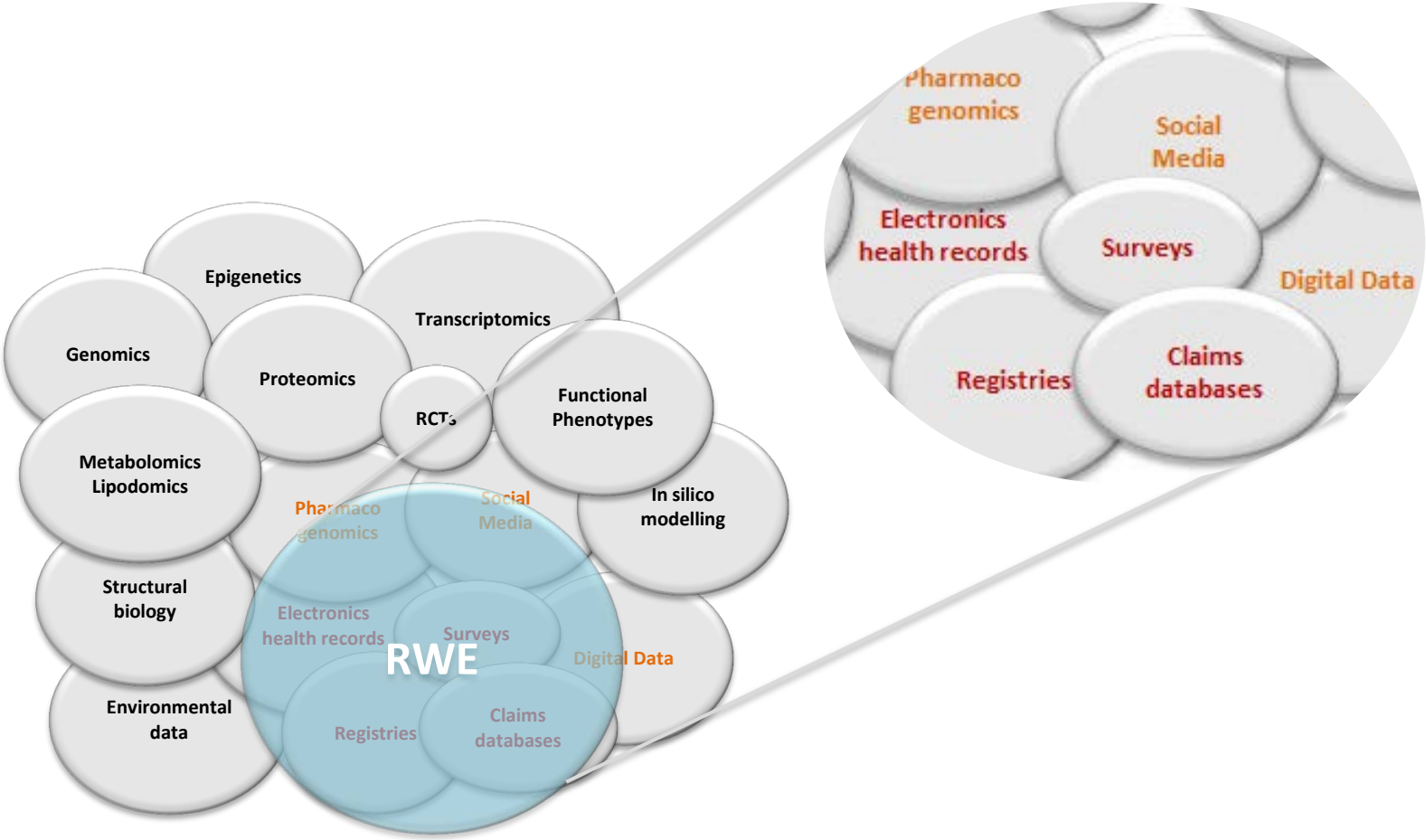
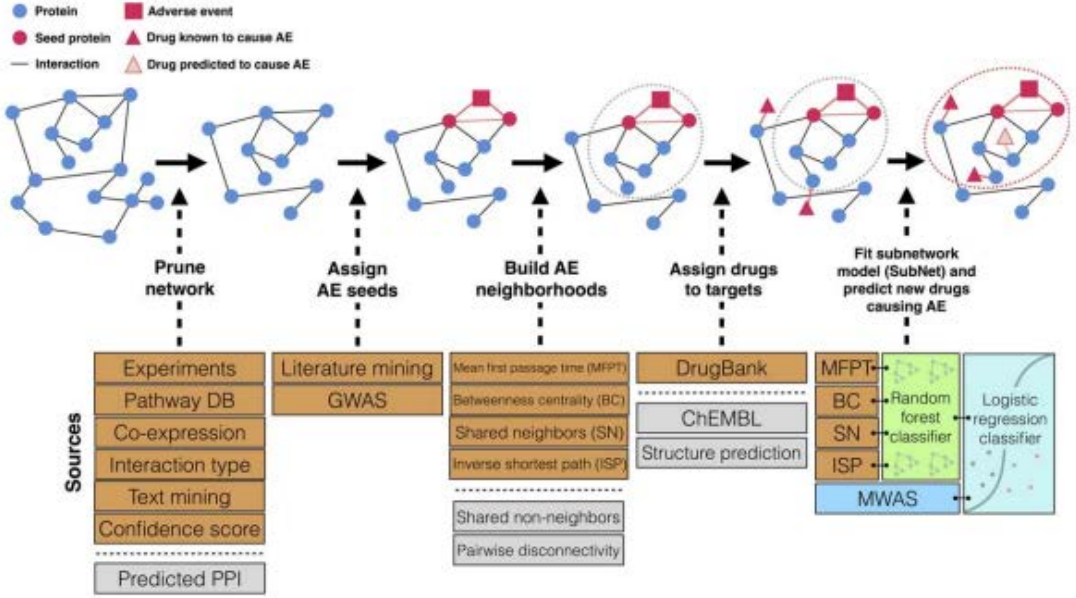
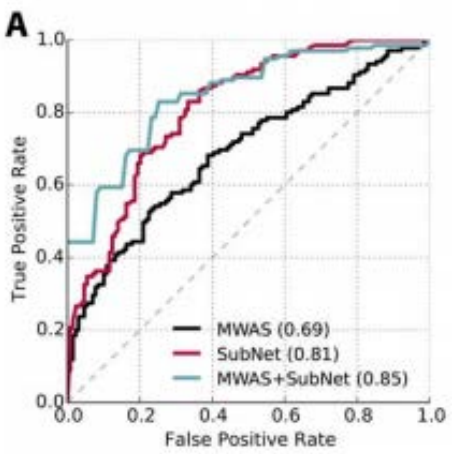


Example – Systems pharmacology

- Using data on drug's target proteins and pathways to guide ADR detection





Lorberbaum T, Nasir M, Keiser M, Vilar S, Hripsak G, Tatonetti N. Systems pharmacology augments drug safety surveillance. Clin Pharm & Ther 2015: 97(2): 151-158

Looking to the future: Data Linkage to Provide Additional Insight

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A Systematic Review of Economic Evaluations of Pharmacogenetic Testing for Prevention of Adverse Drug Reactions

Catrin O. Plumpton, Daniel Roberts, Munir Pirmohamed, Dyfrig A. Hughes

Integration of genomics into the electronic health record: mapping terra incognita

Joseph L. Kannry MD & Marc S. Williams MD

Genetics in Medicine (2013) **15**, 757–760 | doi:10.1038/gim.2013.102
Received 15 June 2013 | Accepted 17 June 2013

emerge network
ELECTRONIC MEDICAL RECORDS AND GENOMICS

i2b2
Informatics for Integrating Biology & the Bedside

U-PGx | Ubiquitous Pharmacogenomics

But

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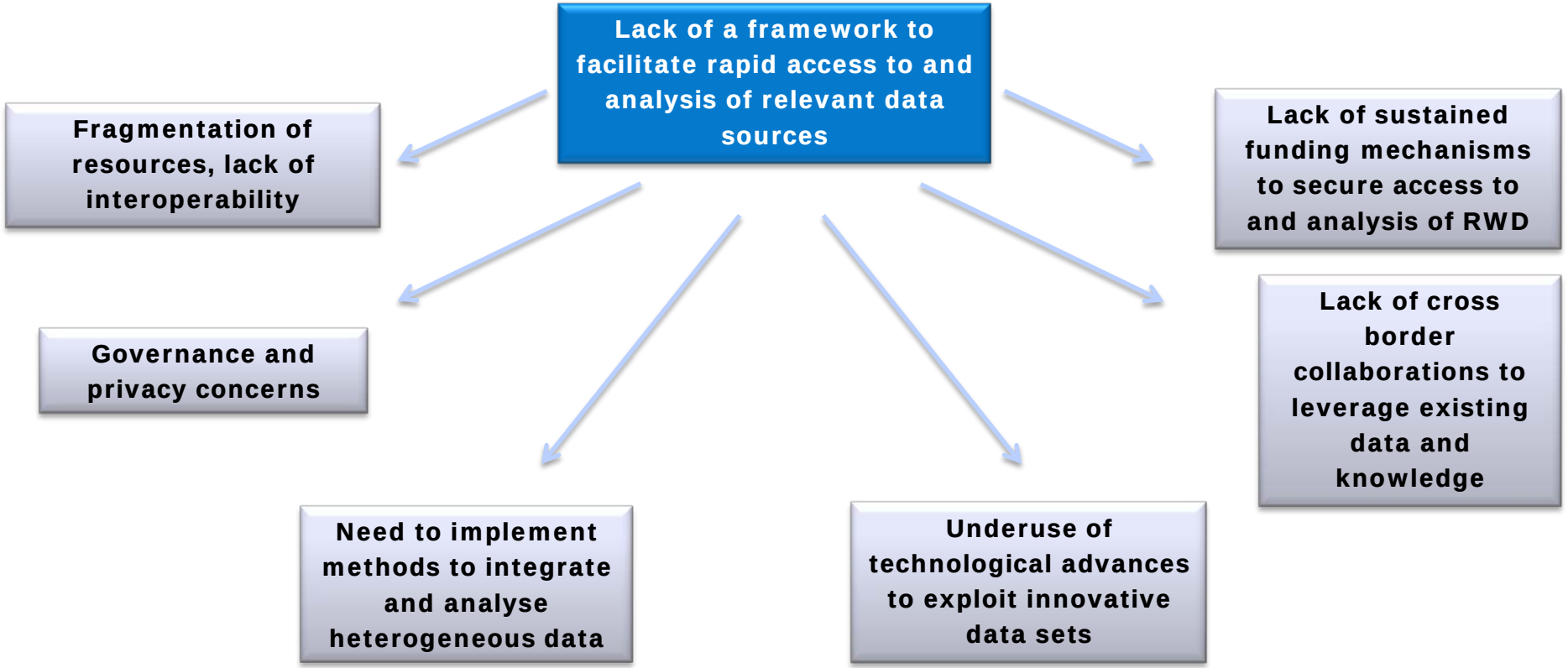
There is limited access to RWE across the EU to support decision making



What is the current European landscape?

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Looking to the future

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Collaboration between stakeholders can support access to and analysis of an extensive range of multi-national real world data to optimise medicines development and decision making

Patient Registry Initiative

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Patient registries

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Patient registries are organised systems that use observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, and that is followed over time. Patient registries can play an important role in monitoring the safety of medicines. The European Medicines Agency (EMA) has set up an initiative to make better use of existing registries and facilitate the establishment of high-quality new registries if none provide adequate source of post-authorisation data for regulatory decision-making.

The **patient registry** initiative will explore ways of expanding the use of patient registries by introducing and supporting a more **systematic and standardised approach** to their contribution to the benefit-risk evaluation of medicines within the European Economic Area.

Related documents

- Briefing note to marketing authorisation holders/applicants on the European Medicines Agency Patient Registry Initiative (15/04/2016)
- Initiative for patient registries - Strategy and pilot phase

PARENT
cross-border
PAtient REgistries iNiTiative

Benefits of planning and embracing epidemiology

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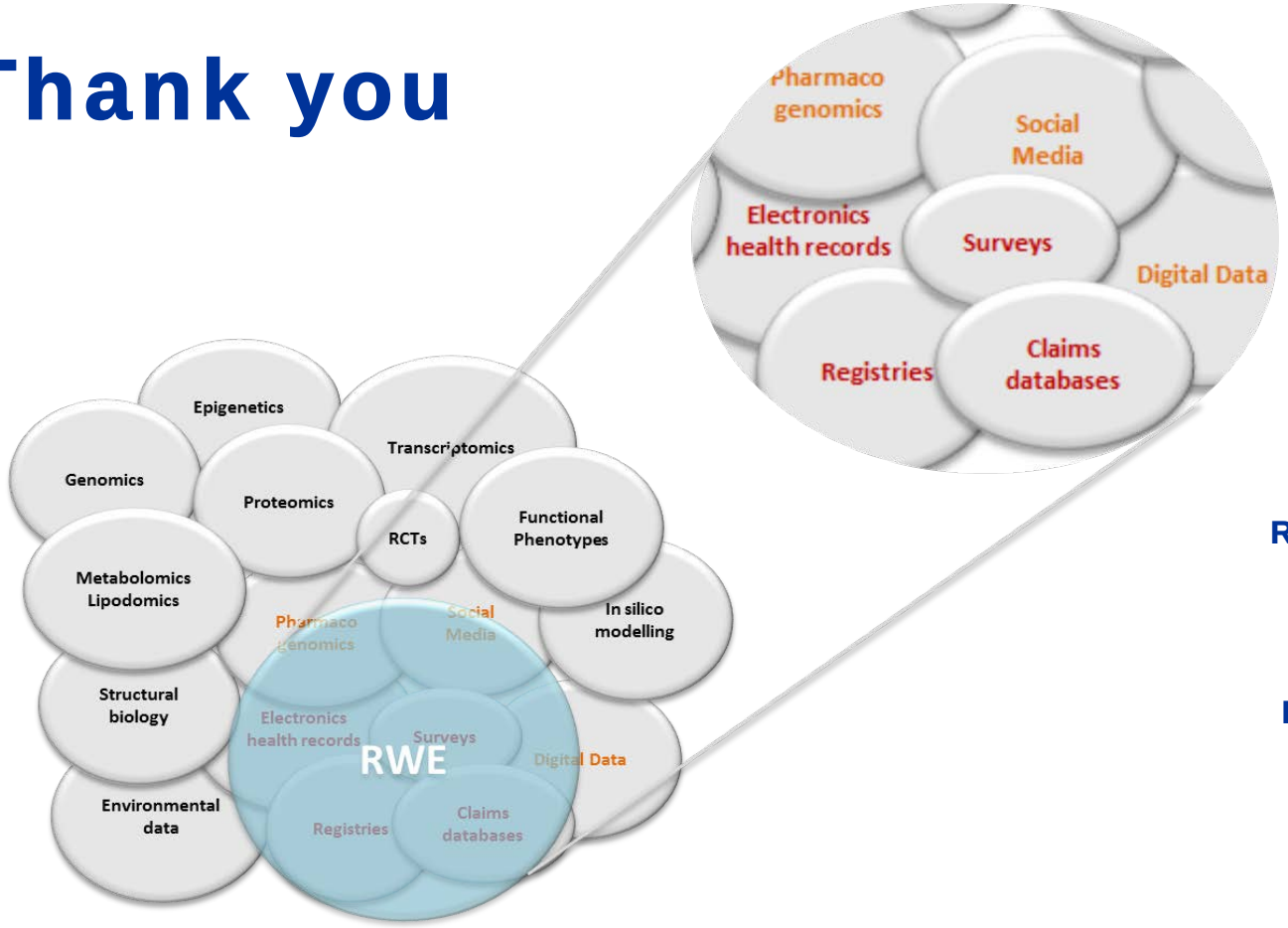
- Improved access to real world data
- Reducing cost of development
- Enabling innovation
- Optimise indications
- Safe, accelerated access to medicines
- New outcome measures
- Effectiveness data
- Improved EMA and HTA decision making
- Patient stratification for benefit and risk
- Faster identification and assessment of safety issues
- Determining safety and efficacy in high risk groups
- Ability to define the impact of regulatory / HTA decisions
- Optimising use of medicines through ongoing monitoring

Key messages

- Pharmacoepidemiology and pharmacovigilance play critical roles in medicines regulation
- Planning data collection and integrating knowledge starts in early development and is life-long
- It is critical to embrace the evidence spectrum: different data and methods are best to address different questions
- Use of real world evidence holds great promise to support drug development and in the fulfilment of unmet needs
- Further integration of big datasets with real world data holds further promise for the future.

Thank you



Registries workshop
28th October

Big Data Workshop
14-15th November

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Fluoroquinolones + Retinal Detachment

Study name	Rate ratio	Lower limit	Upper limit	p-Value
Etminan et al, 2012 (case-control)	4.50	3.56	5.69	0.00
Fife et al, 2014 (case-control_CCAE)	1.39	1.01	1.91	0.04
Fife et al, 2014 (case-control_Optum)	1.19	0.68	2.07	0.54
Kapoor et al, 2014 (cohort)	1.82	0.26	12.89	0.55
Eftekhari et al, 2014 (cohort)	0.56	0.08	4.03	0.56
Pasternak et al, 2013 (cohort)	1.29	0.53	3.13	0.57
Kuo et al, 2014 (cohort)	2.07	1.45	2.96	0.00
Chui et al, 2014 (case series)	1.26	0.65	2.46	0.50
Fife et al, 2014 (case series_CCAE)	1.13	0.99	1.29	0.07
Fife et al, 2014 (case series_Optum)	0.85	0.66	1.09	0.20
	1.47	0.95	2.27	0.09

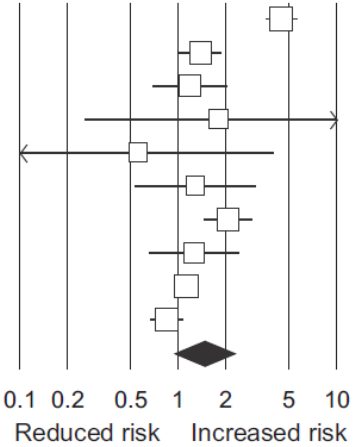

Fig. 2. Pooled rate ratio and 95% CI of retinal detachment associated with fluoroquinolones.

Alves C, Penedones A, Mendes D, Marques F. A systematic review and meta-analysis of the association between system fluoroquinolones and retinal detachment. Acta Ophthalmol. 2016: 19: e251-e259

A key RWE platform for efficacy / safety studies

- Use of existing disease registries to identify natural history of the disease, current SoC, resource utilisation, adherence to treatment.
- Potential to support single arm studies for rare diseases compared with outcomes inferred from disease registries
- Open label salvage studies in patients with no remaining therapeutic options, with the purpose of obtaining an expansion of the indication;
- Collection of efficacy and safety data from early access/compassionate use programs to supplement RCTs in small populations;
- Post-authorisation drug registries for effectiveness, long-term outcomes, drug utilisation, time to treatment failure and diagnosis confirmation

What is Available Data?

Termed Real World Evidence which is defined as data that are collected outside the constraints of conventional randomised clinical trials.

Opportunities for unmet medical need

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- Product development can fulfil unmet medical need. This is supported by robust planning of evidence generation where epidemiology is key:
  - Scientific advice for products in development
  - Risk management planning at authorisation and post-authorisation
- Hypothesis generation
  - Signalling safety issues
  - Creating new directions for research
- Supporting assumptions
  - Validation of surrogate outcomes
  - Validation of modelling and simulation
  - Extending clinical trial data
    - Longer term outcomes
    - Clinical pathways for HTA analyses
- Outcome evaluation of regulatory interventions
- Evaluation of safety concerns
- Evaluation of efficacy