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SCIENCE MEDICINES HEALTH

# What are the real-world evidence tools and how can they support decision making?

**EMA-EuropaBio Info Day – 22nd November 2016**

Dr Alison Cave,
Principal Scientific Administrator,
Pharmacovigilance and Epidemiology Department

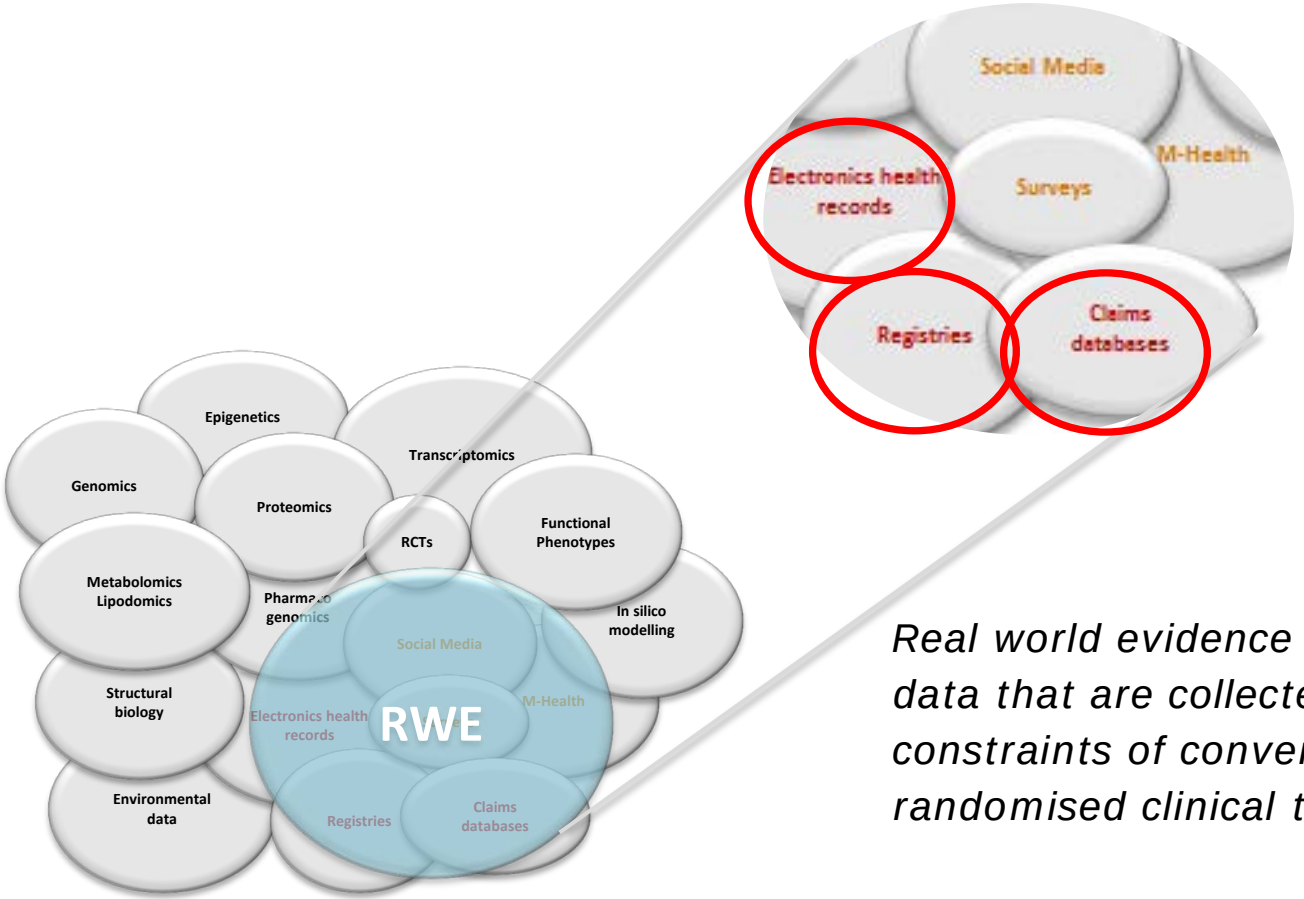
# Disclaimer

The views expressed in this presentation are my personal views and may not be understood or quoted as being made on behalf of or reflecting the position of the European Medicines Agency or one of its committees or working parties.

# Objectives

- **Which data and When?**
- **Opportunities for real world data**
- **Patient Registries Initiative**
- **Conclusions**

# Data – Which data and when?




*Real world evidence is defined as data that are collected outside the constraints of conventional randomised clinical trials.*

# RWE - What are the Opportunities across the product life cycle?

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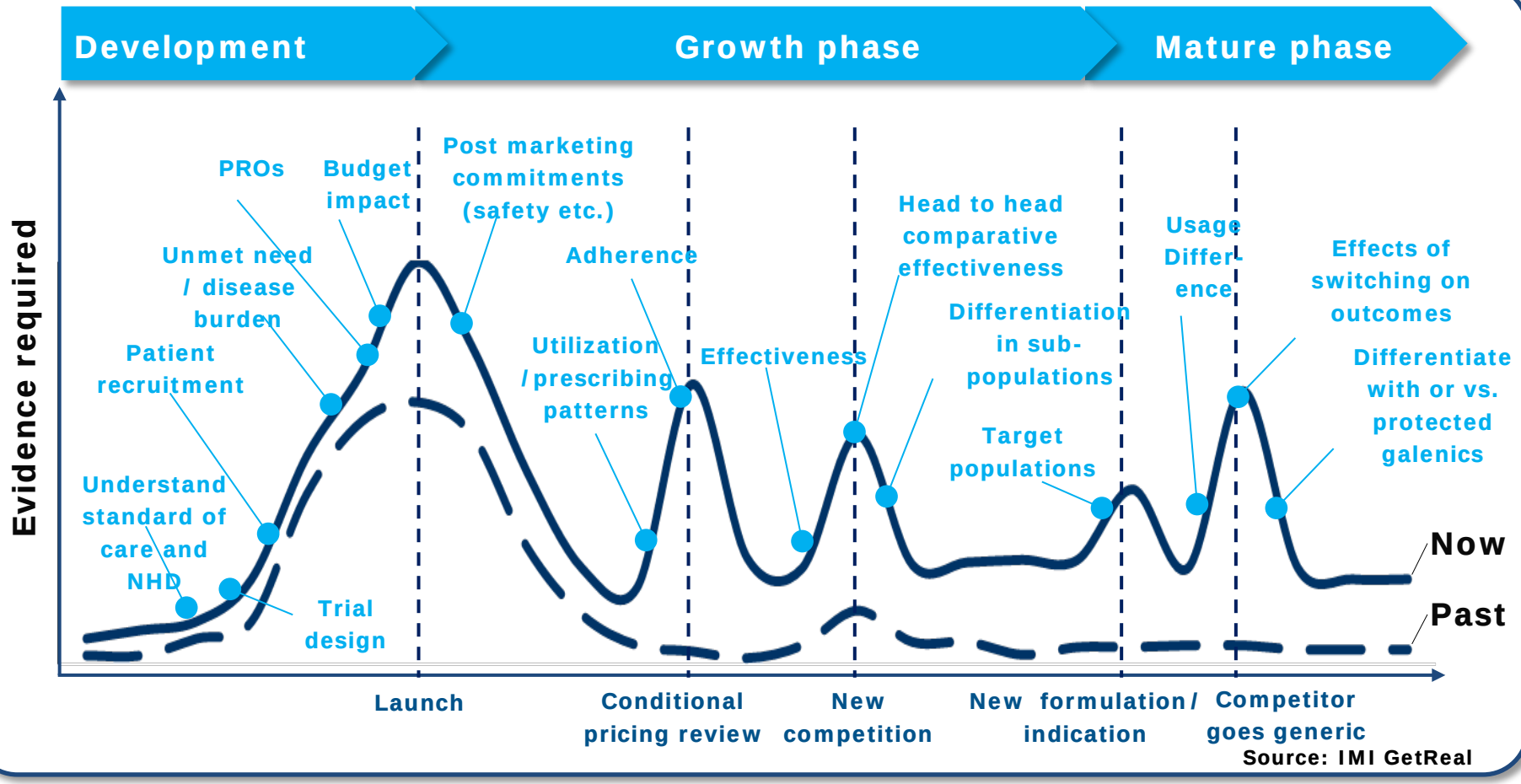
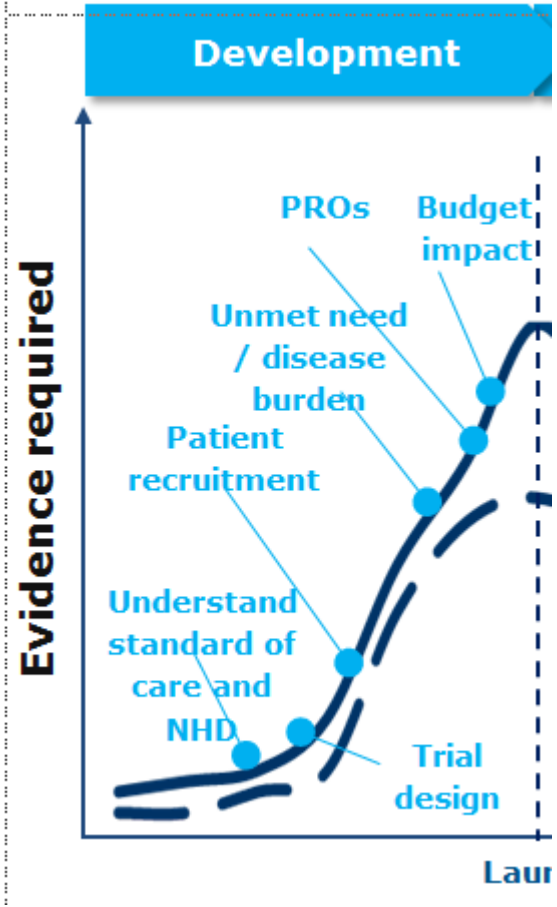
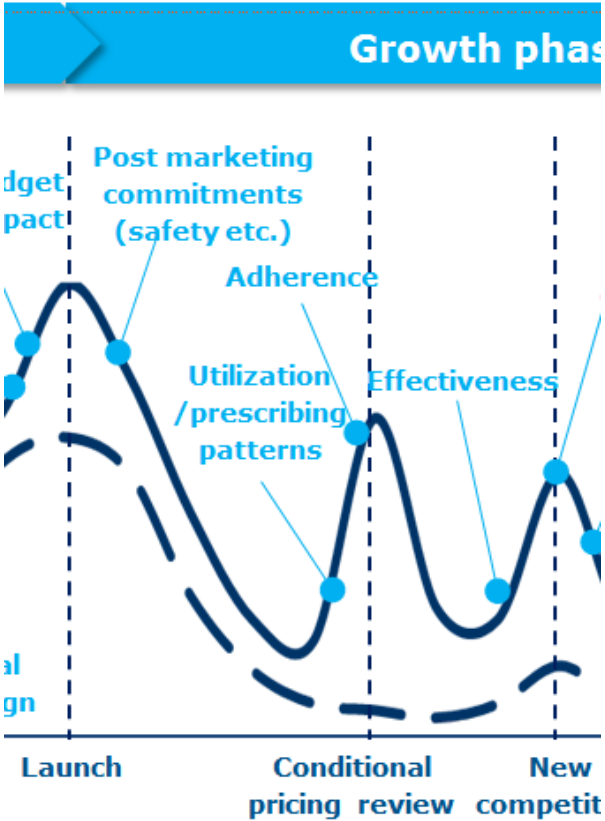



Source: IMI GetReal



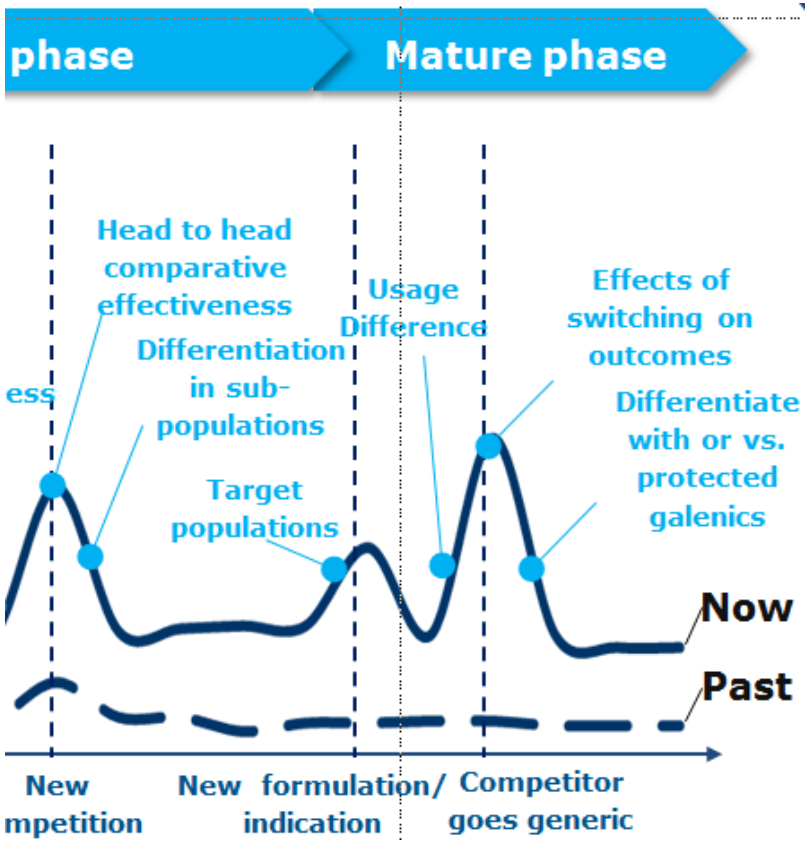

## Medicines Development

- 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




## 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




# 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

# Data – Which data and when?

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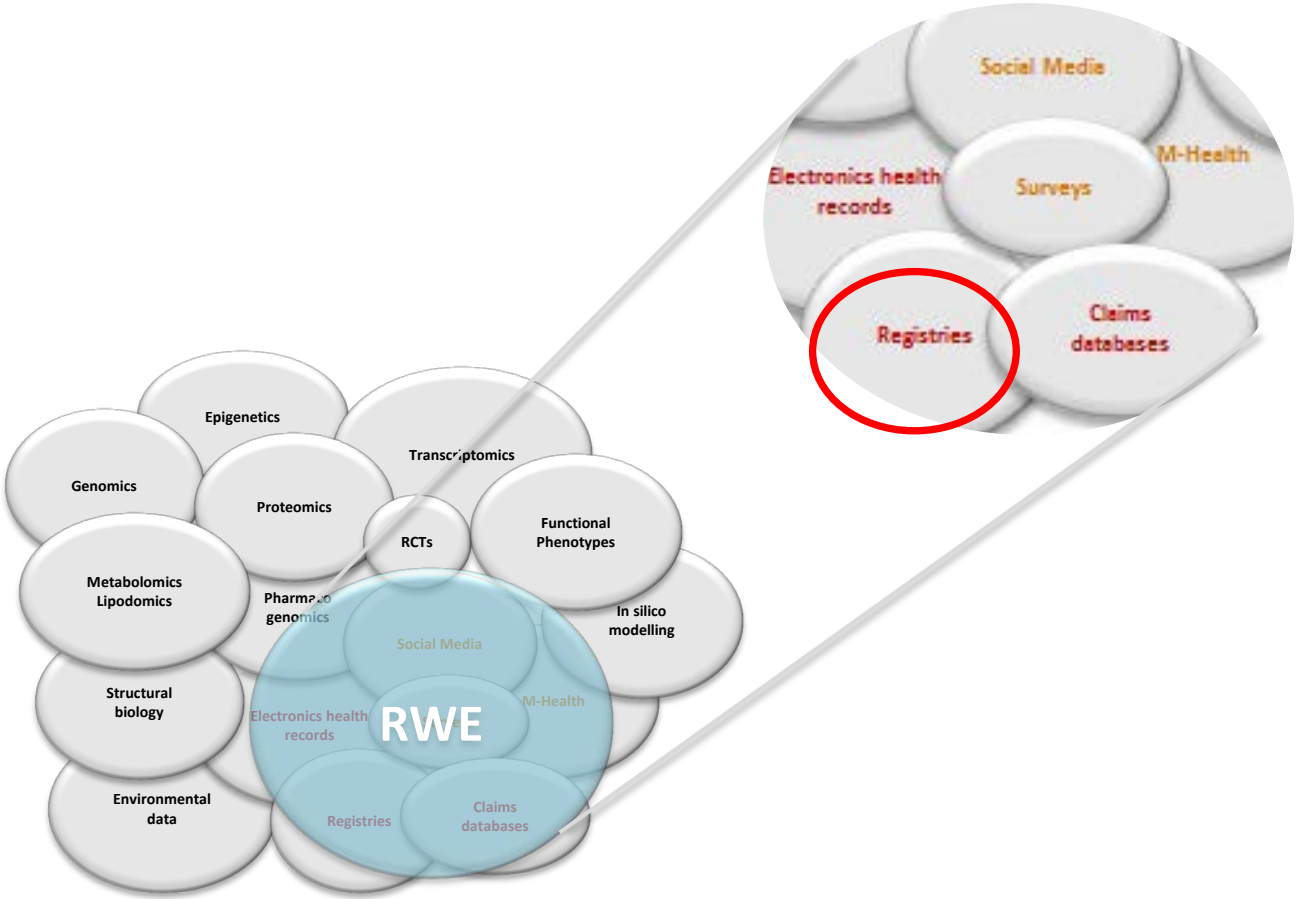

# Registry roles

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**Multiple:**

- **Describe natural history of a disease**
- **Determine clinical effectiveness of healthcare products / services**
- **Measure / monitor safety / harm**
- **Measure quality of care**

**All may inform research and medicines approval & monitoring**

# EMA Activities: Registry analysis 2005-2013

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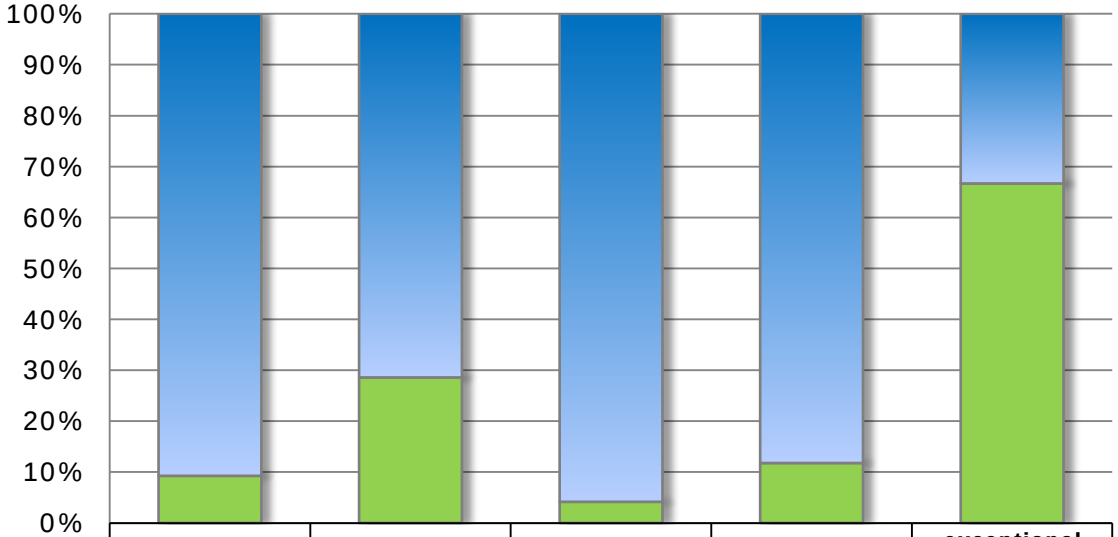
**Registry Analysis 2005-2013:**

**Determined number of registries imposed as an obligation at the time of authorisation from 2005-2013**




| | all (n=335) | orphan (n=70) | non-orphan (n=265) | conditional (n=17) | exceptional circumstances (n=21) |
|---|---|---|---|---|---|
| no registry | 304 | 50 | 254 | 15 | 7 |
| registies | 31 | 20 | 11 | 2 | 14 |

# Registry analysis 2005-2013

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**Results**

## Registries characteristics

| Registries characteristics | N | % |
|---|---|---|
| Disease registry | 11 | 35 % |
| Product registry | 20 | 65 % |
| New registry | 24 | 77 % |
| Existing registry | 6 | 19 % |
| Both (combination of new and existing) | 1 | 3 % |

# Registry analysis 2005-2013

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**Results** → **Registry objectives**

| Primary objectives | N | % |
|---|---|---|
| Safety | 22 | 71 % |
| Effectiveness / efficacy | 3 | 10 % |
| Safety in pregnancy | 3 | 10 % |
| Other | 3 | 10 % |
| Secondary objective effectiveness / efficacy | 12 | 39 % |

# Registry analysis 2005-2013

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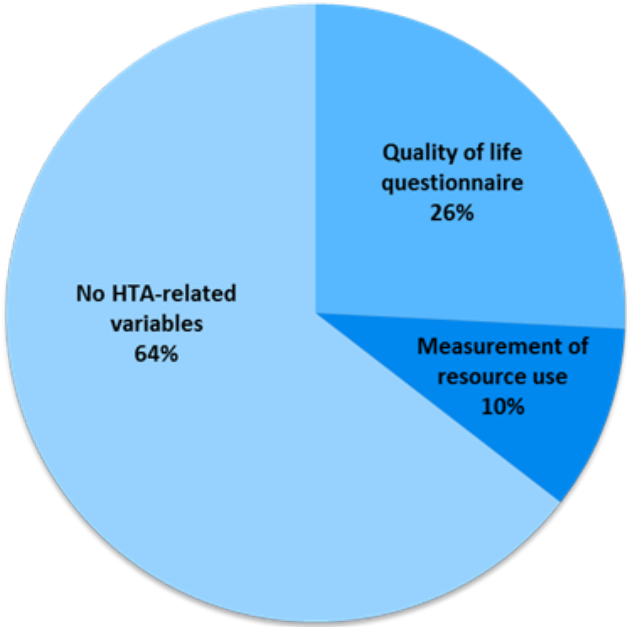
**Results**

**Collection of HTA-related variables in registry**



# Registry analysis 2005-2013

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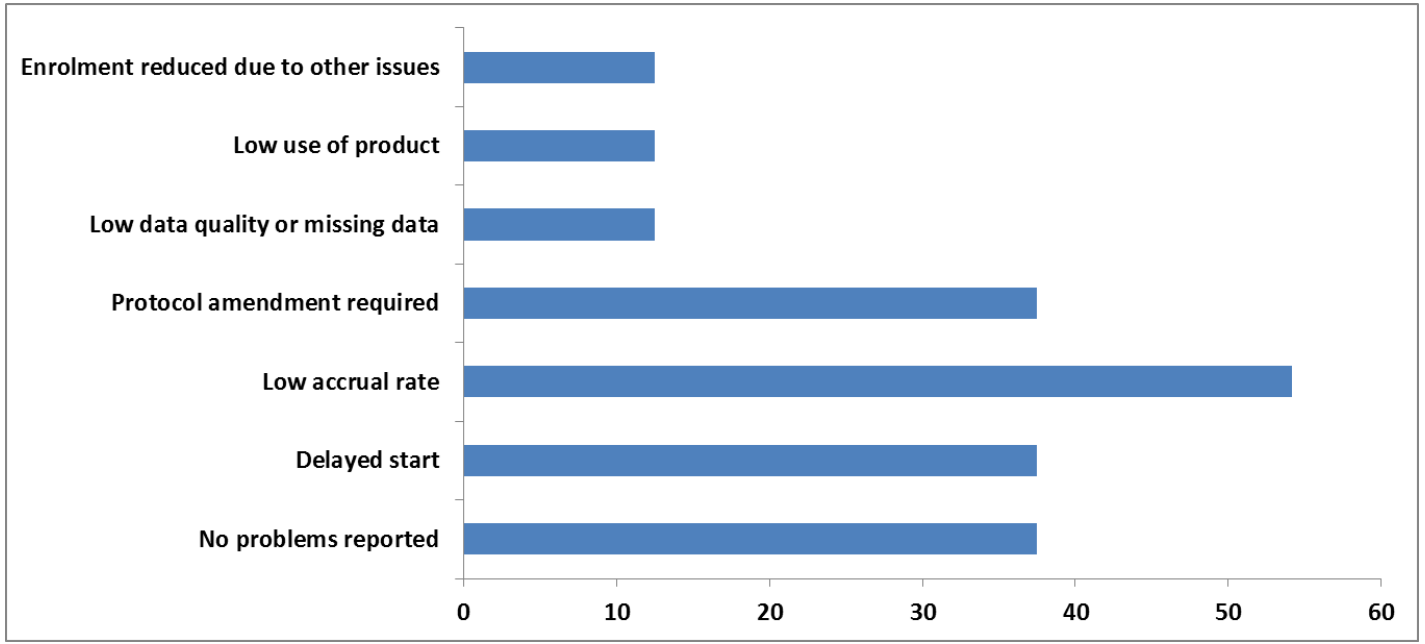
**Results**

## Problems reported with registries




- Percentages are based on a total of 24 registries that initiated patient inclusion.

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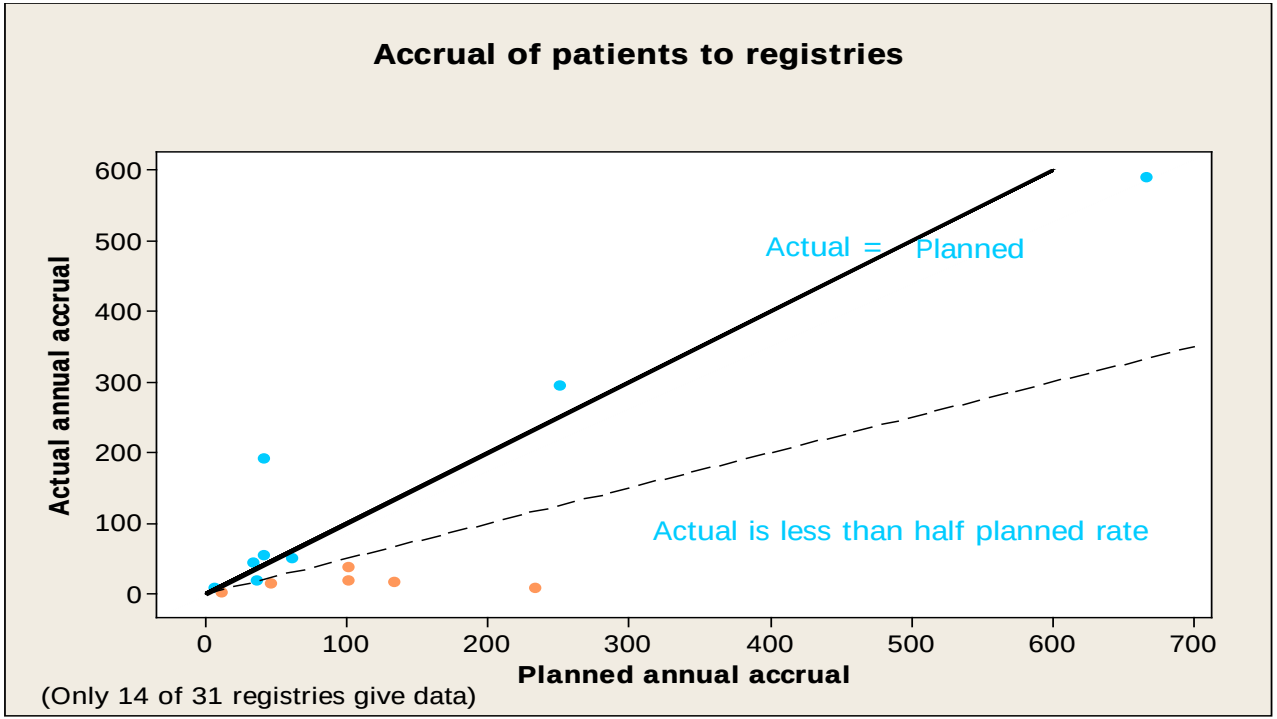
# Difference between planned numbers of patients and actual numbers of patients included



# Current Challenges with Registries

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- Majority of imposed registries are for orphan products and/or products approved under exceptional circumstances and imposed for safety reasons.
- Registries face challenges around:
  - Recruitment: lack of physician engagement due to administrative burdens, patient consent, low product usage and competing registries
  - Data Quality: compliance, study design, representativeness of registry population
  - Companies predominantly choose to establish individual product registries rather than utilise existing disease registries.
- This often results in duplication of effort, a likely slower resolution of the initial concern and multiple, relatively inflexible registries with limited application in the future
- Lack of sustainability of current disease registries

# EMA Strategy on Registries

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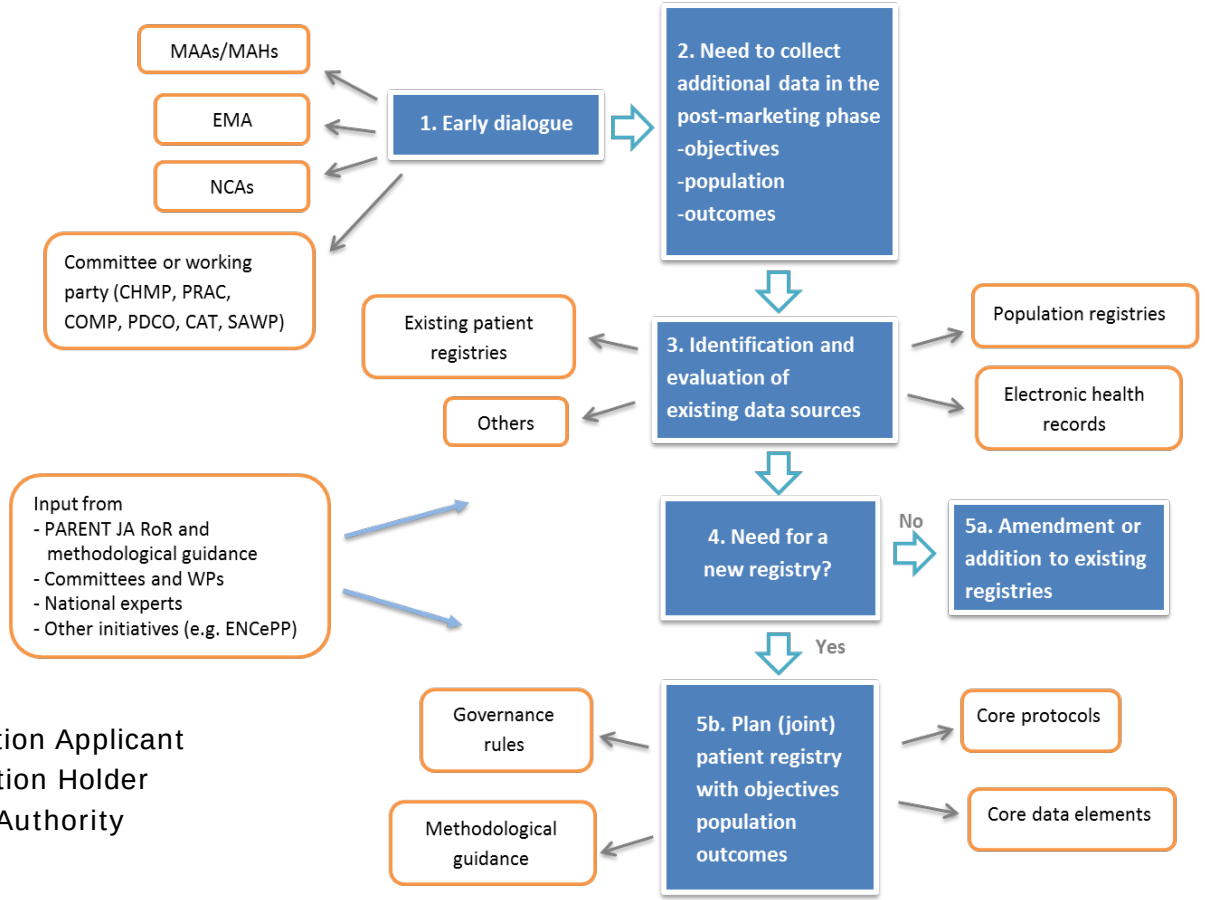


**MAA** = Marketing Authorisation Applicant
**MAH** = Marketing Authorisation Holder
**NCA** = National Competent Authority

# Status of Pilot Phase

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- Creation of a taskforce composed of representatives of EMA Scientific committees and working parties, the European Commission, experts from national competent authorities and EMA staff
- Currently >12 expressions of interest received (pharmaceutical companies and registry managers)
- Suitability of candidates discussed within the Cross-Committee Task Force
- Four case studies have been identified which together represent the need to
  - Establish a new registry
  - Use of an existing disease registry
  - Switching from product registry to disease registry

# Learnings to date

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Collaborations would be facilitated by:

- Early dialogue between the MAHs and registry owners
- Clear lines of communication between the stakeholders
- Definition of a clear protocol at an early stage in order that the registry can establish the feasibility of any collaboration
- Clear governance models to address issues such as consent and data ownership
- Clear information from the registry on the model of collaboration, structure, governance, data collection mechanisms and points of contact.

# Patient Registries Workshop

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Brought together registry owners, industry, HTA representatives, regulators to discuss solutions to better use existing patient registries that collect high-quality data from the use of medicines in clinical practice

**Aims**

- Identify the challenges faced by registries and industry when collaborating;
- Understand the technical challenges presented by disparate datasets;
- Identify solutions to best facilitate collaborations & avoid duplication.

**Output**

Recommendations for tools and standards to support a systematic and standardised approach to best use of registries, especially for post-marketing evaluation of safety & effectiveness - 2017


http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/10/news_detail_002627.jsp&mid=WC0b01ac058004d5c1

# Session 1: *Setting the scene*

## Challenges and Opportunities for Collaboration

**Session Chair: Peter Arlett,** EMA

| | |
|---|---|
| ***09.10-09.30*** | ***Challenges and Opportunities for Collaboration***<br>***European Society for Blood and Marrow Transplantation (EBMT)***<br>**Jürgen Kuball,** Head of Department, Hematology, University Medical Centre, Utrecht, The Netherlands |
| ***09.30-09.50*** | ***Ensuring sustainability***<br>**Jim Green**, President of the International Niemann-Pick Disease Registry, UK |
| ***09.50-10.05*** | ***Product versus disease registry – what drives the choice?***<br>**Jonathan Appleby,** Chief Scientific Officer, Rare Diseases Gene Therapy, GlaxoSmithKline, UK |
| ***10.05-10.20*** | ***The Health Technology Assessment perspective***<br>**François Meyer,** Director, International Affairs, Haute Autorité de la Santé, France and EUnetHTA |
| ***10.20-10.30*** | ***A Regulator's perspective***<br>**Nils Feltelius,** Member of the Rheumatology-Immunology Working Party (RIWP), Senior Expert and Clinical Assessor, Medical Products Agency, Sweden |
| ***10.30-11.00*** | ***Questions and panel discussion***<br>**Panel Moderators:**<br>**Sabine Straus**, Pharmacovigilance and Risk Management Committee (PRAC) member, staff member at the Medicines Evaluation Board, The Netherlands and Associate Professor at the Erasmus Medical Centre, Department of Medical Informatics, Rotterdam<br>**Peter Mol**, Vice-Chair, Scientific Advice Working Party (SAWP), Principal Clinical Assessor, Medicines Evaluation Board, The Netherlands |

# Summary of the challenges

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- Financial stability and sustainability of the registry
- Clarity of data ownership including linked data
- Data access
- Mismatch between the required standards for industry and registry
- Regulatory guidance to increase understanding among registries around MAH obligations and required data standards

# Session 2: Success factors for international collaborations

**Session Chair: Alison Cave,** EMA

| | |
|---|---|
| *11.20-11.40* | ***Standardisation of cancer registries data collection and validation at European level***<br>**Carmen Martos – Joint Research Centre (JRC), ISPRA, Italy** |
| *11.40-12.00* | ***The Pharmachild project: the PRINTO pharmacovigilance registry***<br>**Nicola Ruperto,** Pharmachild project, Genoa, Italy |
| *12.00-12.30* | ***Case Study:***<br>***Challenges of comparator groups and the role of disease registries in medicines development*** |
| 12.00-12.15 | **Jamie Geier**, Senior Director of Epidemiology, Pfizer Inc., USA |
| 12.15-12.30 | **Kimme Hyrich,** Principal Investigator of BSRBR-RA registry, Professor of Epidemiology, University of Manchester, UK |
| *12.30-13.00* | ***Questions and panel discussion***<br>**Panel Moderators:**<br>**Tomas Salmonson,** Chair, Committee for Medicinal Products for Human Use (CHMP), Senior Scientific Advisor, Medical Products Agency, Sweden<br>**Jan Span,** Member of the Cross-Committee Task Force on Registries and Senior Clinical Assessor, Medicines Evaluation Board, The Netherlands |

# Summary of the key success factors

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- Need for guidance on standardised data collection and coding
- Recoding of medicines information, response to treatment, changes in disease state etc
- Flexibility and capacity to accommodate methodological differences across multiple studies
- Defined contact points to facilitate communication
- Appropriate approvals/established governance to allow data access and sharing
- Feedback to healthcare professionals and participating families

# Session 3: Possible solutions

**Session Chair: Xavier Kurz,** EMA

| | |
|---|---|
| ***14.00-14.20*** | ***Is the answer active data extraction from hospital records?*** |
| | **Fergus Caskey** – Medical Director, UK Renal Registry |
| ***14.20-15.05*** | ***Integration of data across multiple data sources*** |
| 14.20-14:35 | **Jan Hillert**, Group Leader, Neurogenetics, Multiple Sclerosis, Karolinska Institute, Sweden |
| 14.35-14.50 | **Metka Zaletel,** PARENT Joint Action, Head of Health Data Centre, National Institute of Public Health, Slovenia |
| 14.50-15.05 | **Johan van Bussel**, Head of healthdata.be, Scientific Institute of Public Health, Brussels, Belgium |
| ***15.05-15.25*** | ***Designing integrated platforms for rare diseases research*** |
| | **Emma Heslop,** Project Manager, RD CONNECT, UK |

# Possible solutions



**……..to facilitate the consistent use of registry data for post-marketing evaluation of medicines.**

- Sustainable funding
- Need to establish common infrastructure/platform, consistent ontologies and common data elements
- European inter-operability framework principles
- Need for good governance and data management
- Need for bioinformatics and statistical skills
- Sharing of collaborative experiences

# Deliverables from the Workshop and the Initiative

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- An understanding of the challenges faced by registries and industry alike when collaborating
- An understanding of how regulators can better facilitate relations to avoid duplication of effort
- The identification and evaluation of existing data tools
- A toolkit of methodological guidelines building on those created by PARENT JA
- A review and evaluation of privacy and governance models

# Conclusions

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- Planning the collection of data and information is a critical success factor for product development throughout the lifecycle.
- Planning for the post-authorisation phase and for real-world evidence collection is as important as pre-authorisation and clinical trials.
- Scientific Advice provides a vehicle to bring stakeholders together and ensure expert input on planning data collection.
- The EMA initiative on patient registries was initiated based on the observation that 75% of all registries requested by regulators to industry were product registries. While we see increased interest from companies to collaborate with patient registries, registries coordinators will also need to raise to the challenge to establish mechanisms to facilitate such collaborations.
- Together with the EU regulatory network, the EMA is committed to play a role in this critical development. The workshop demonstrated that this involvement will include supporting initiatives to deliver maximum utility of registries for the benefit of all patients through better governance principles, better access to high quality data, facilitation of collaborations and mechanisms for sustainable funding.
- This will require a concerted effort from all stakeholders

# Thank you for your attention

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# Back up slides

## 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

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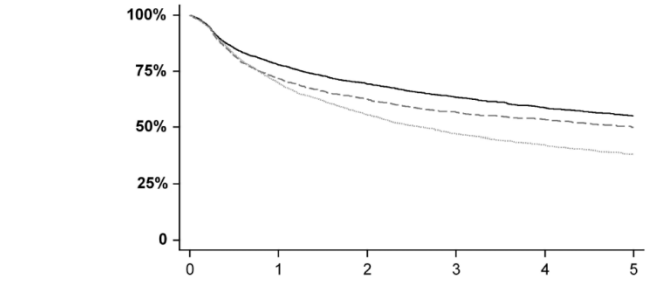
Journal of Obesity
Volume 2011, Article ID 459263, 7 pages
doi:10.1155/2011/459263

*Research Article*

## Usage, Risk, and Benefit of Weight-Loss Drug

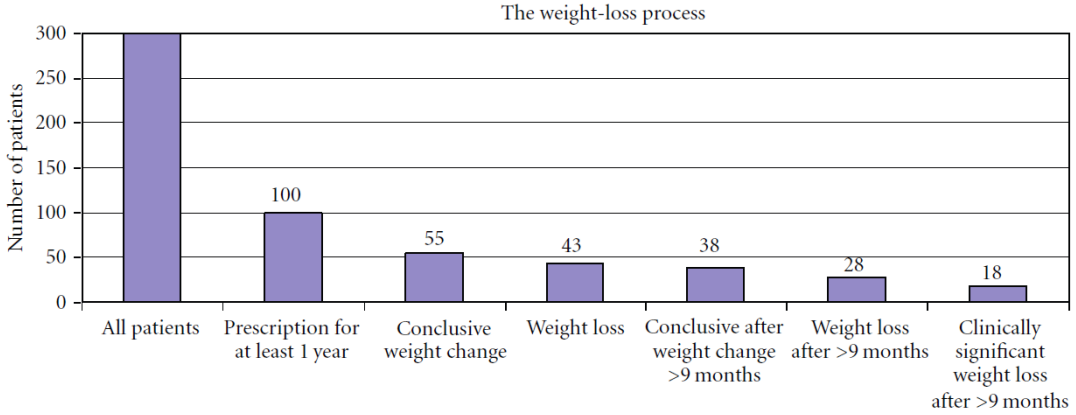
**Tomas Forslund,[1] Pauline Raaschou,[2] Paul Hjemdahl,[2] Ingvar Krakau,[3] and Björn Wettermark[4]**




**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

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The New England Journal of Medicine

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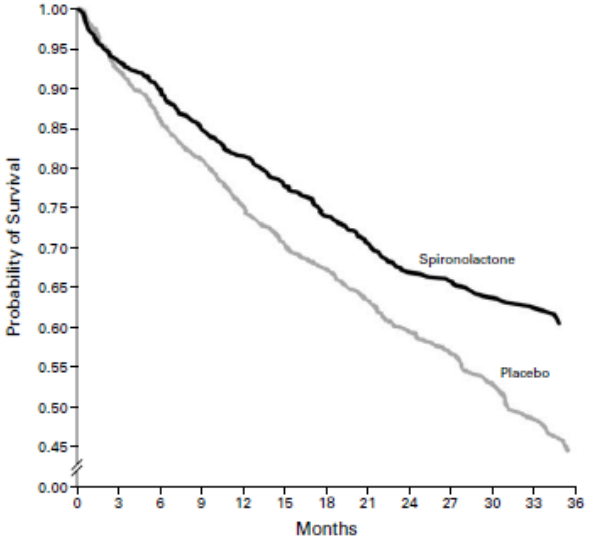
VOLUME 341 SEPTEMBER 2, 1999 NUMBER 10

## 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.

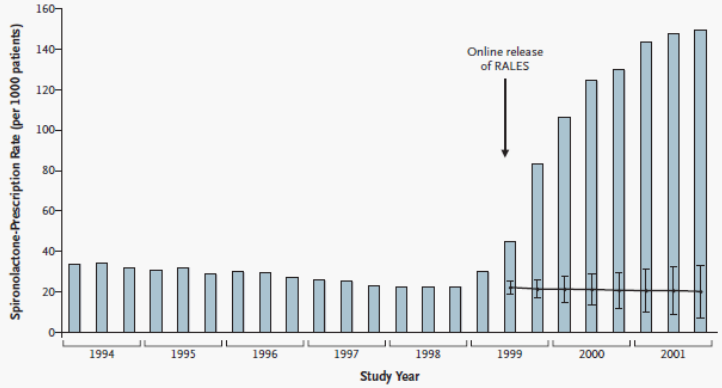



**Figure 1. Rate of Prescriptions for Spironolactone among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.**

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.

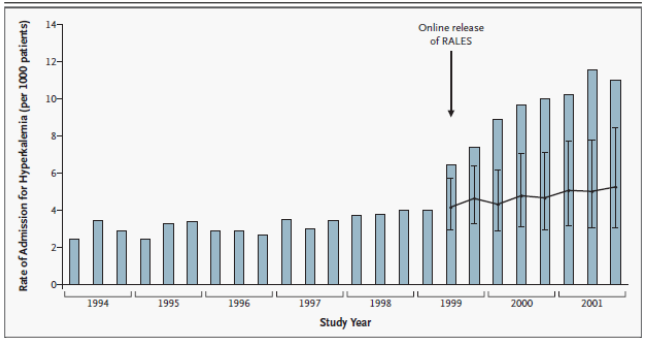



**Figure 2. Rate of Hospital Admission for Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.**

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.

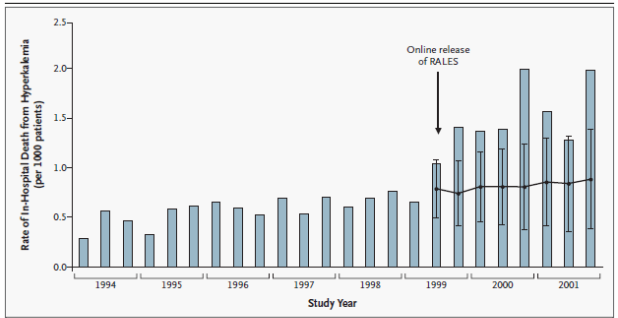



**Figure 3. Rate of In-Hospital Death Associated with Hyperkalemia among Patients Recently Hospitalized for Heart Failure Who Were Receiving ACE Inhibitors.**

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