EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

MHRA
Regulating Medicines and Medical Devices

A regulatory perspective
What do I want to know?

June M Raine MHRA, UK

11 December 2017

What does regulator want to know?

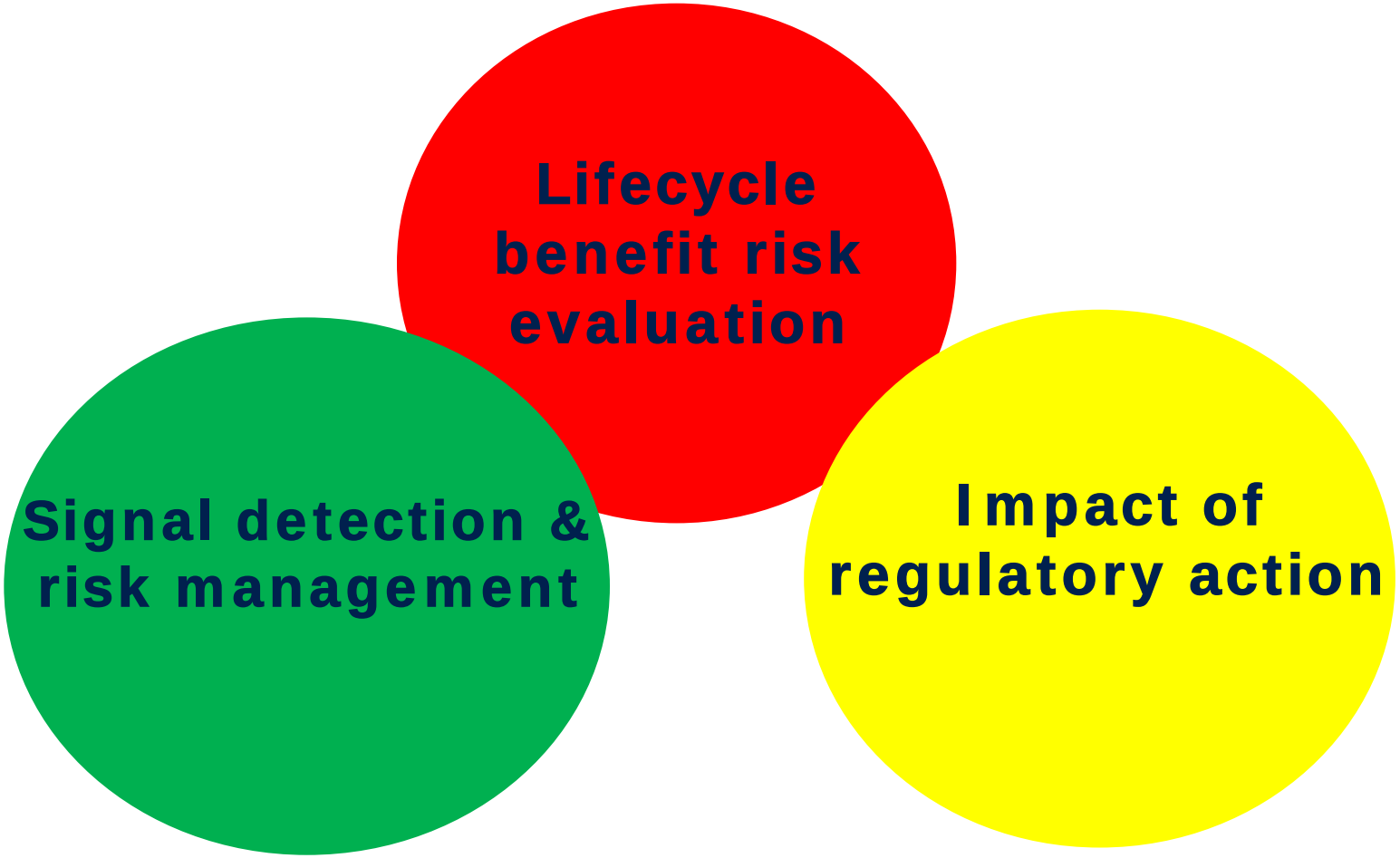
Regulatory decision-making responsibilities

Answering the regulatory questions

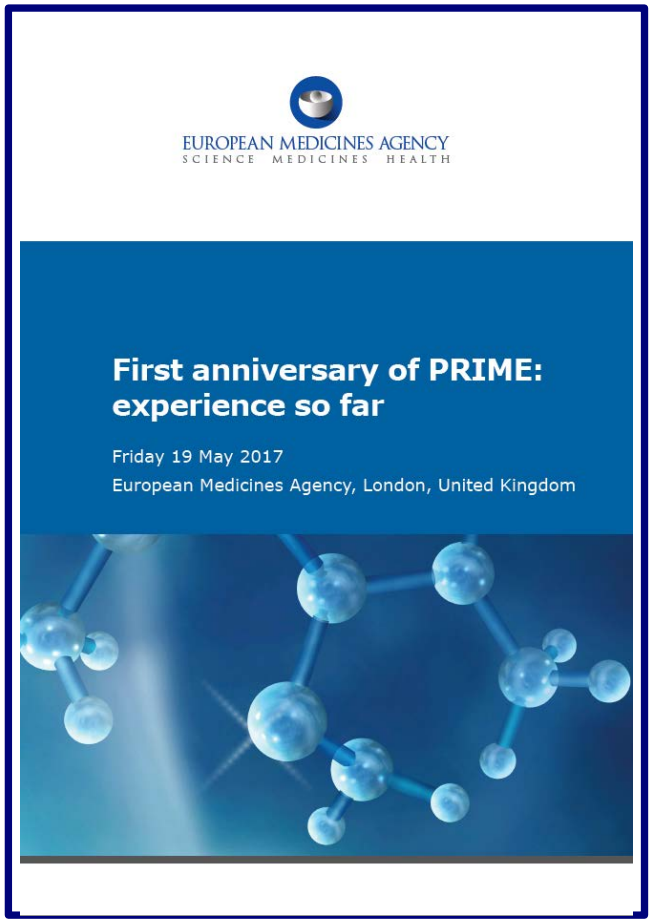
Accessing decision-relevant data

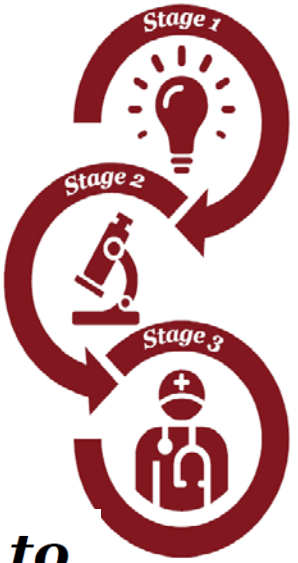
Moving forward …how can we do better?

Regulatory decision-making responsibilities



Today’s challenge - earlier access to medicines





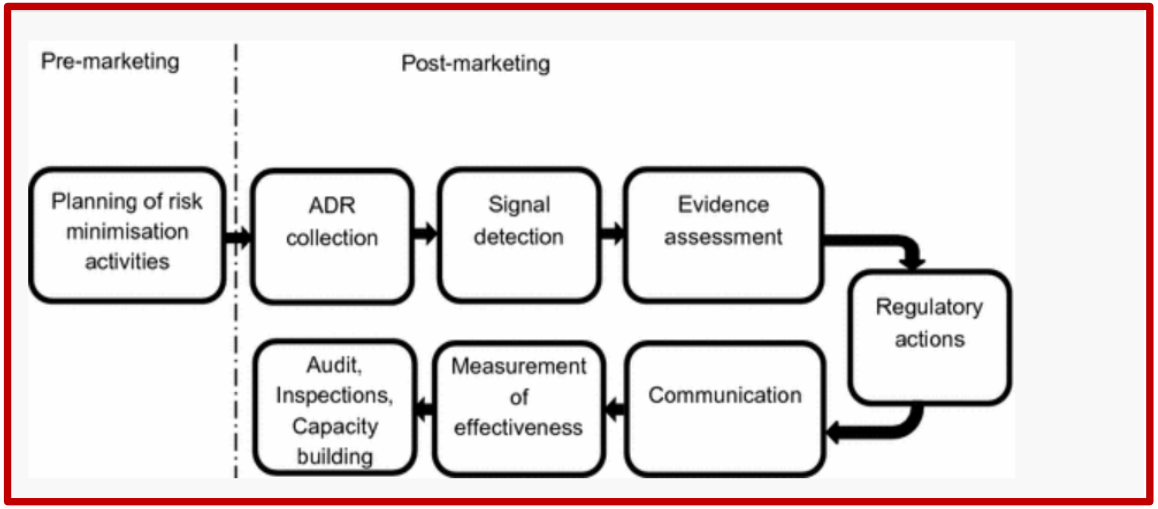
The Early Access to Medicines Scheme (EAMS)

Drug Saf (2017) 40:855–869
DOI 10.1007/s40264-017-0572-8

LEADING ARTICLE

Promoting and Protecting Public Health: How the European Union Pharmacovigilance System Works

Aniello Santoro[1] · Georgy Genov[1] · Almath Spooner[2,3] · June Raine[3,4] · Peter Arlett[1]



Santoro et al 2017 Drug safety 40:855-869

Uncertainties at time of approval

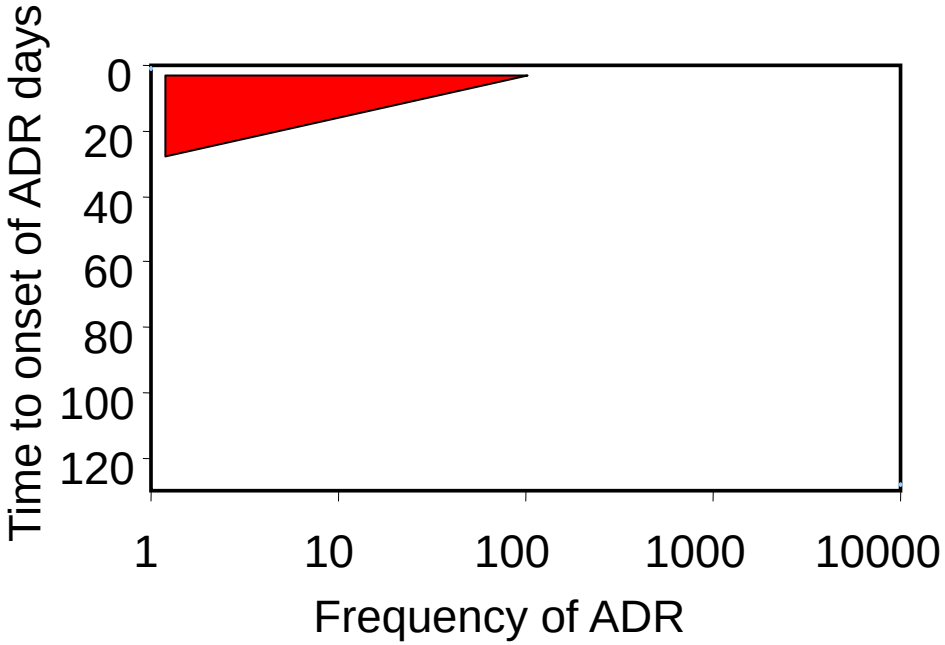
Benefit risk in wider clinical use

Effectiveness

Populations not studied

Rare ADRs

Long latency ADRs



Size of clinical database before approval

OPEN ACCESS Freely available online

PLOS | MEDICINE

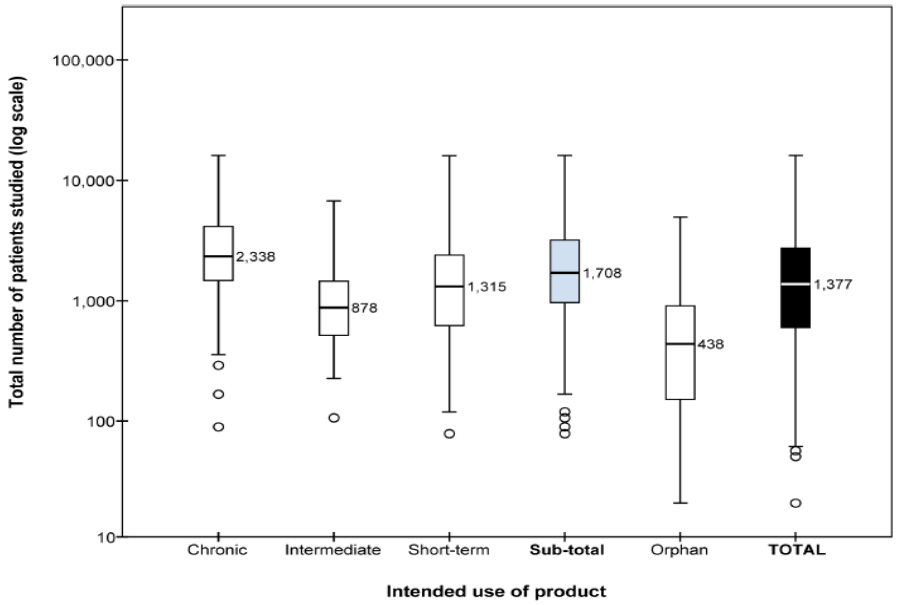
Number of Patients Studied Prior to Approval of New Medicines: A Database Analysis

Ruben G. Duijnhoven[1,2], Sabine M. J. M. Straus[2,3], June M. Raine[4], Anthonius de Boer[1], Arno W. Hoes[5], Marie L. De Bruin[1,2]*

1 Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands, **2** Medicines Evaluation Board, Utrecht, Medical Informatics, Erasmus Medical Center, Rotterdam, the Netherlands, **4** Medicines and Healthcare products Regulatory Agency, Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands

Abstract

Background: At the time of approval of a new medicine, there are few long-term data on the
balance. Clinical trials are designed to demonstrate efficacy, but have major limitations with regar
patient exposure and length of follow-up. This study of the number of patients who had been adm
the time of medicine approval by the European Medicines Agency aimed to determine the total numb
as well as the number of patients studied long term for chronic medication use, compared
Conference on Harmonisation's E1 guideline recommendations.



For **200** new "standard" medicines median total no patients= **1708**

For orphan drugs = **438** patients

For 84 medicines for chronic use **79.8%** met guidelines (at least 100 patients for 1Yr)

Duijnhoven et al PLoS March 2013

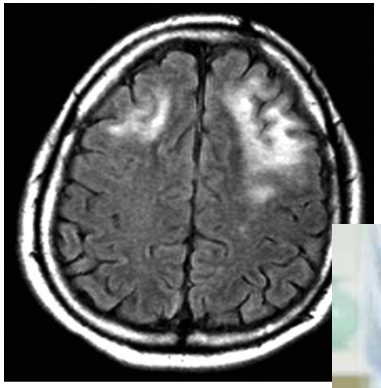
Important knowledge gaps to be filled

Special populations

- pregnancy
- paediatrics
- elderly

At risk groups eg immunosuppressed

Long term safety



Detecting new safety issues in EU

Simplified reporting of ICSRs to EudraVigilance and re-routing to MS

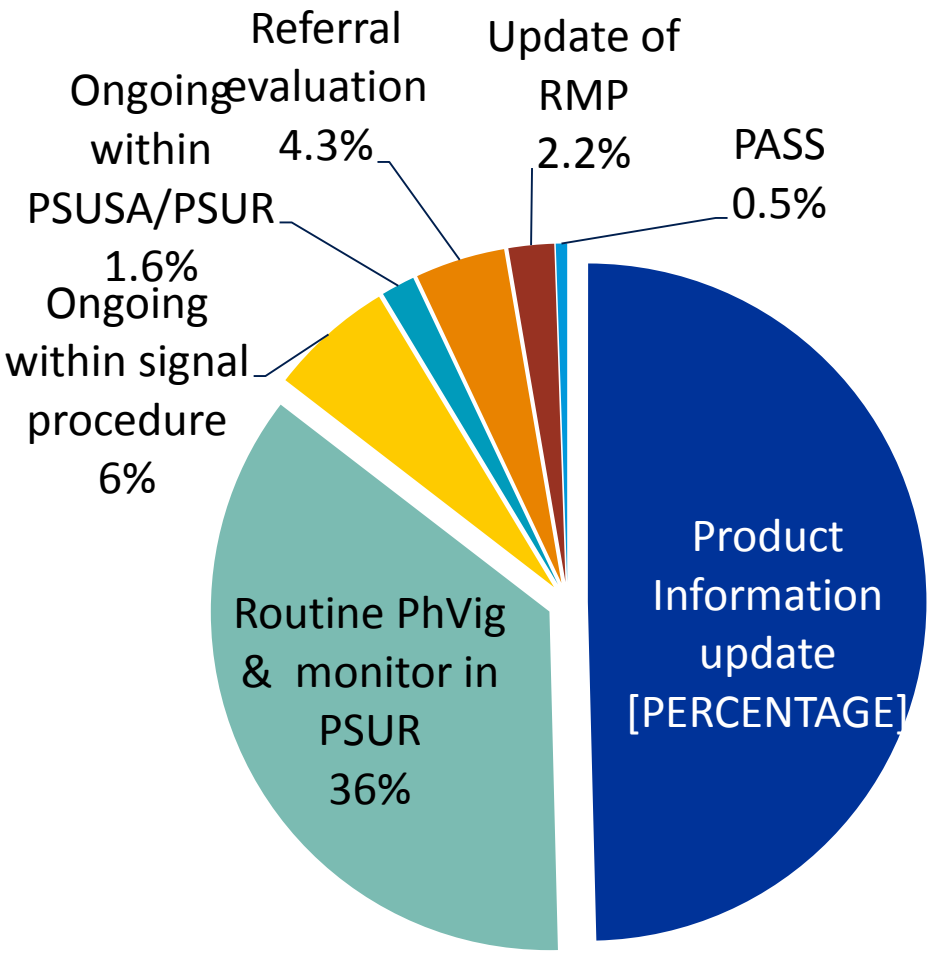
Improved quality and completeness of Individual Case Safety Report data – better searchability & efficiency

Enhanced signal detection and data analysis tools to support signal detection by member states & MAHs

Better detection of new or changing safety issues enabling rapid action to protect pubic health

Outcomes of signal assessment

PRAC Sep 2012 – Jun 2017



pact Pharmacovigilance | EMA ext | EMAPlus | ENCePP web | ENCePP | Presentations | SAP | SIAMED

BJCP British Journal of Clinical Pharmacology

SYSTEMATIC REVIEW AND META-ANALYSIS

Measuring the impact of medicines regulatory interventions – systematic review and methodological considerations

Thomas Goedecke ✉, Daniel Morales, Alexandra Pacurariu, Xavier Kurz

Accepted manuscript online: 5 November 2017 Full publication history

DOI: 10.1111/bcp.13469 View/save citation

Cited by (CrossRef): 0 articles Check for updates Citation tools ▼

Am score 2

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2017
EMA/59474/2017
Inspections, Human Medicines Pharmacovigilance and Committees

Workshop: measuring the impact of pharmacovigilance activities

Workshop report

5 - 6 December 2016
European Medicines Agency, London, United Kingdom

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An agency of the European Union

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What do I want to know?

How the medicine is being used

What is drug exposure

Outcomes of interest

Background rates of events of interest

What is drug attributable risk

Has regulatory action minimised risk

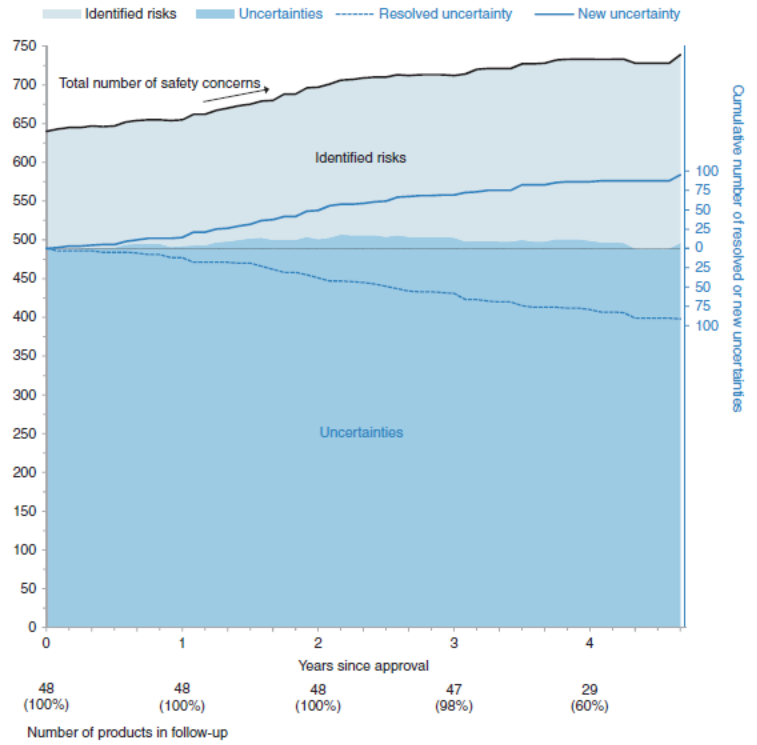
When will I get the answers

Answering regulatory questions - RMPs

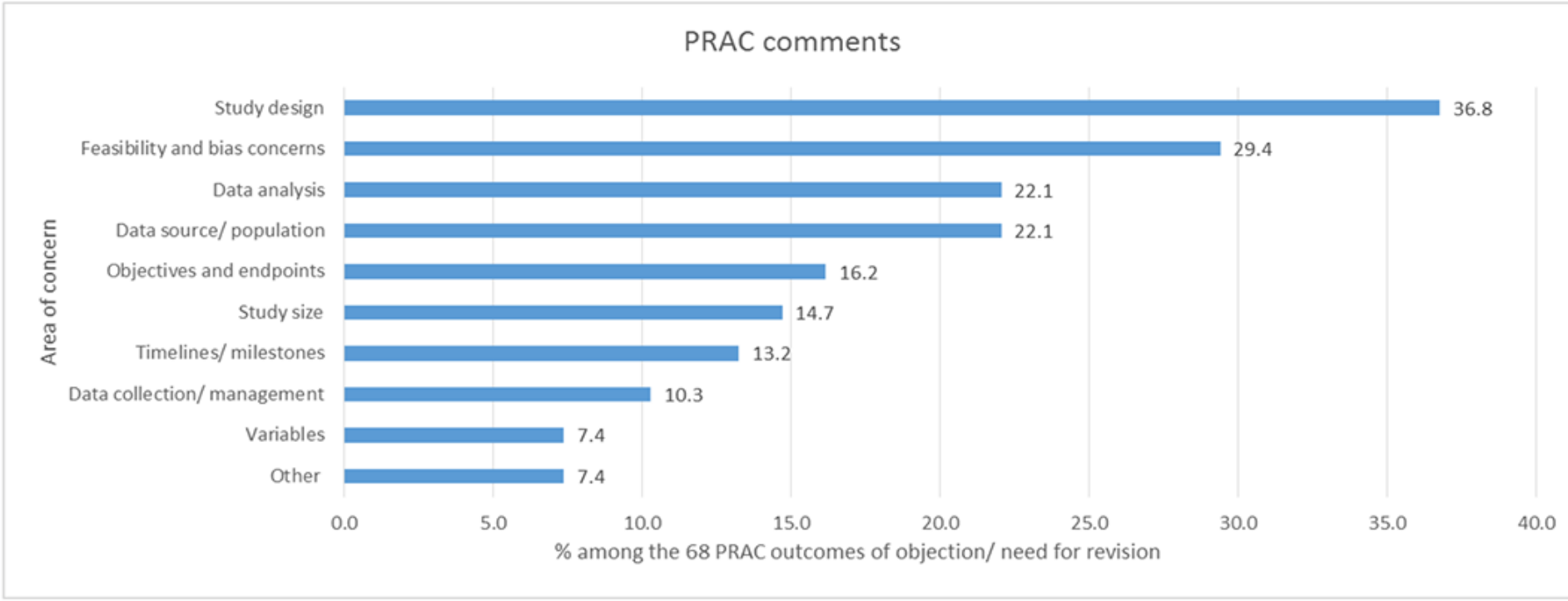
Risk Management Plans as a Tool for Proactive Pharmacovigilance: A Cohort Study of Newly Approved Drugs in Europe

NS Vermeer[1,2], RG Duijnhoven[1,2], SMJM Straus[2,3], AK Mantel-Teeuwisse[1], PR Arlett[4], ACG Egberts[1,5], HGM Leufkens[1,2] and ML De Bruin[1,2]

In the first 5 years after approval, 20.7% of uncertainties identified at approval were resolved



Answering regulatory questions - PASS



Note: Among the 68 PASS protocol submissions for which the PRAC outcome was protocol objection or need of further protocol revision. Other ad hoc comments were related to data protection, change of obligation status (to imposed), safety reporting and rational/background

British Journal of Clinical Pharmacology
Volume 83, Issue 4, 884-893


BJCP British Journal of Clinical Pharmacology

British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) 83 884–893 884

DRUG SAFETY

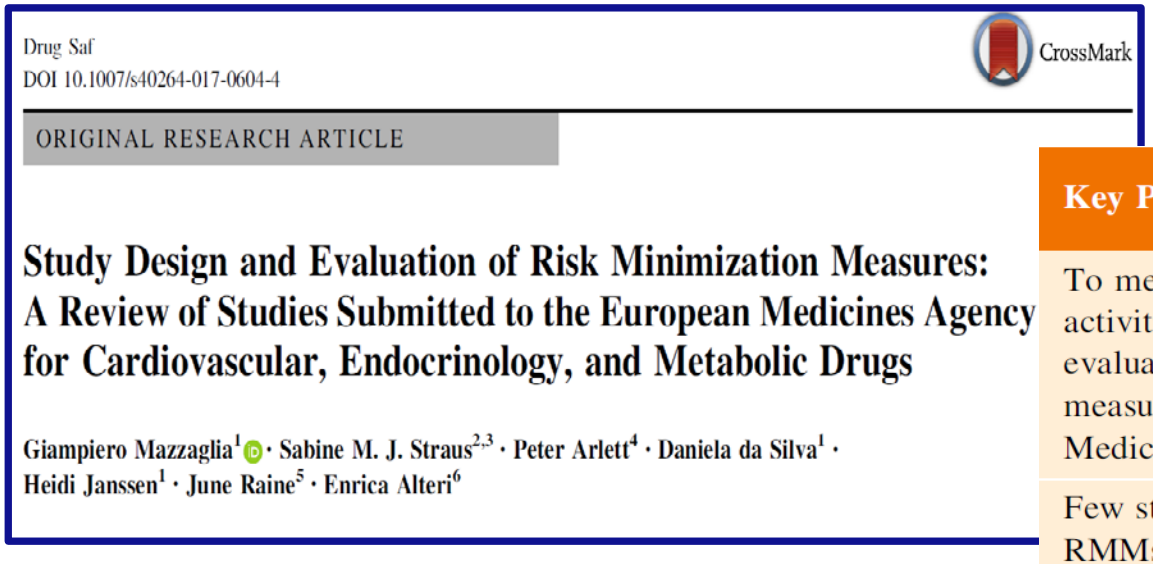
Lessons learned on the design and the conduct of Post-Authorization Safety Studies: review of 3 years of PRAC oversight

Correspondence Pierre Engel, Real-World Insights, QuintilesIMS, 151–161 Boulevard Victor Hugo, 93400 Saint Ouen, France. Tel.: + 33 1 72 29 24 88; E-mail: pierre.engel@quintilesims.com

Received 14 June 2016; Revised 18 October 2016; Accepted 23 October 2016

Pierre Engel[1,*], Mariana Ferreira Almas[2,*], Marieke Louise De Bruin[3,4], Kathryn Starzyk[5], Stella Blackburn[5] and Nancy Ann Dreyer[5]

Answering regulatory questions - RMMs



Drug Saf
DOI 10.1007/s40264-017-0604-4

CrossMark

ORIGINAL RESEARCH ARTICLE

Study Design and Evaluation of Risk Minimization Measures: A Review of Studies Submitted to the European Medicines Agency for Cardiovascular, Endocrinology, and Metabolic Drugs

Giampiero Mazzaglia[1] · Sabine M. J. Straus[2,3] · Peter Arlett[4] · Daniela da Silva[1] · Heidi Janssen[1] · June Raine[5] · Enrica Alteri[6]

Key Points

To measure the impact of pharmacovigilance activities, we reviewed industry-sponsored studies evaluating the effectiveness of risk minimization measures (RMMs) received by the European Medicines Agency.

Few studies were designed to measure the impact of RMMs in reducing the occurrence of adverse drug reactions, or used an appropriate study design to evaluate their effectiveness.

Optimal evaluation may be hampered by the limited data available when the RMM is introduced, and by the time required to obtain this information.

Efficient evaluation may benefit from an integrated measurement of the different elements of the RMMs. This should help regulators to gain timely information and undertake prompt adjustment of risk minimization strategies as needed.

Accessing decision-relevant data

Database studies

- Eg risk characterisation, investigation of targeted AEs, impact of regulatory action

Drug utilisation studies

- Eg to assess patterns of use, effectiveness of risk minimisation or help plan PASS

Registries (prospective cohorts)

- Eg assess safety profile, health outcomes in clinical use, consider comparator

Strengths and limitations of registries

Strengths

- Relevant clinical parameters
- Natural history of disease
- Standard of care
- Patient stratification
- RCTs
- Open label studies possible
- Capture off label use
- Information on high risk groups
- Patient reported outcomes

Limitations

- Substantial set up & running costs
- Time consuming to initiate
- Medications commonly missing
- ADRs not routinely recorded
- Co-morbidities missing
- Data ownership/governance
- Data Quality
- If no comparator will limit utility

Patient registries – research ready?

Biologics

Haemophilia

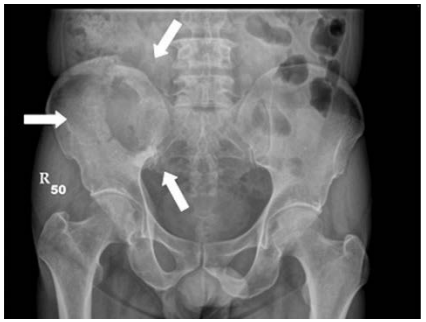
Pregnancy

Multiple Sclerosis

Blood and Marrow Transplantation

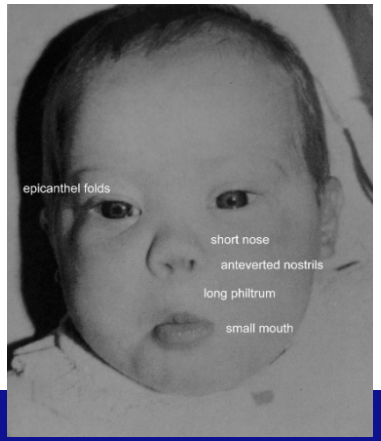
Examples of some EU regulatory questions

How is Radium 223 used in non-symptomatic or mildly symptomatic metastatic prostate cancer?



Is Human Papilloma Virus Vaccine associated with increased risk of fatigue syndromes in adolescent girls?

Are risk minimisation measures to reduce harm of exposure to valproate in pregnancy effective?



Understanding how medicine is used

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

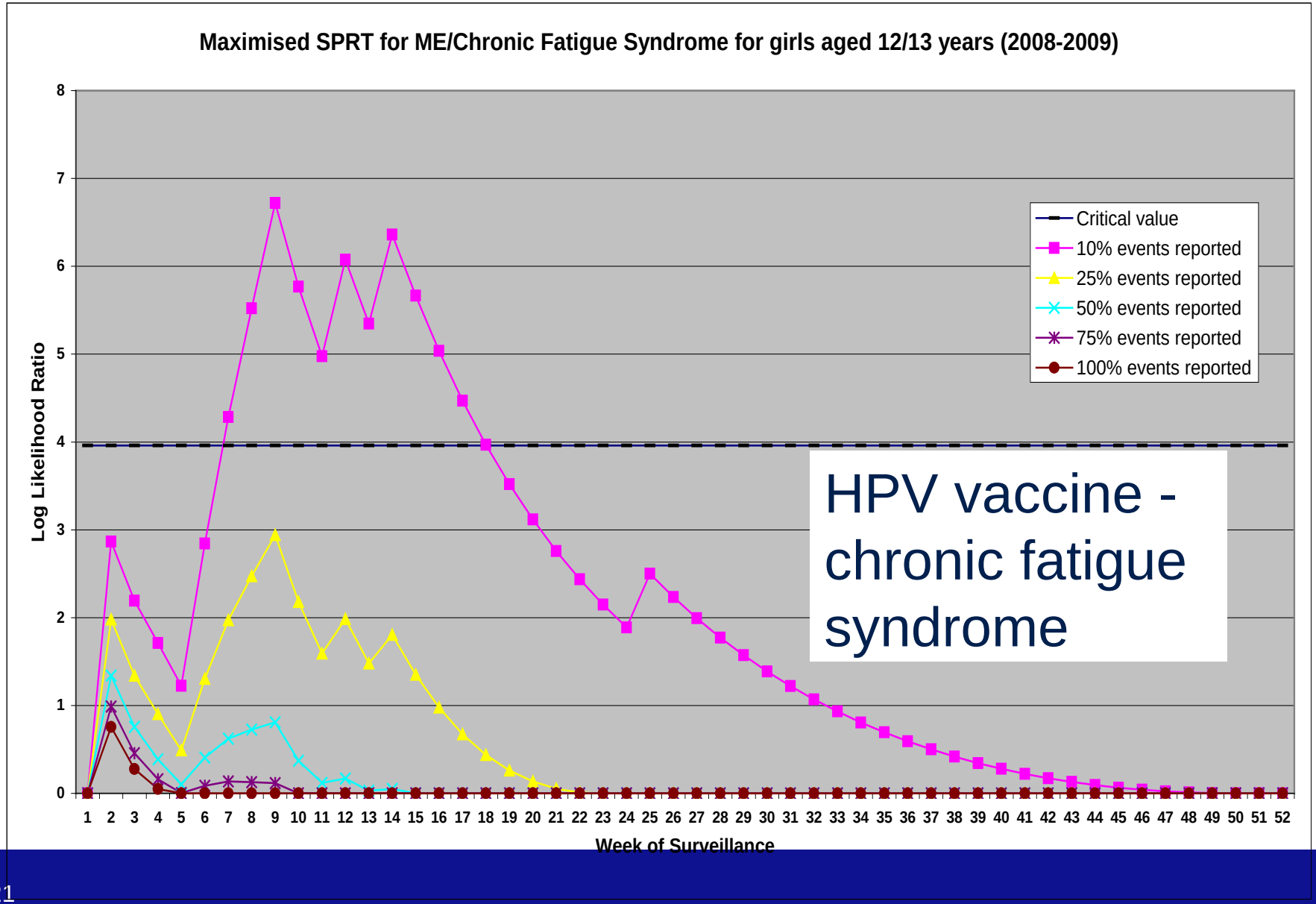
1 December 2017
EMA/789952/2017

Warning about use of prostate cancer medicine Xofigo in combination with Zytiga and prednisone or prednisolone

Ongoing clinical trial shows an increased risk of death and fractures

Establishing extent of concomitant use of Radium 223 and abiraterone plus steroids across EU while urgent safety review is taken forward

ADR reports - observed vs expected analysis



HPV vaccine - background rates of CFS

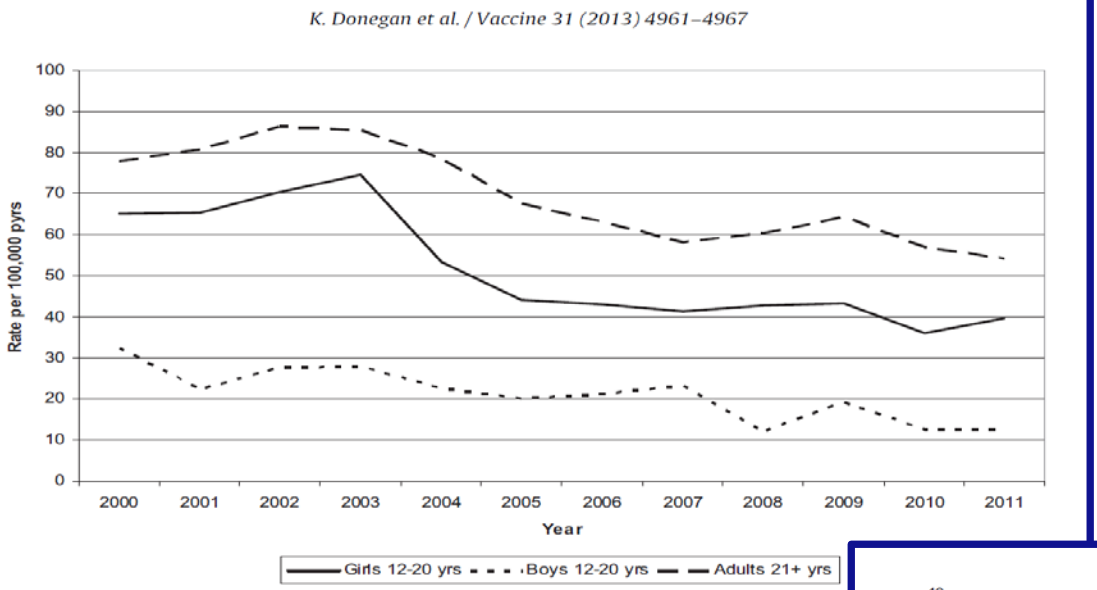


Fig. 2. The incidence of fatigue syndromes in the CPRD 2000–2011.

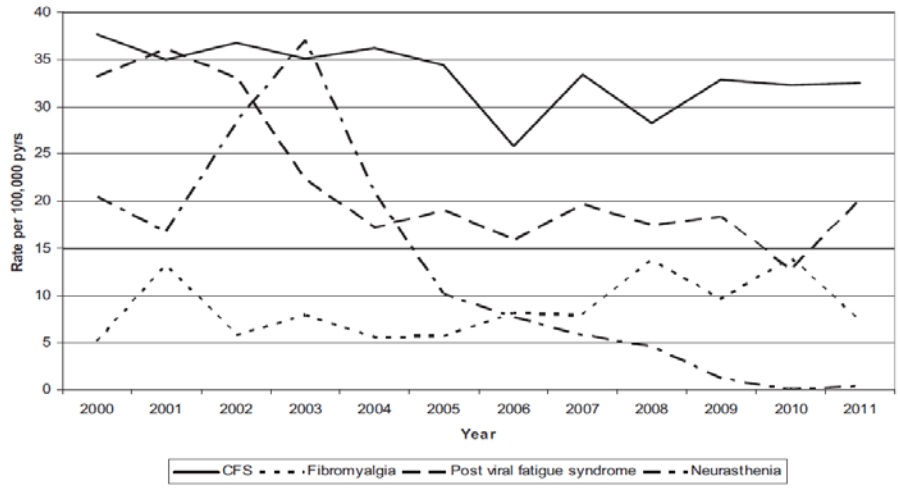
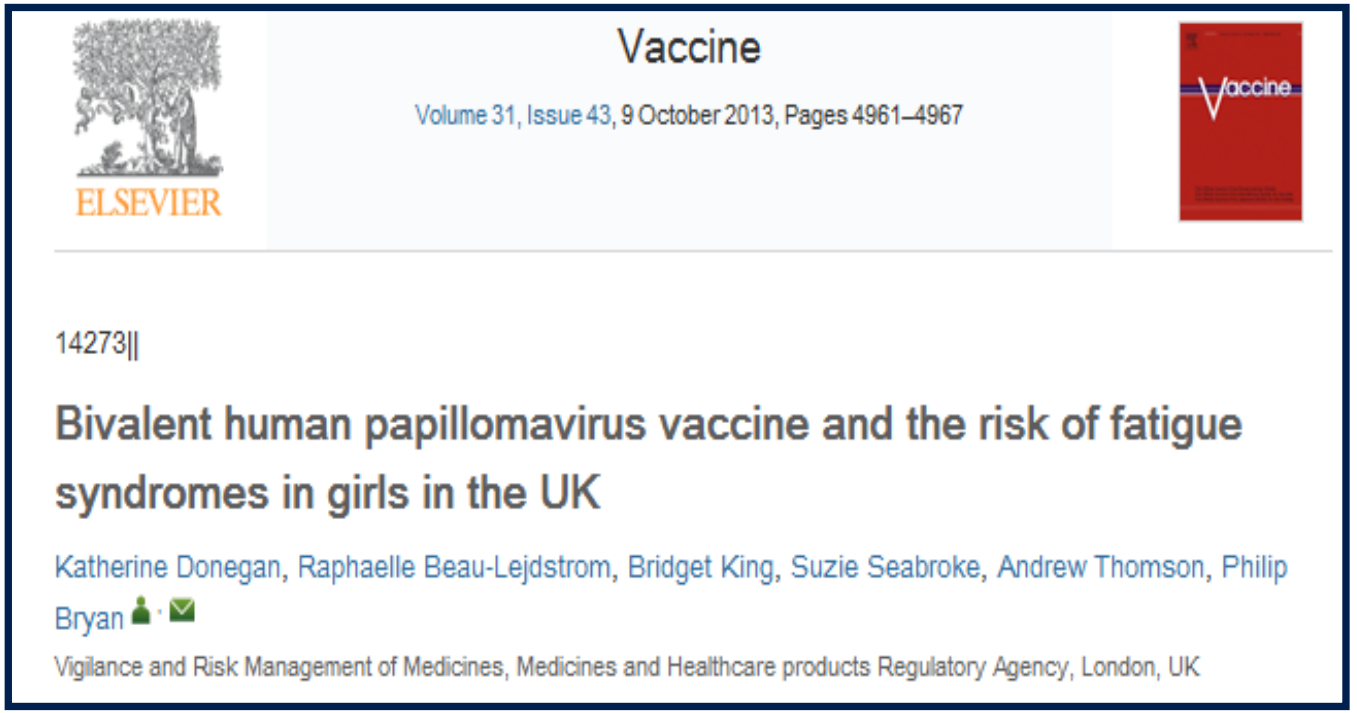


Fig. 3. The incidence of fatigue syndromes in girls aged 12–20 years by type of diagnosis 2000–2011.

Investigating vaccine signal using RWE



Vaccine

Volume 31, Issue 43, 9 October 2013, Pages 4961–4967

14273||

Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK

Katherine Donegan, Raphaelle Beau-Lejdstrom, Bridget King, Suzie Seabroke, Andrew Thomson, Philip Bryan

Vigilance and Risk Management of Medicines, Medicines and Healthcare products Regulatory Agency, London, UK

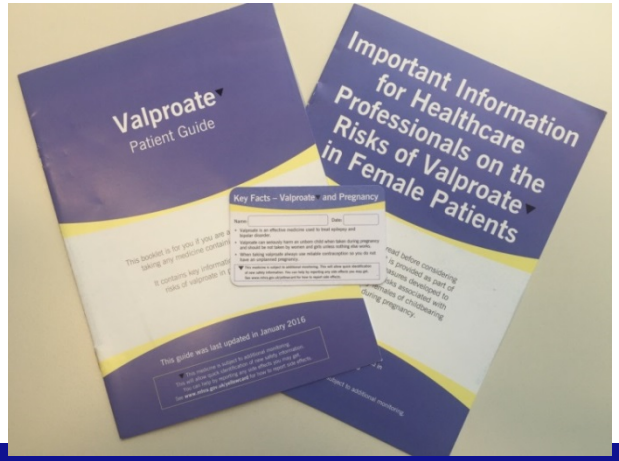
Results: The number of spontaneous reports of chronic fatigue following Cervarix vaccination was consistent with estimated background rates even assuming low reporting. Ecological analyses suggested that there had been no change in the incidence of fatigue syndromes in girls aged 12–20 years after the introduction of the vaccination despite high uptake (IRR: 0.94, 95% CI: 0.78–1.14). The SCCS, including 187 girls, also showed no evidence of an increased risk of fatigue syndromes in the year post first vaccination (IRR: 1.07, 95% CI: 0.57–2.00, p = 0.84).

Donegan et al 2013, Vaccine 31, 43, 4961-7

Impact of regulatory action - valproate

Developmental disorders up to 30 -40% of pre-school children exposed in utero in addition to 11% risk of birth defects

EU referral in 2014 – strengthened warnings and extensive communications



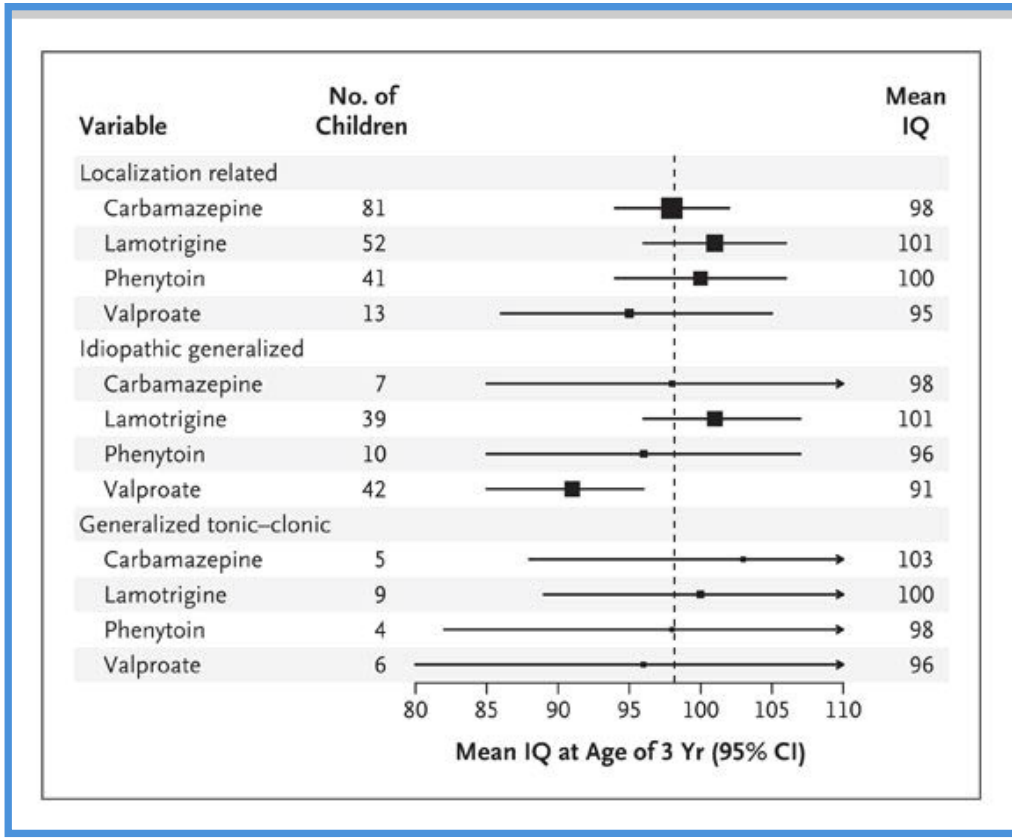


Figure 2. IQ Scores of Children Who Were Exposed to Antiepileptic Drugs In Utero, According to Drug and Type of Maternal Epilepsy.

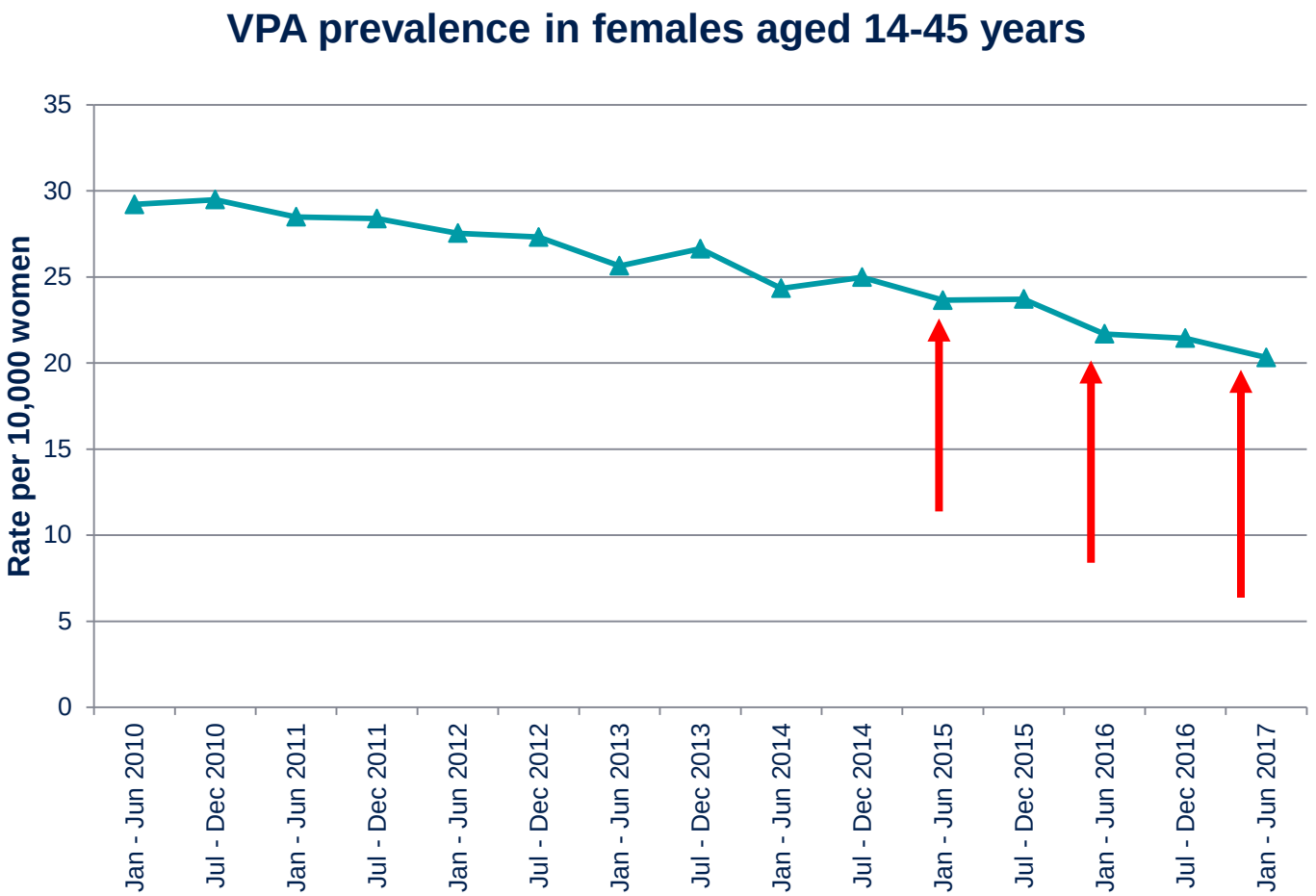
Meador et al NEJM 2009

Understanding valproate use in member states

Estimation of number of treatment-years by country and indication in female patients aged 15-49 years from 2010 to 2012

	From 2010 to 2012				
MSs	**Epilepsy**	**Bipolar disorders**	**Migraine**	**Other**	**Total**
UK	42 409 (43.7%)	17 232 (17.7%)	740 (0.8%)	36 745 (37.8%)	**97 125**
France	7 432 (4.8%)	98 286 (63.1%)	402 (0.3%)	49 650 (31.9%)	**155 770**
Germany	19 410 (70.7%)	120 (0.4%)	348 (1.3%)	7 566 (27.6%)	**27 444**
Italy	46 222 (46.4%)	17 481 (17.5%)	204 (0.2%)	35 716 (35.9%)	**99 623**
Spain	21 545 (42.9%)	15 877 (31.6%)	352 (0.7%)	12 455 (24.8%)	**50 229**
Total	**137 018 (31.9%)**	**148 995 (34.6%)**	**2 046 (0.5%)**	**142 132 (33.0%)**	**430 191**

Effect of valproate action in UK



Communications disseminated

Moving forward – how can we do better?

Real World Data in Adaptive Biomedical Innovation: A Framework for Generating Evidence Fit for Decision-Making

S Schneeweiss[1], H-G Eichler[2], A Garcia-Altes[3], C Chinn[4], A-V Eggimann[5], S Garner[6], W Goettsch[7], R Lim[8], W Löbker[9], D Martin[10], T Müller[11], BJ Park[12], R Platt[13], S Priddy[14], M Ruhl[15], A Spooner[16], B Vannieuwenhuyse[17] and RJ Willke[18]

Analyses of healthcare databases (claims, electronic health records [EHRs]) are useful supplements to clinical trials for

Schneeweiss S et al 2016
Clin Ph Ther 100 6 633-46

Meaningful evidence

Valid evidence

Expedited evidence

Transparent evidence

Generating meaningful evidence

To be meaningful, evidence must be relevant and decision-focused. To obtain meaningful evidence…		
1	**Data quality**	Must *be fit for purpose*
2	**Data appropriateness**	Must *match data type to the question*
3	**Meaningful statistics**	Must *employ metrics that matter*

Rassen J at ISoP Liverpool, 2017

Generating timely evidence

Example: Has prescribing of codeine in children changed following regulatory action in 2013?

Common protocol reduces variability due to misaligned definitions, analytical models

Makes use of existing regulatory network

- ✓ Access to high quality electronic health records
- ✓ Effective allocation of existing resources
- ✓ Sharing of expertise and data

Greater part of EU population in same study

Pilot study to gain experience

The risk of respiratory depression outweighs the benefits of using codeine for moderate pain in children under 12 years as there are safer alternatives | SCIENCE PHOTO LIBRARY

Assessment of data by PRAC in 2018

The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA has recommended that use of codeine-containing medicines in children be restricted to those aged over 12 years with acute moderate pain that cannot be relieved by other analgesics, for example, paracetamol or ibuprofen.

Moving forward – how can we do better?

Agree on common goal – timely access to decision-relevant data to achieve measurable public health outcomes

Scenario-specific planning for capability to link local or distributed data sources at global level, support rapid cycle analysis

Multi-disciplinary teams including regulators, data providers, pharma and academia to work on common data format

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Regulators are ready to support!

Pharmacovigilance Risk Assessment Committee