Academic perspective

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9th stakeholders forum PhV legislation
September 15, 2015

Universiteit Utrecht

Declaration of Interest

- Assistant Professor in Pharmacoepidemiology, Utrecht Institute of Pharmaceutical Sciences
  - Scientific coordinator of the EU-FP7 project CARING (CAncer Risk and INsulin analoGues, grant nr 282526)
  - Drug Regulatory Science projects (Escher/TIPharma, Strategic collaboration CBG-MEB)

- Regulator
  - Pharmacovigilance expert at the Dutch Medicines Evaluation Board (MEB)
  - Independent Scientific Expert at the Pharmacovigilance Risk Assessment Committee (PRAC) - European Medicines Agency (EMA) -> ENCePP SG

Outline

- Scientific view
- Where did we come from?
- What have we achieved in 3 yr?
- Future directions

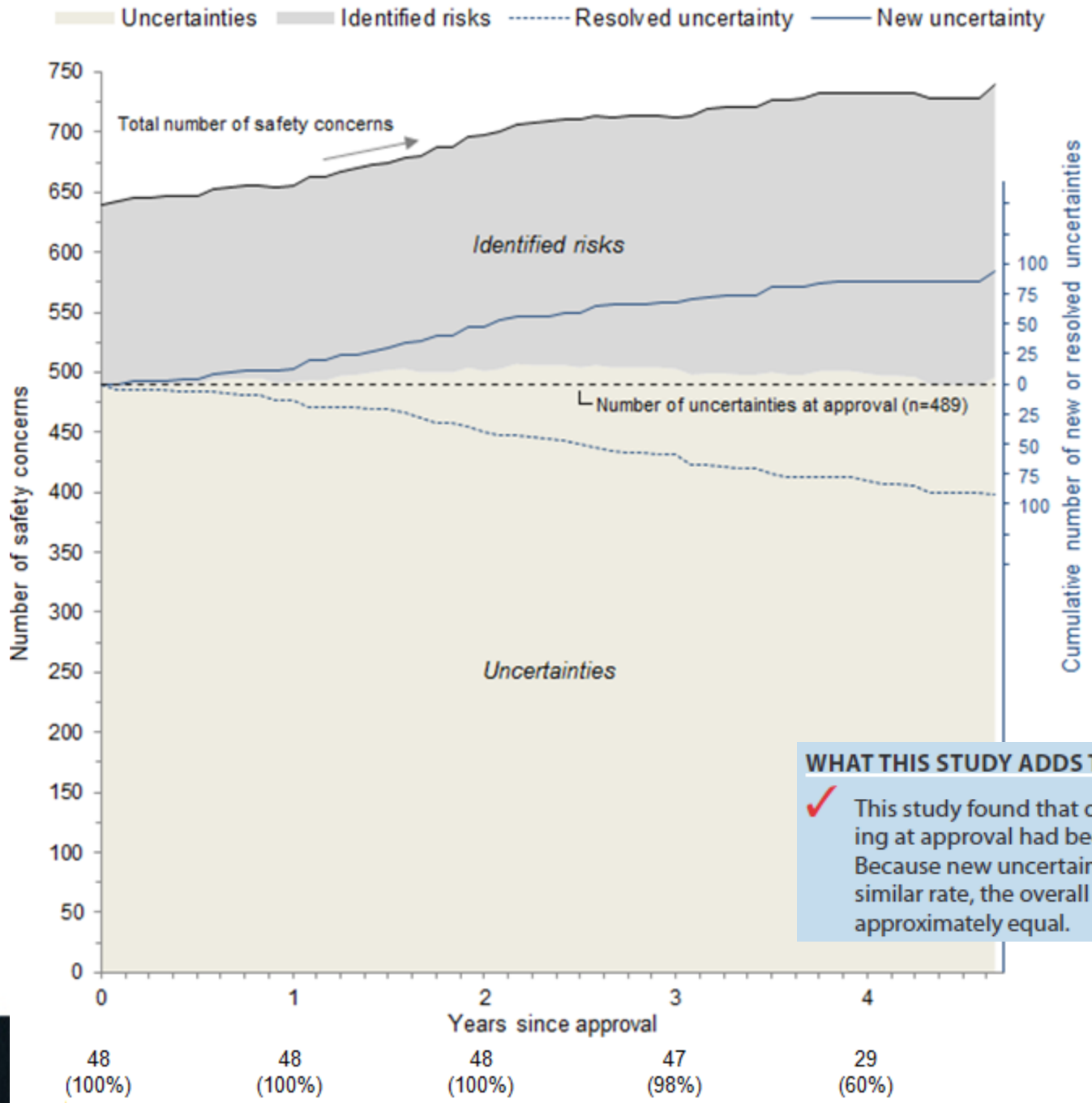
Risk Management Plans as a Tool for Proactive Pharmacovigilance: A Cohort Study of Newly Approved Drugs in Europe

Clin Pharmacol Ther 2014

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]

Study aim

To examine the development of the RMP after approval, to provide insight into the knowledge gain over time, by quantifying changes in listed safety concerns and study factors associated with change



WHAT THIS STUDY ADDS TO OUR KNOWLEDGE

✓ This study found that one-fifth of the uncertainties existing at approval had been resolved 5 years after approval. Because new uncertainties were included in the RMP at a similar rate, the overall number of uncertainties remained approximately equal.

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" The relatively modest accrual of knowledge, as demonstrated in this study through resolution of uncertainties, suggests that opportunities for optimization exist while ensuring feasible and risk-proportionate pharmacovigilance planning."

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Lessons Learned on the Design of European Post Authorisation Safety Studies (PASS): Review of 24 Months of PRAC Oversight.

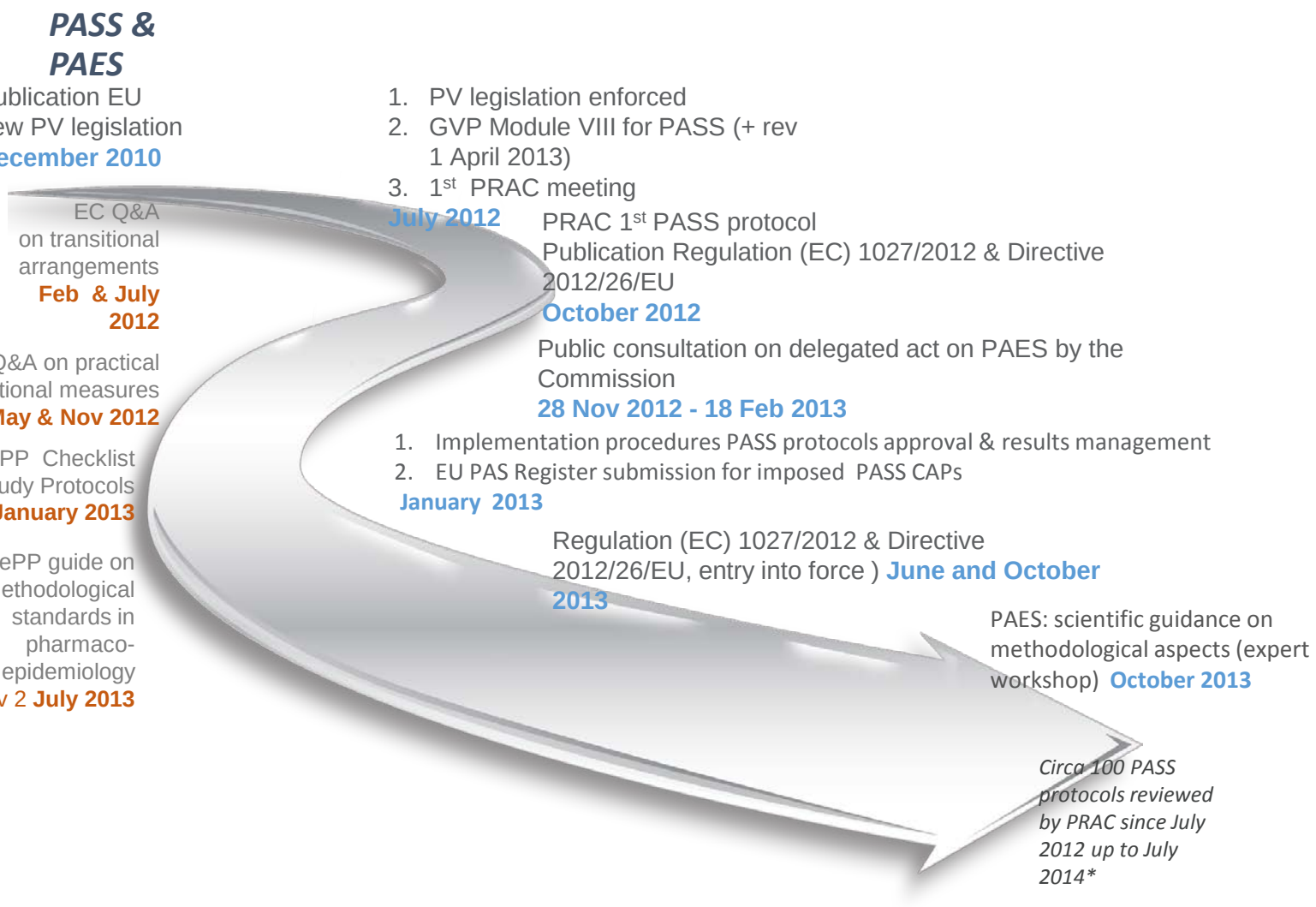
ENCePP Plenary Session (25 November 2014)

Pierre Engel, Marieke De Bruin

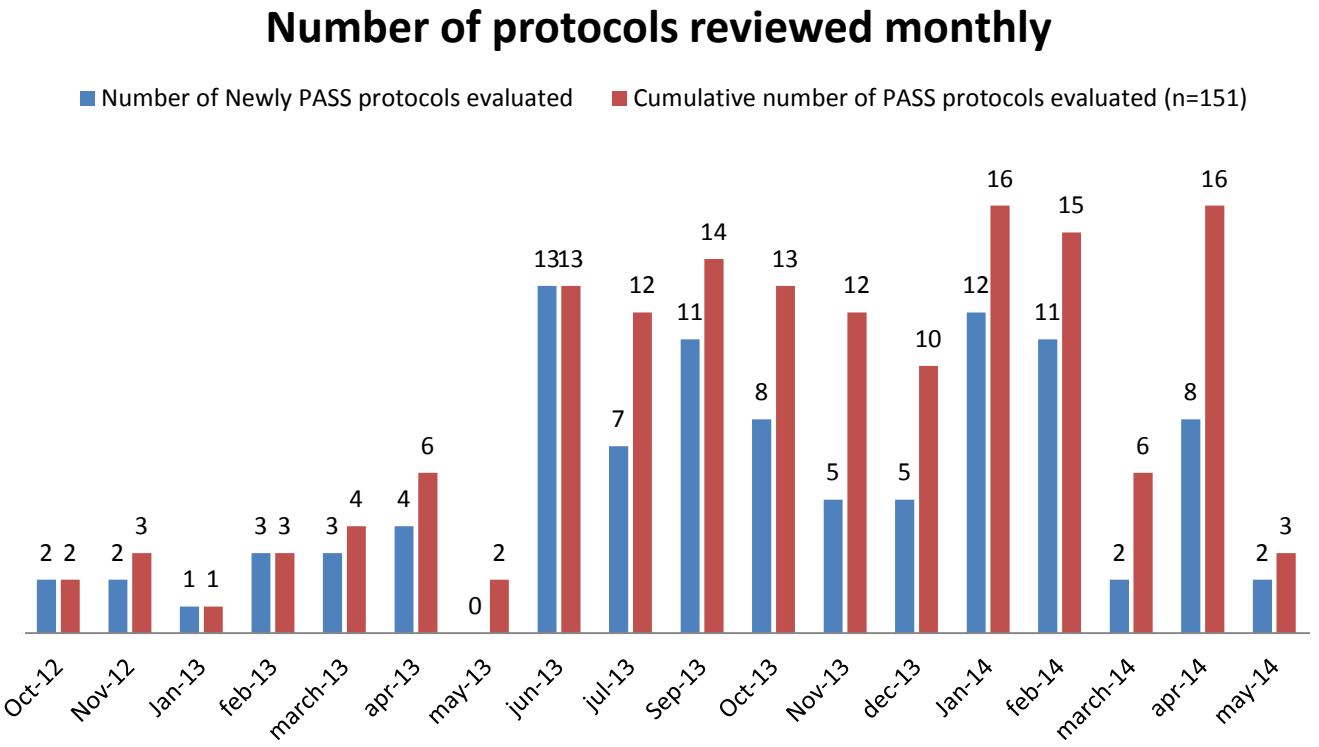
These slides are available at:
http://www.encepp.eu/publications/PlenaryMeetingReports.shtml

A New Era of Safety

The Making of the new PV Legislation



PRAC Review cycles



From July to August 2012: inaugural meetings, no protocol reviewed

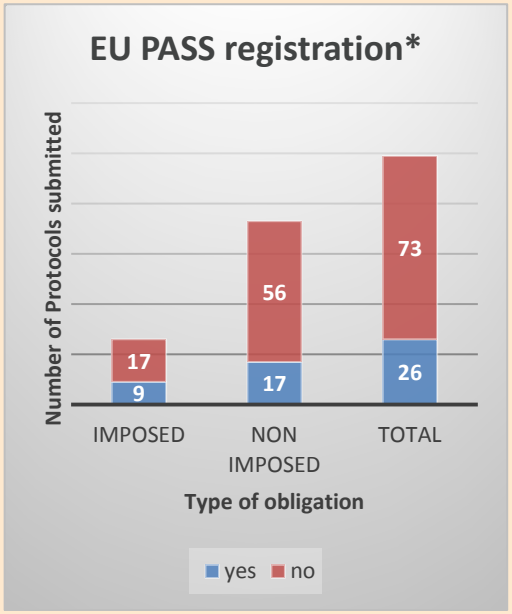
- 99 new protocols evaluated from July 2012 to July 2014 (26 imposed): Overal 150 protocols reviewed
- After one year of meetings, average of 15 protocols evaluated per month
- Median 2 rounds of review for imposed, and 1 round for non imposed

PASS protocols and EU PAS register

GVP Guidelines

- The 2010 PV legislation requires that protocols and abstracts of results of PASS imposed as an obligation are published in a publicly available register*
- For non imposed studies, no legal obligation to register but recommended
- Registration for imposed studies must be made no later than at the time of the final study report
- Final report of imposed studies must provide the date of registration in the register

PRAC Figures*

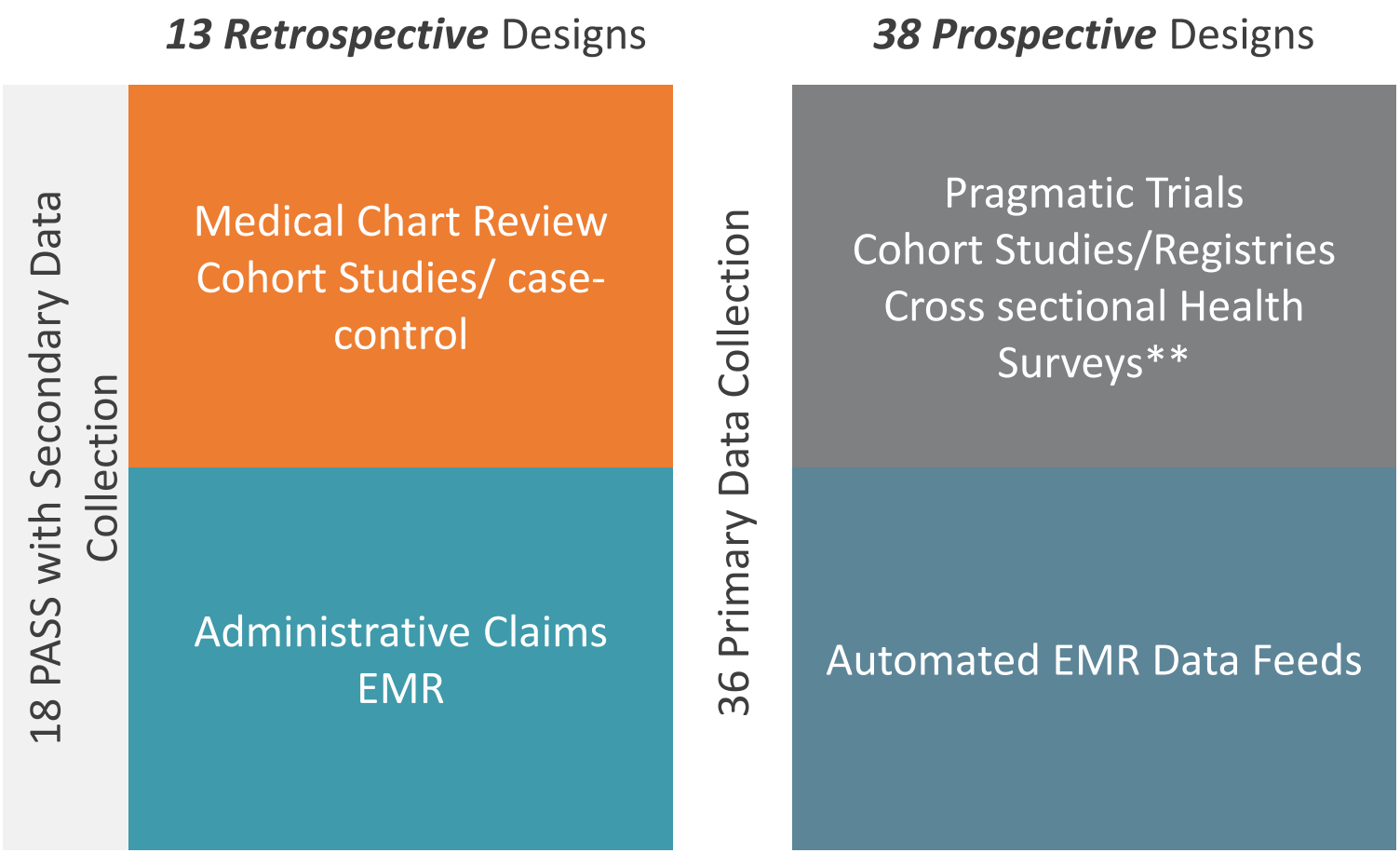


- 35% of imposed and 23% of non imposed studies are registered*
- Between July 2012 and July 2013 these proportions were higher with respectively 40% registration for imposed and 28% for non imposed

Discussion

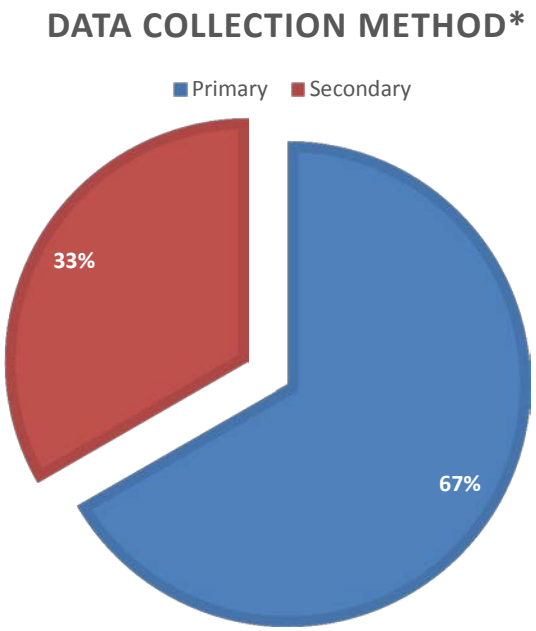
- Overall one out three PASS are registered with an slightly higher proportion for imposed as compared to non imposed
- Although legal obligation only mandate registration at the time of study report, still transparency of PASS registration could be increased especially for non imposed studies.
- With hindsight, compliance with GVP requirements for registration of completed studies should be checked.

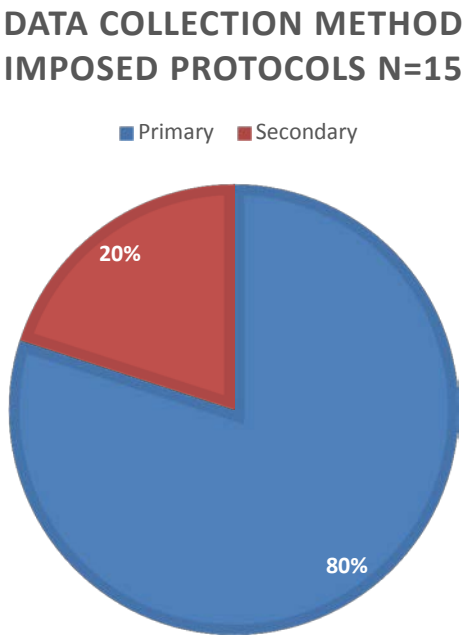
Overview of PASS designs since July 2012*

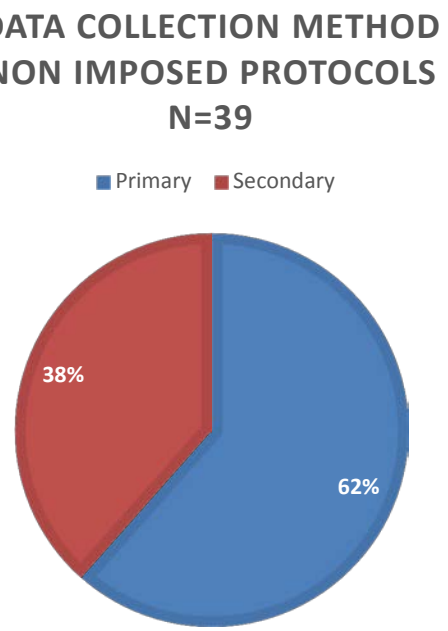


*38 PASS with missing info regarding design
** 11 PASS involving Cross Sectional Risk Minimization surveys

PASS protocols & DC method



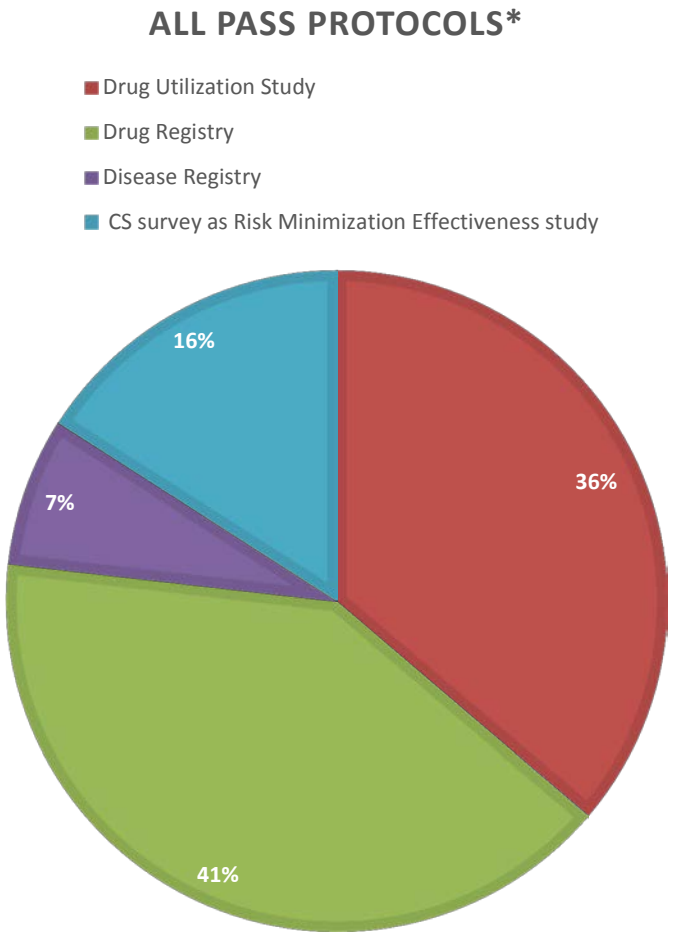


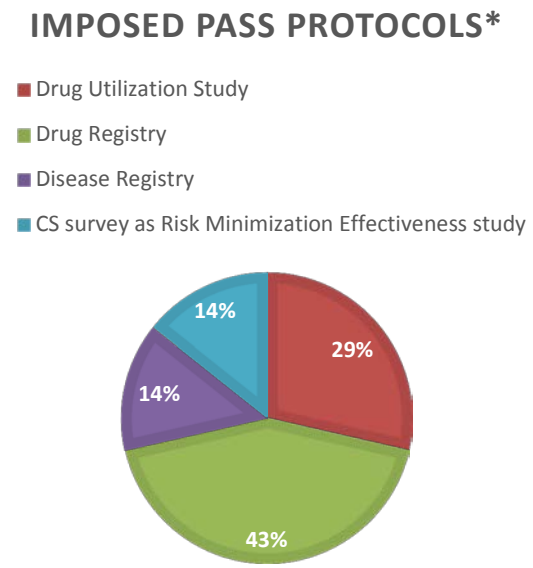


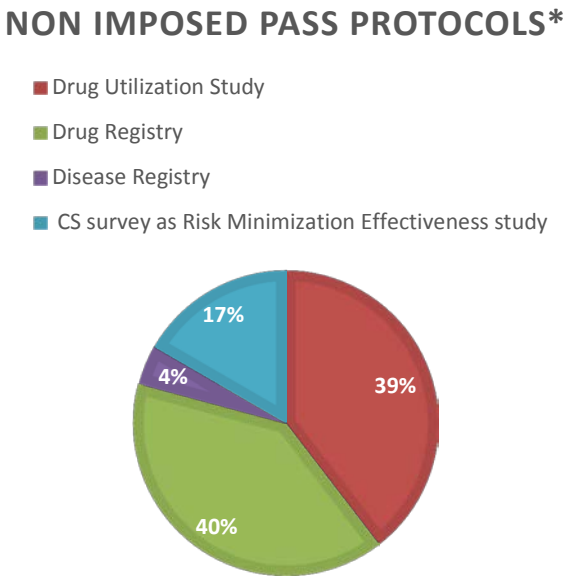
Further considerations:

- Overall ++ prospective PASS with primary DC for both imposed and non imposed studies
- More retrospective secondary DUS among non imposed studies
- Almost half of the retrospective DUS are leveraging EU multinational administrative claims/data source providers, the others = ad hoc medical chart review
- Mostly new applications, new drugs on the market among imposed studies
- Immediate start up to prospectively look at unforeseen safety concerns
- Need to adjudicate the clinical events per routine practice

PASS major categories/objectives: PRAC figures







Lessons learned from the PRAC

- 73 Non-Imposed (9 protocols with no info available)
  - 70% (n = 45) were endorsed at the first round of review pending further clarifications on list of questions
  - 30% had revision due to
    - Sample size
    - Statistical analyses
    - Missing timelines
    - Enrolment strategy
    - Representativeness
    - Bias and confounding
    - Observational nature of the study an inadequate proposed study design to meet the study objectives

- 26 Imposed (7 protocols with no info avalaible)
  - 58% were rejected due to an inadequate proposed study design to meet the study objectives
  - 42% (n=8) were endorsed at the first round of review pending further clarifications on a list of questions

Clinical Pharmacology & Therapeutics

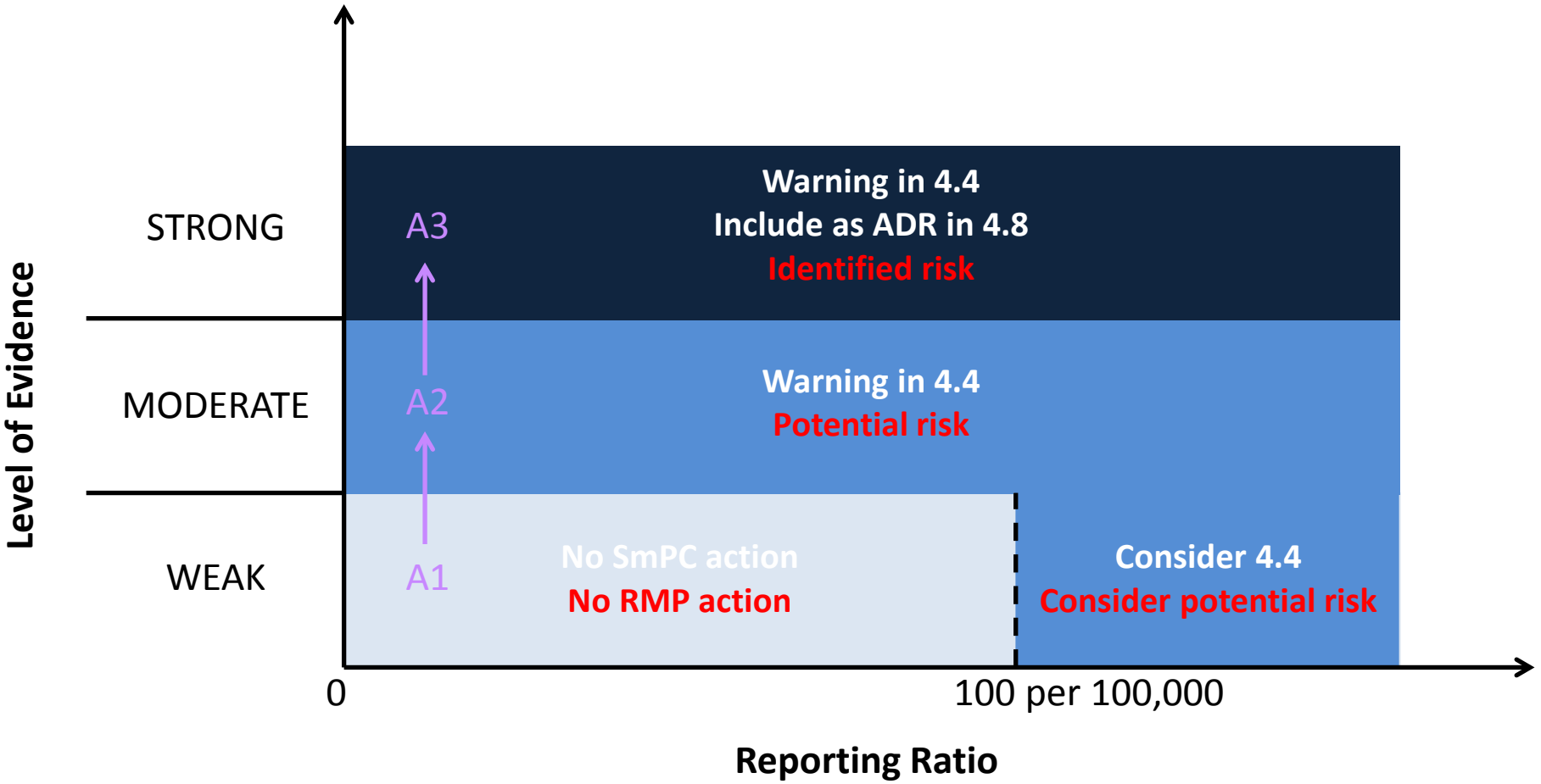
Strategy in regulatory decision making for management of PML

Andrej Segec[1], Brigitte Keller-Stanislawski[2], Niels S Vermeer[3,4], Carmela Macchiarulo[5], Sabine M Straus[4], Ana Hidalgo-Simon[1] and Marie Louise De Bruin[3,4] [Accepted 2015 doi: 10.1002/cpt.199]

" Considering the need for consistent outcomes of regulatory decisions, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) used PML as an example to develop a systematic approach to labelling and risk minimization."

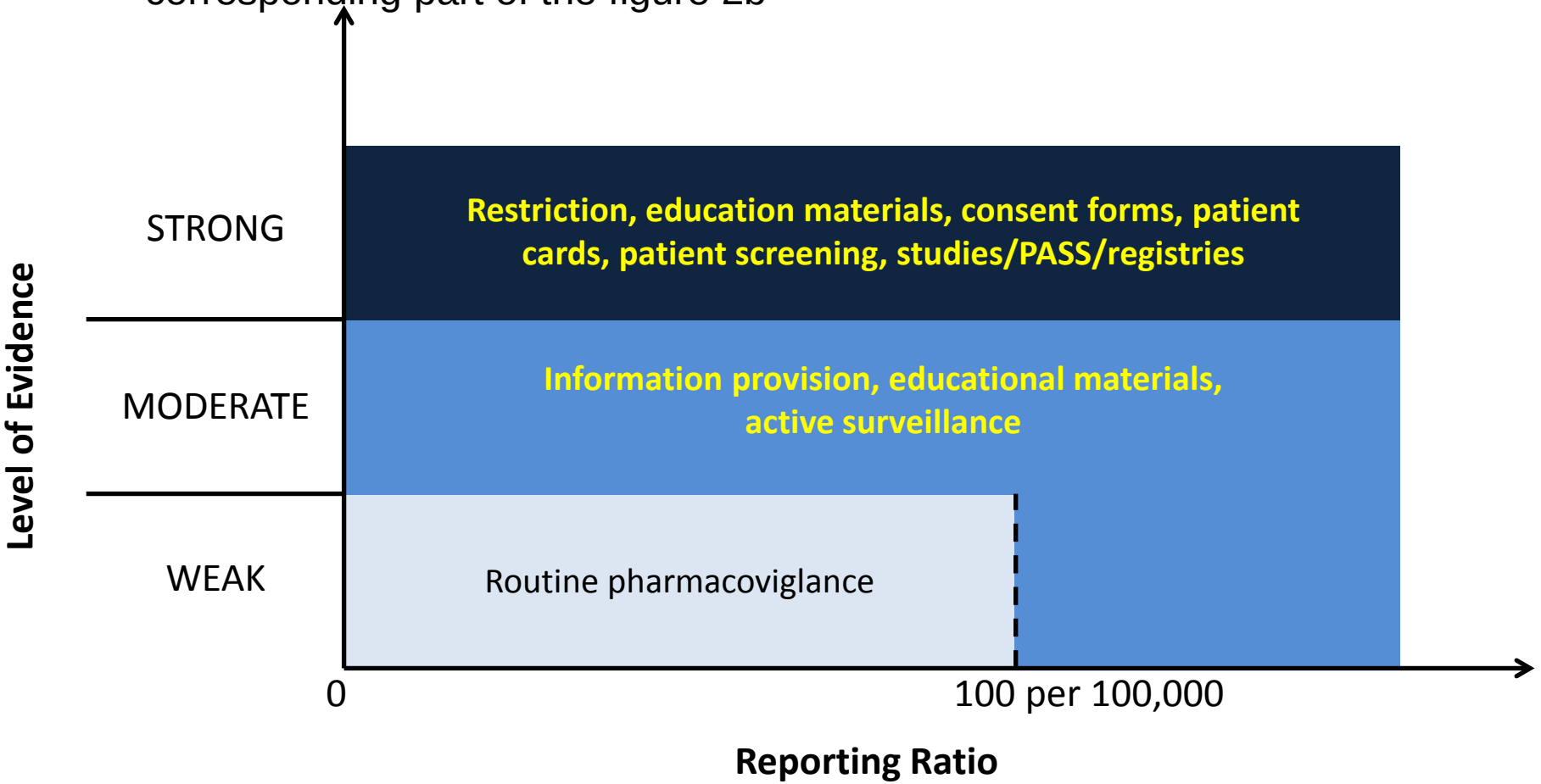
Decision grid for SmPC (white) and RMP classification (red) of PML

Step 1 Locate reporting ratio on x-axis (A1)
Step 2 Locate level of evidence from reports of PML on y-axis based (A2)
Step 3 Adjust position on y-axis after considering additional evidence (A3)
Step 4 The actions corresponding to the strong level of evidence apply to the product



Decision grid for consideration of risk minimization activities for PML

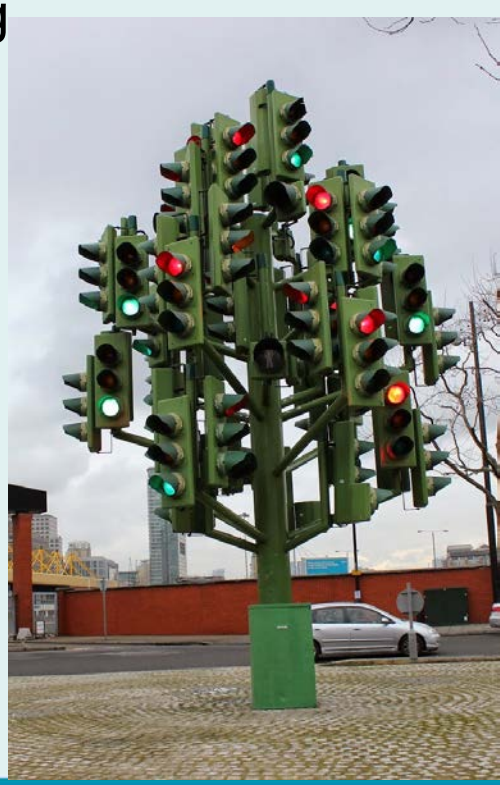
Step 1 Locate reporting ratio on x-axis (A1)
Step 2 Locate level of evidence from reports of PML on y-axis based (A2)
Step 3 Adjust position on y-axis after considering additional evidence (A3)
Step 4 The actions corresponding to the strong level of evidence apply to the product
Step 5 The risk minimization activities to be considered are included in the corresponding part of the figure 2b



Future directions

- Further strengthening collaboration academia & regulators (e.g. ENCePP, research projects)
- More opportunities for guided decision making
- Need to keep reflecting on what we do
  - What works / what not?
  - Consistency

  -> more Drug Regulatory Science



Thanks

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