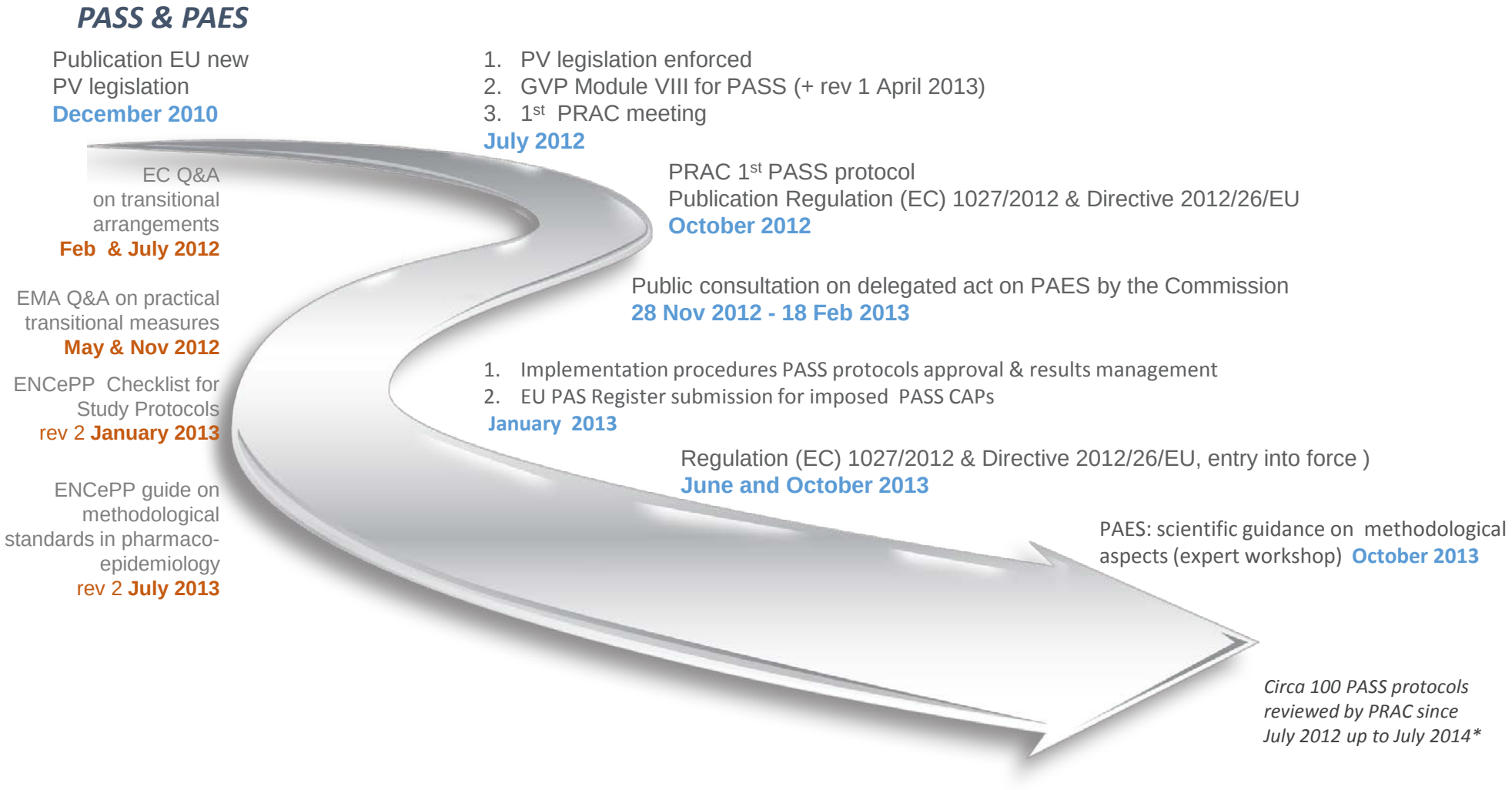
European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

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

ENCePP Plenary Session
Pierre Engel, Quintiles, ENCePP Steering Group
Marieke De Bruin, PRAC, ENCePP Steering Group

A New Era of Safety

The Making of the new PV Legislation



Post Authorization Safety Studies

The GVP module VIII

"Any study relating to an authorised medicinal product conducted with the aim of identifying, characterising or quantifying a safety hazard, confirming the safety profile of the medicinal product, or of measuring the effectiveness of risk management measures."*

- PASS initiated, managed or financed by a MAH
  - Pursuant to an obligation imposed by a competent authority
    - as a condition to the granting of the marketing authorisation, or after the granting of a marketing authorisation if there are concerns about the risks of the authorised medicinal product
    - as part of a marketing authorisation granted under exceptional circumstances.
  - Voluntarily
    - studies required in the risk management plan to investigate a safety concern or evaluate the effectiveness of risk minimisation activities
    - any other PASS

PRAC transparency of activities

PRAC minutes

- **Agenda** is published on Day 1 of PRAC by mid-day *[next meeting 3rd Feb 2014]*
- **Meeting** highlights are published on Friday of PRAC week *[next 7th Feb 2014]*
- **Safety** referrals are published on Friday of PRAC week *[next 7th Feb 2014]*
- **Minutes** are published on the following month after adoption *[next approx 6 weeks after meeting]*

Extract PRAC Minutes Meeting 2-5 Dec 2013

16. ANNEX I Post-authorisation Safety Studies (PASS)

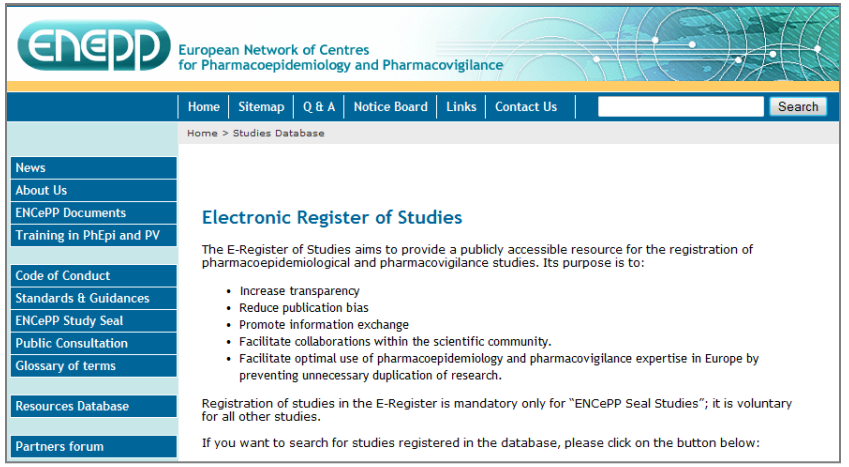
Since all comments received on the assessment of these measures were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs on the assessment of the relevant protocols or study reports for the medicines listed below.

EMA website serves as the EU Medicines Web-portal

ENCePP

The EU-PAS register, GVP and legal obligations driving available protocols

- Guideline on Good PV Practice, Module VIII PASS - VIII.B.4. Study registration
  - "the MAH should make study information […] available in the EU electronic register of post-authorisation studies (EU PAS Register)
  - "The study protocol should be entered in the register before the start of data collection."
- Legal obligations
  - The 2010 PV legislation requires that protocols and abstracts of results of PASS imposed as an obligation are published in a publicly available register
  - It also specifies that the final report of such studies must provide the date of registration in this register
  - Registration for imposed studies must be made no later than at the time of the final study report
  - For imposed studies: does not replace regulatory submission

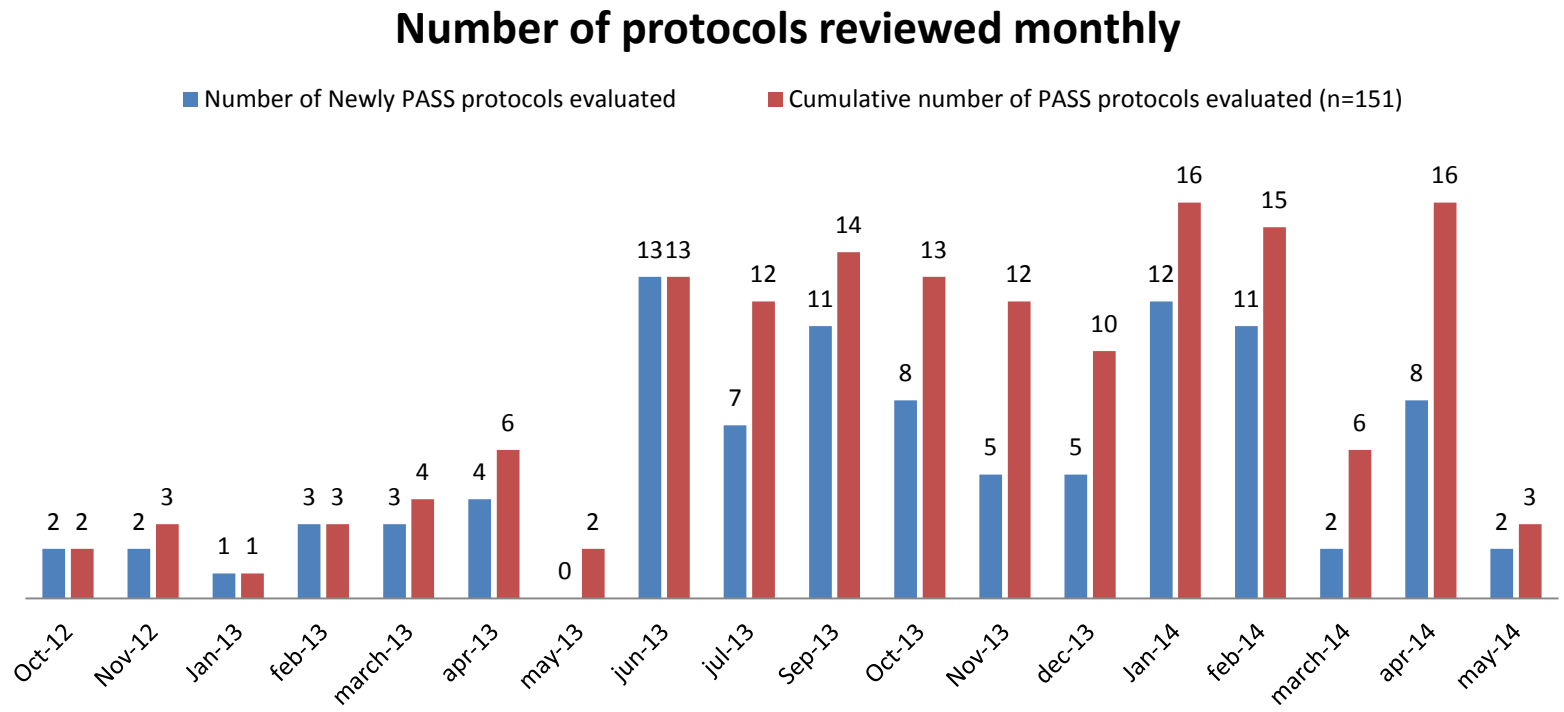


Transitional period:

- ENCePP E-Register of Studies to be used
- Guide for study registration was amended for MAH-sponsored NI-PASS required by a regulatory authority:
  - Acknowledgment email sent by EMA to MAH
  - All Member States informed by EMA of the registration with: title, name of sponsor, countries, link to registry
- **EU PAS Register** is being developed as upgrade of ENCePP E-Register of Studies and will include already

PRAC Review cycles

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



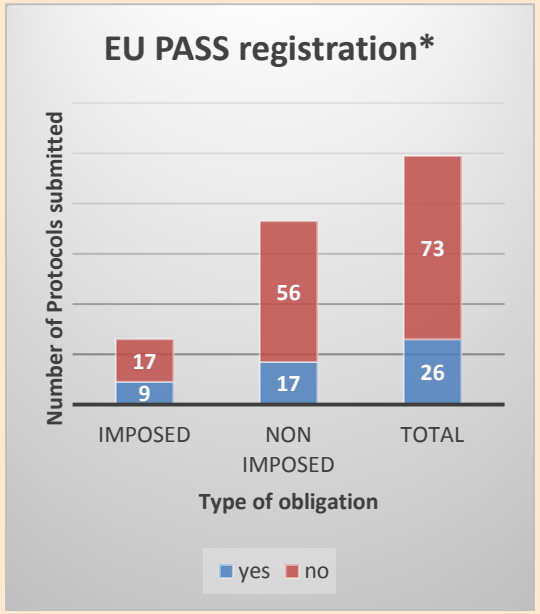
- 99 new protocols evaluated from July 2012 to July 2014 (26 imposed): Overal 150 protocols reviewed
- After one year of meetings, average of 15 protocols evaluated per month
- Median 2 rounds of review for imposed, and 1 round for non imposed

PASS protocols and EU PAS register

GVP Guidelines & Legislation

- GVP guidelines recommend study registration and protocol posting before start of data collection
- However, the legislation requires that protocols and abstracts of results of PASS imposed as an obligation are published in a publicly available register
- 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
- For non imposed studies, no legal obligation to register but recommended

PRAC Figures*

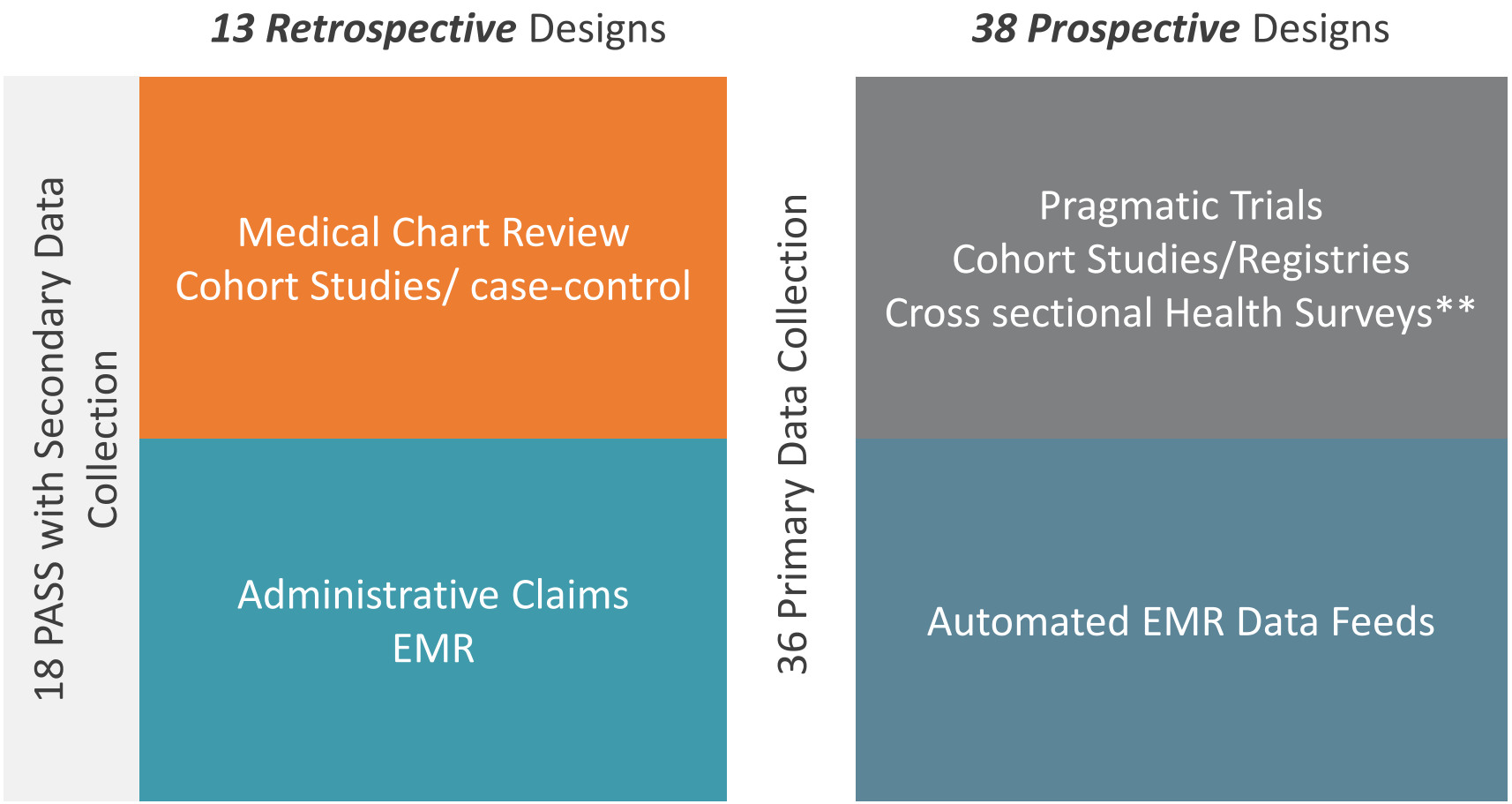


- 35% of imposed and 23% of non imposed studies are registered*
- Between July 2012 and July 2013 these proportions were higher with respectively 40% registration for imposed and 28% for non imposed

Discussion

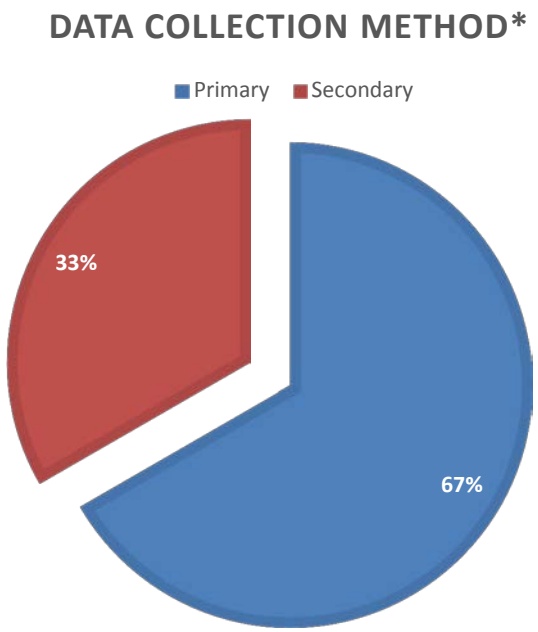
- Overall one out three PASS are registered with an slightly higher proportion for imposed as compared to non imposed
- Although legal obligation only mandate registration at the time of study report, still transparency of PASS registration could be increased especially for non imposed studies.
- With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

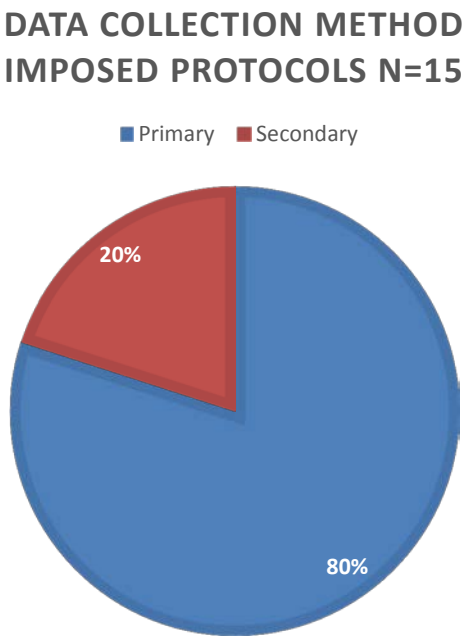
Overview of PASS designs since July 2012*

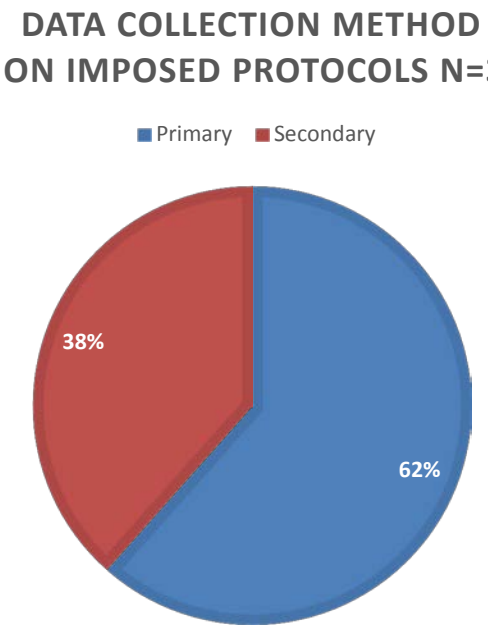


*38 PASS with missing info regarding design
** 11 PASS involving Cross Sectional Risk Minimization surveys

PASS protocols & DC method



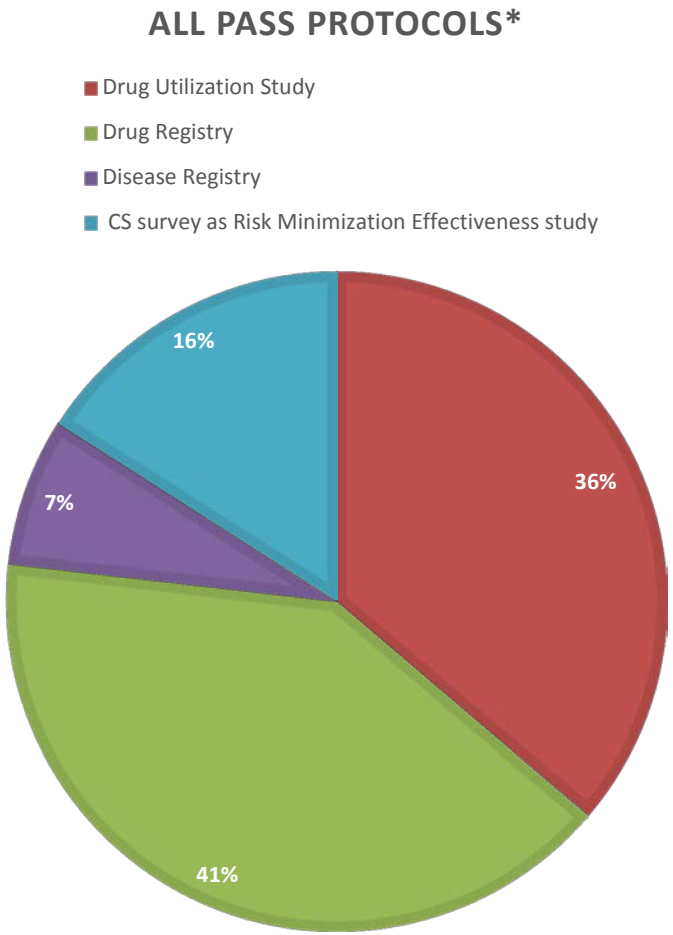


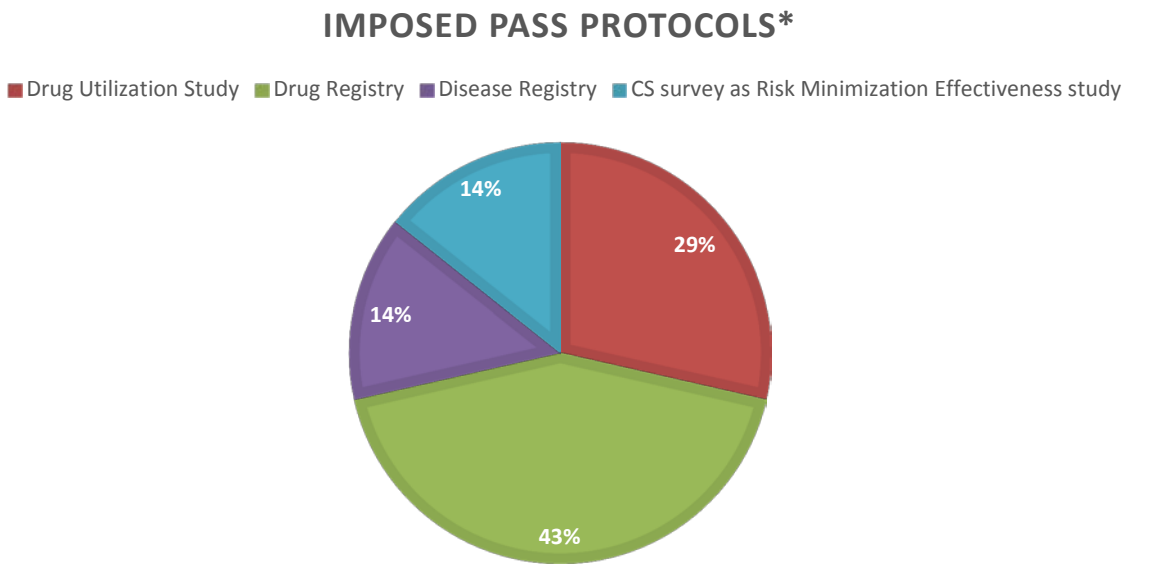


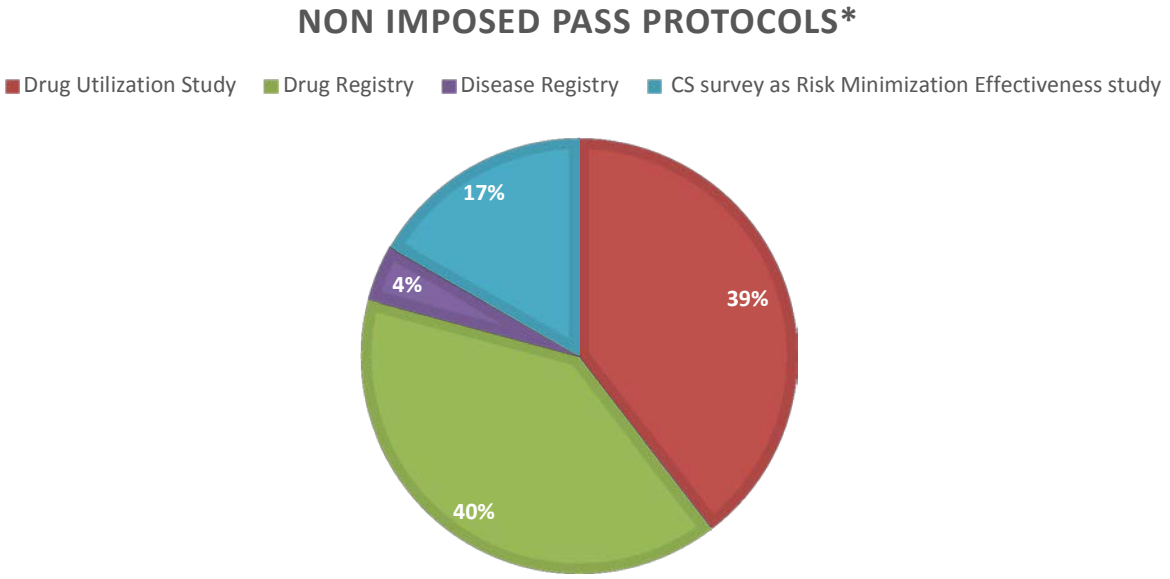
Further considerations:

- 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

Discussion

- Limitation: missing information, complicated processes, endorsement and protocol acceptance not always available
- Data that could support the anticipation of possible design issues, mitigation of methodological challenges to ultimately improve PASS quality standards and expedite endorsement processes.
- Good agreement between data from PRAC Assessment Reports and publicly available data released by the EMA
- Need to
  - Increase transparency and strengthen compliance with ENCePP standards and requirements (code of conduct, checklists, EU-PAS registration)
  - Increase collaboration, communication between ENCePP, EMA committees and other stakeholders
- Upcoming paper to provide metrics on the design and the feedback from the PRAC in the first 2 years of review

Questions?

Pierre.engel@quintiles.com