HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority

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Post Authorisation Safety Studies – PRAC experience

8th Stakeholders forum – 15 September 2014

Presented by Dr. Almath Spooner, Pharmacovigilance and Risk Management Lead, Health Products Regulatory Authority, Dublin, Ireland and Vice Chair, PRAC, EMA, London.

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Regulatory evolution

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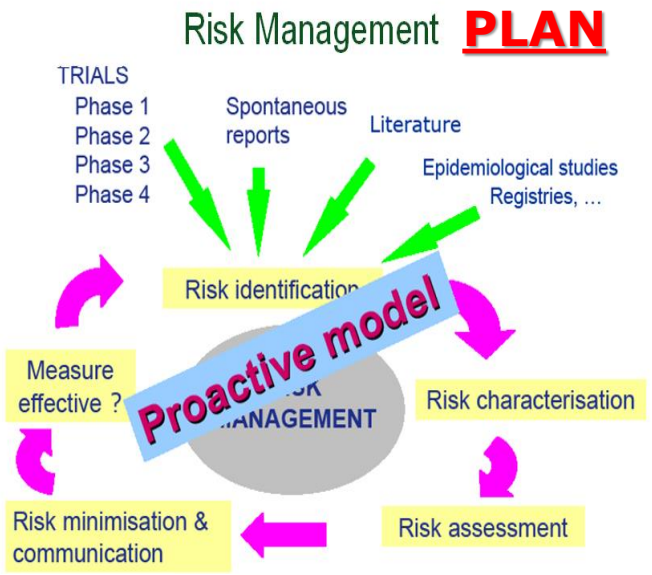
Historical perspective– Binary licensing decision, reactive pharmacovigilance with over-reliance on spontaneous reports.

With RMPs, move towards more proactive PV, **strengthening methodologies for investigating drug safety**.



ICH E2E principles –
identify what is known and important, what is unknown and prioritise **most important uncertainties - plan data collection to reduce**.

PV requires variety **of data streams**.

Today, ambition is for benefit-risk monitoring, integrated throughout product life cycle.

Regulatory evolution

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19 March 2014
EMA/420892/2013
Press Office

Press release

European Medicines Agency launches adaptive licensing pilot project

Improving timely access for patients to new medicines: pilot explores adaptive licensing approach with real medicines in development

The European Medicines Agency (EMA) is inviting companies to participate in its adaptive licensing pilot project. Companies who are interested in participating in the pilot are requested to submit ongoing medicine development programmes for consideration as prospective pilot cases.

A framework to guide discussions of individual pilot studies has been published.

The adaptive licensing approach, sometimes called staggered approval or progressive licensing, is part of the Agency's efforts to improve timely access for patients to new medicines. It is a prospectively planned process, starting with the early authorisation of a medicine in a restricted patient population, followed by iterative phases of evidence gathering and adaptations of the marketing authorisation to expand access to the medicine to broader patient populations.

EMA Adaptive Licensing Project

2. Real-world monitoring, data collection and use, as a complement to RCT data, in subsequent regulatory decision making. This is assisted by good definition of the target population (e.g through restricted indication), and additional risk minimisation measures, such as educational programmes, controlled access programmes, including patients registries) that promote the likelihood of real-world data collection.

NEWDIGS NEW Drug Development ParadIGmS Initiative

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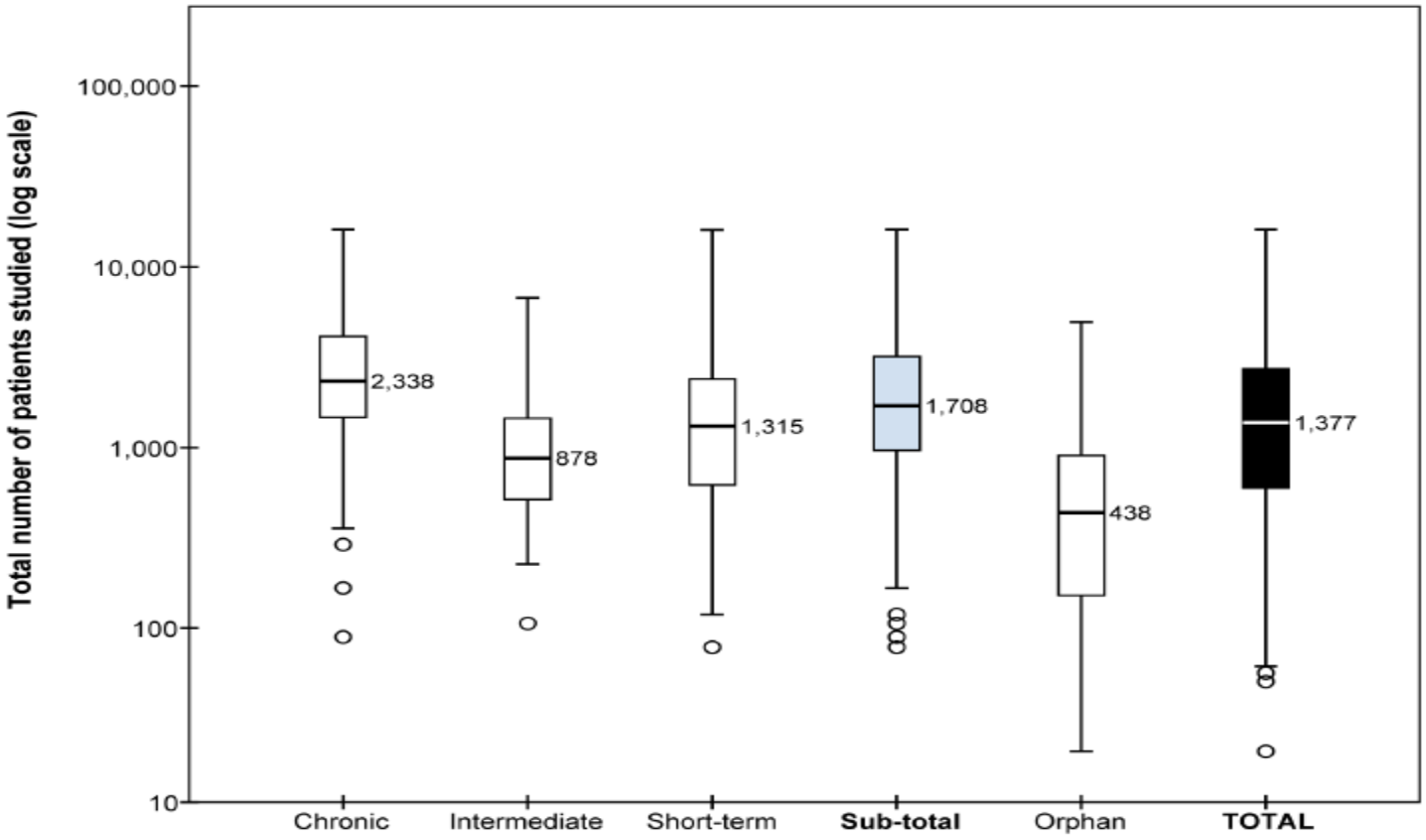
imi

efpia
European Federation of Pharmaceutical Industries and Associations

MIT Massachusetts Institute of Technology

Understanding uncertainty

Ruben G. Duijnhoven et al. 2013. PLOS Medicine. Number of Patients Studied Prior to Approval of New Medicines: A



Road map for PRAC

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- Supporting generation of **the necessary robust evidence** to support regulatory decision making and identification of relevant data streams for benefit-risk assessments – improve use and understanding of pharmacoepidemiology and pharmogenomics.

- **Optimal use of new methodologies** and tools – characterisation and quantification of risk and benefit-risk.

- **Stakeholder engagement** in benefit-risk evaluation and risk minimisation.

- Building capacity and **sustainability**, supporting **lifecycle B/R management** and risk proportionality.

Risk Management Plans – Building Phase

- Identifying **critical uncertainties** regarding B/R
- **Safety specification** – prioritising **'important'** safety concerns and how to address uncertainties, provide reassurance of safety, investigate population use.
- Will **Routine PhV sufficiently** reduce uncertainties (time)
- If not, consider need for **PASS**, other **additional PhV – data source and analytical design appropriate to the question.**
- **Risk Minimisation activities** – safety concerns addressed by labelling? Any uncertainties? Other tools? Effectiveness assessment? Impact on patients and HCPs?
- Adjustments during review process - discussions PRAC, CHMP, EMA, SAG etc; connecting B/R discussions and RMP building.

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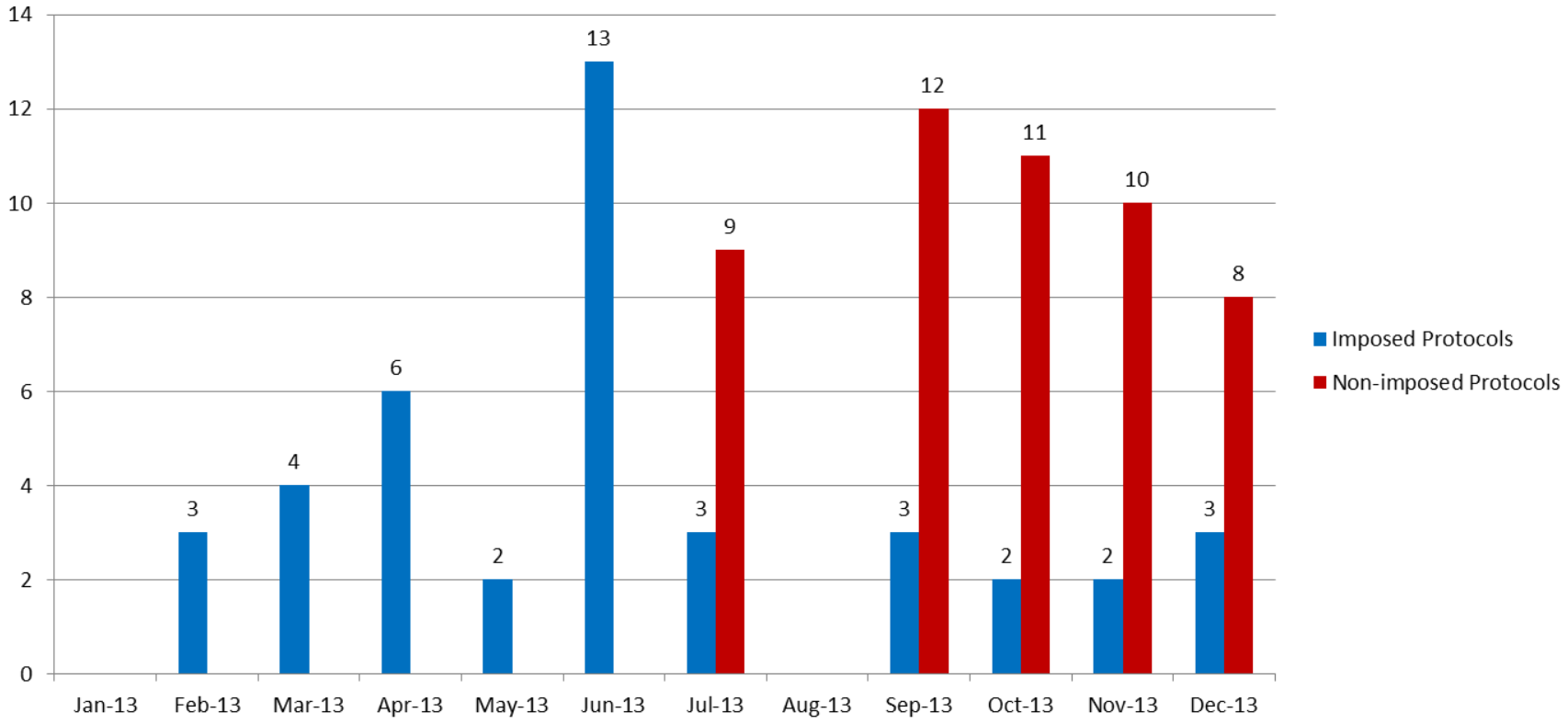
PASS Protocols on PRAC Agendas in 2013



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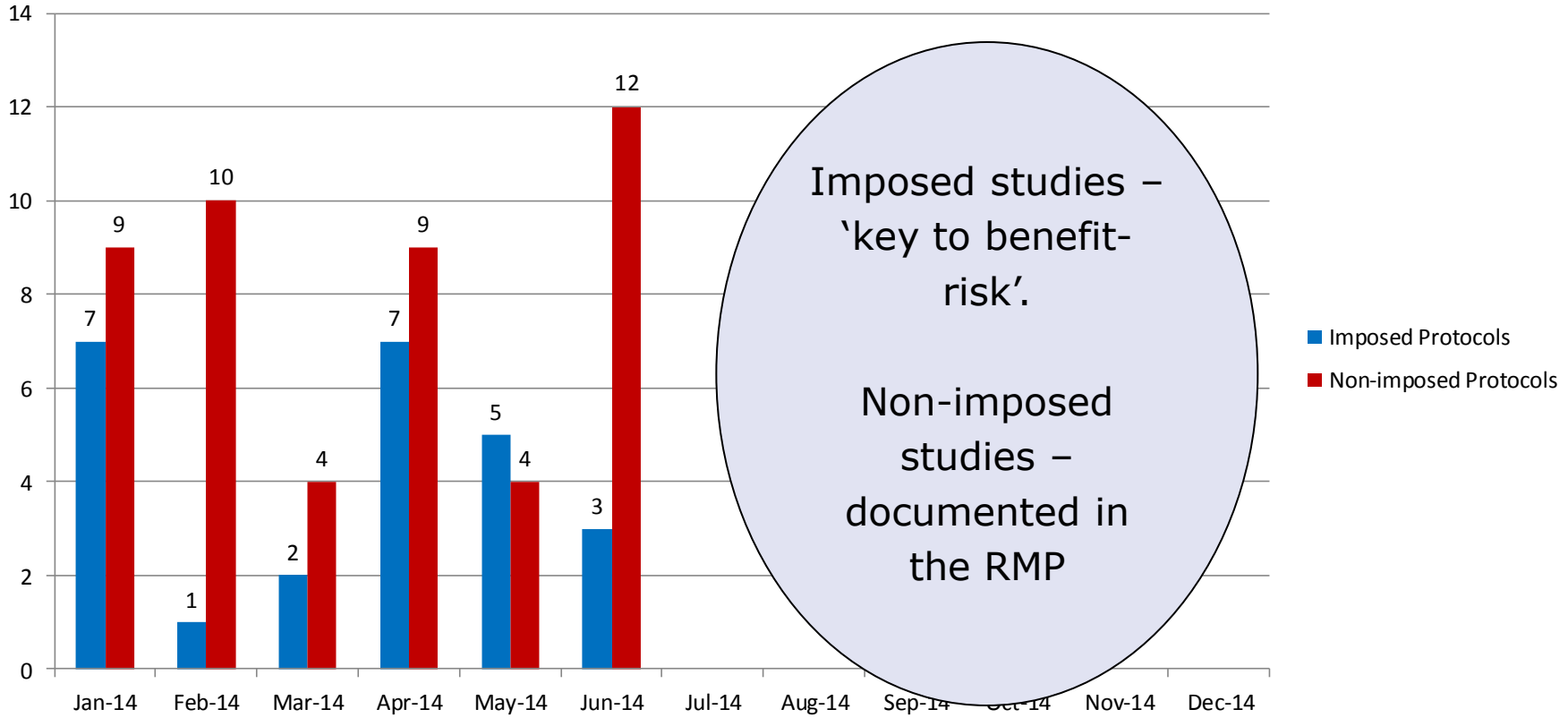
PASS Protocols on PRAC Agendas from January-June 2014



Examples of types of PASS included in RMPs and/or reviewed by PRAC

Registries (prospective cohorts)

For example, to assess safety profile of (orphan) drugs, **health outcomes** in patients treated in clinical practice – non-interventional, safety and effectiveness. Early feasibility planning is important – existing infrastructure. Consideration of comparator.

Database studies

For example, for risk characterisation, investigation of targeted AEs. Matching database availability with population exposure. Information on confounders. Comparators.

Drug Utilisation Studies (DUS)

For example, to assess effectiveness of additional risk minimisation or as a foundation for pharmacovigilance planning/signal management.

Special populations: pregnancy registries, paediatrics, elderly.

Medication errors: Human Factor Studies

Published pharmacoepidemiological studies

Protocol assessment at PRAC

VIII.C.4.2. Roles and responsibilities of the PRAC and national competent authority

When the PRAC is involved in the oversight of the study, the PRAC will nominate a PRAC rapporteur responsible for the supervision of the PASS. The PRAC rapporteur should write a protocol assessment report, including a list of questions if appropriate, and submit it for review and approval by the PRAC.

If the study proves to be interventional, the PRAC rapporteur should not provide an assessment report but should issue an explanatory statement to the marketing authorisation holder that the study is a clinical trial falling under the scope of Directive 2001/20/EC.

Within 60 days from submission of the draft protocol, the national competent authority or the PRAC shall issue a letter endorsing the draft protocol, a letter of objection or a letter notifying the marketing authorisation holder that the study is a clinical trial falling under the scope of Directive 2001/20/EC. The letter of objection shall set out in detail the grounds for the objection in any of the following cases:

- it is considered that the conduct of the study promotes the use of a medicinal product;
- it is considered that the design of the study does not fulfil the study objectives [DIR Art 107n(2)].

Methodological challenges to be addressed in drug safety research

1. Channelling

2. Confounding by indication/disease severity

3. Exposure measurement

4. Practical feasibility (and being realistic) – uptake, power

Data source and study design appropriate to question

Need to deal with systematic as well as random error.

PASS in practice

- There is an established role for observational studies to study post-marketing safety
- However, many challenges when designing, executing, interpreting, etc
- Difficult to develop guidelines, as challenges are often related to the specific drug-adverse event pair studied
  - Good Pharmacoepidemiology Practices (ISPE)
  - Guide on methodological standards (ENCePP)
  - GVP Module VIII: PASS (EMA)

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Post-authorisation safety studies (PASS)

A post-authorisation safety study (PASS) is a study that is carried out aft further information on a medicine's safety, or to measure the effectivene Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRA imposed PASSs and for assessing their results.

The purpose of the information in PASSs is to evaluate the safety and benef decision-making. They aim to:

- identify, characterise or quantify a safety hazard;
- confirm the safety profile of a medicine, or;
- measure the effectiveness of risk-management measures.

PASSs can either be **clinical trials** or **non-interventional studies**.

Imposed and voluntary PASSs

PASSs are either imposed or voluntary:

- EMA studies : in house, commissioned
- ENCePP contribution
- FP7 studies to date

SEVENTH FRAMEWORK PROGRAMME

ENEPP European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

30

Post marketing data collection in a multi-stakeholder environment – investigating drug safety and population use of medicines

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eunethta

11 July 2014
EMA/299386/2014

Final Minutes of EMA/EUnetHTA meeting
15 May 2014 – chaired by Hans-Georg Eichler and Finn Børlum Kristensen

Role	Name
Chairs	Hans-Georg Eichler and Finn Børlum Kristensen

Encouraging' use of disease registries, joint studies

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What do we currently ask for in RMPs?

Data for all new MA with RMP from 1/1/2010 to 31/12/2012:

How many of the RMP for new MA mention a registry?

- Of the 123 RMPs identified, 30 had a registry (24%)
- All of these were additional PhV activities

Number of RMPs by risk	Identified Risk	Potential risk	Missing information
Number of RMPs with registry	11	13	24

s to be addressed by working group 3 – Registries

tailed information on patients diagnosed with a certain disease or treated with a certain
d setting, established registries provide an opportunity to assess patient outcomes,
veness.[4] However, their recruitment is not always exhaustive, they may include
under treatment and a comparator group may not be available.

pes of research questions are established registries particularly appropriate when
icacy? For which ones are they not appropriate?

be design options for studies on efficacy based on established registries?

t is the feasibility of setting up registries in different health care systems? What is the
ibility of merging several registries, and of merging registries with other datasets (e.g. with
ital/laboratory data)?

How to encourage companies to collaborate

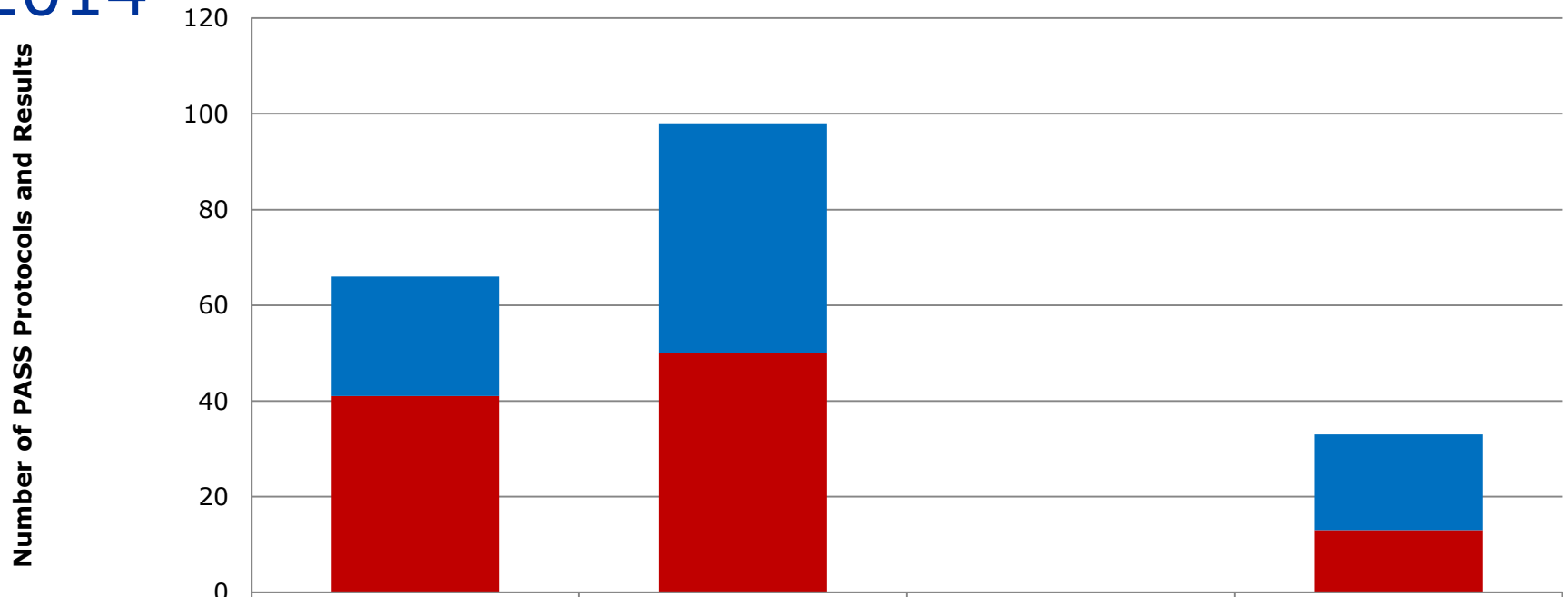
- By imposing to several different companies the obligation to create a registry at the same time
- Not imposing registry but sitting companies toge discuss creating of a disease registry
- Identify and approach a suitable academic/patie organization and suggest collaboration with rele companies

ENCePP Centres with experience in registries

Currently listed 77 centres which have established at least one registry:

Adobe Acrobat Document

PASS: agenda items relating to protocols and results on PRAC Agenda from 2013 to June 2014



	Imposed Protocols	Non-imposed Protocols	PASS Results on Imposed Protocols	PASS Results on non-Imposed Protocols
Up to June 2014	25	48	0	20
2013	41	50	0	13

Interpreting observation study results

- Key challenge is to be convincing on causality

- The estimation of possible bias is very difficult. Sampling error and confidence intervals do not capture this uncertainty.

- "Real world" but not necessarily as real as you may think - exclusion criteria important for causality (perhaps) but bad for generalisability

- B/R balance must be assessed on an absolute scale (Absolute Rate, AR – rate per person time). Analysis usually on a relative risk scale (Risk Ratio; Odds Ratio; Hazard Ratio; Incidence Rate Ratio) but the interpretation and any assessment of benefit risk balance has to be done on an absolute scale

- Risk/benefit balance will usually vary with time . Rate per Person time assumes the hazard (instantaneous rate) is constant.

Some recent examples of systematic reviews and meta-analyses informing regulatory decision making

Efficacy and safety of dual blockade of the renin-angiotensin system: meta-analysis of randomised trials

OPEN ACCESS

Harikrishna Makani *fellow in cardiovascular medicine*[1], Sripal Bangalo *outcomes group, assistant professor of medicine*[2], Kavit A Desouza *fe medicine*[1], Arpit Shah *resident in internal medicine*[1], Franz H Messerli *p*

CARING FOR THE CRITICALLY ILL PATIENT

Association of Hydroxyethyl Starch Administration With Mortality and Acute Kidney Injury in Critically Ill Patients Requiring Volume Resuscitation

A Systematic Review and Meta-analysis

Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

Coxib and traditional NSAID Trialists' (CNT) Collaboration*

Evaluating effectiveness of risk minimisation

Effectiveness assessment often requires evidence from multiple domains/metrics rather than a single measure.

Ability to make comparison to non-intervention group can be limited.

Outcome evaluation- effectiveness vs. Burden

-Determining metrics and collecting data to allow assessment of 'burden' and 'access' – distinguishing 'undue' from 'total' and 'unintended' from 'intended' – stakeholder input?

- **Establishing target thresholds**

-No consensus on appropriate level - further improvement or maintenance over time is often the goal- do measures ever become standard of care/integrated into clinical practice??

Future directions?

- Earlier planning?

- Greater dialogue?

- How to facilitate patient and HCP engagement?

- Clear objectives, understanding of data source, study design and analytical design, implementable methodology.

- Avoid duplication of effort.

-Measure impact –what are PASS delivering, how are uncertainties reduced, see impact on the RMP over time.

- How to communicate results – promoting understanding of different data streams, differentiating absolute risks from relative risks, increased use of graphics?

Conclusions

•Proactive investigation of drug safety is a PRAC priority.

• Real world data increasingly contributing to benefit-risk monitoring.

• Requires multi-stakeholder approach to ensure that the necessary evidence is available for benefit-risk monitoring.

• Pharmacovigilance planning should support prioritisation of important safety concerns, ideally incorporating data streams well adapted to answering clearly defined research questions. Routine pharmacovigilance systems need to be entirely robust in order to deal with '*unknown unknowns*'.