Flip the Coin: The Next Epoch of Drug Development

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Content

- Why do we conduct non-interventional studies(s)
- Design and reporting of NIS, Challenges in conduct and its impact
- Real time Experiences

Current drug development process....

- Controlled, Randomized, comparative clinical trials
- Well defined regulatory guidelines and regulations
- Standard way of reporting clinical trial data
- Standard statistical methods used
- Working in "*My Function*"!!

Why drug recall from market

- "Drug is removed from the market when its risks outweigh its benefits"- US-FDA
- A case of Vioxx[1] (Rofecoxib)
  - Drug in Market for 5.3 years (May 20, 1999 to Sept 30, 2004)
  - Why recall: Increased risk of heart attack and stroke

[1]*MSNBC Staff, "Report: Vioxx Linked to Thousands of Deaths," www.nbcnews.com, Oct. 6, 2004*

What is missing....

- What happens after drug approval- “Monitoring of drug”
- How the **effectiveness** of drug is assessed in “real-life”

Effectiveness of Drug in “**Clinical Practice**” need more focus

Non-Interventional Studies

Regulatory Considerations

Non-interventional Studies

HMA
Heads of Medicines Agencies

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

8 September 2014
EMA/873138/2011 Rev 1*

Guideline on good pharmacovigilance practices (GVP)

Module VI – Management and reporting of adverse reactions to medicinal products (Rev 1)

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Why Non-Interventional Studies (NIS)

- Trials conducted in development phase of the product
  - Phase 1-4; efficacy of an investigational product
  - Patient population which has been selected according to **strong** inclusion and exclusion criteria
- To collect and provide **Real World Data** from our patients
- **80%** of patients are **enrolled in NIS,** only 20% are enrolled in clinical trials
- NIS have become a **focus point internally and externally** due to changes in European legislation, compliance issues and audit and inspection findings.

Requirement for NIS

Study Protocol and Informed Consent Form (ICF)

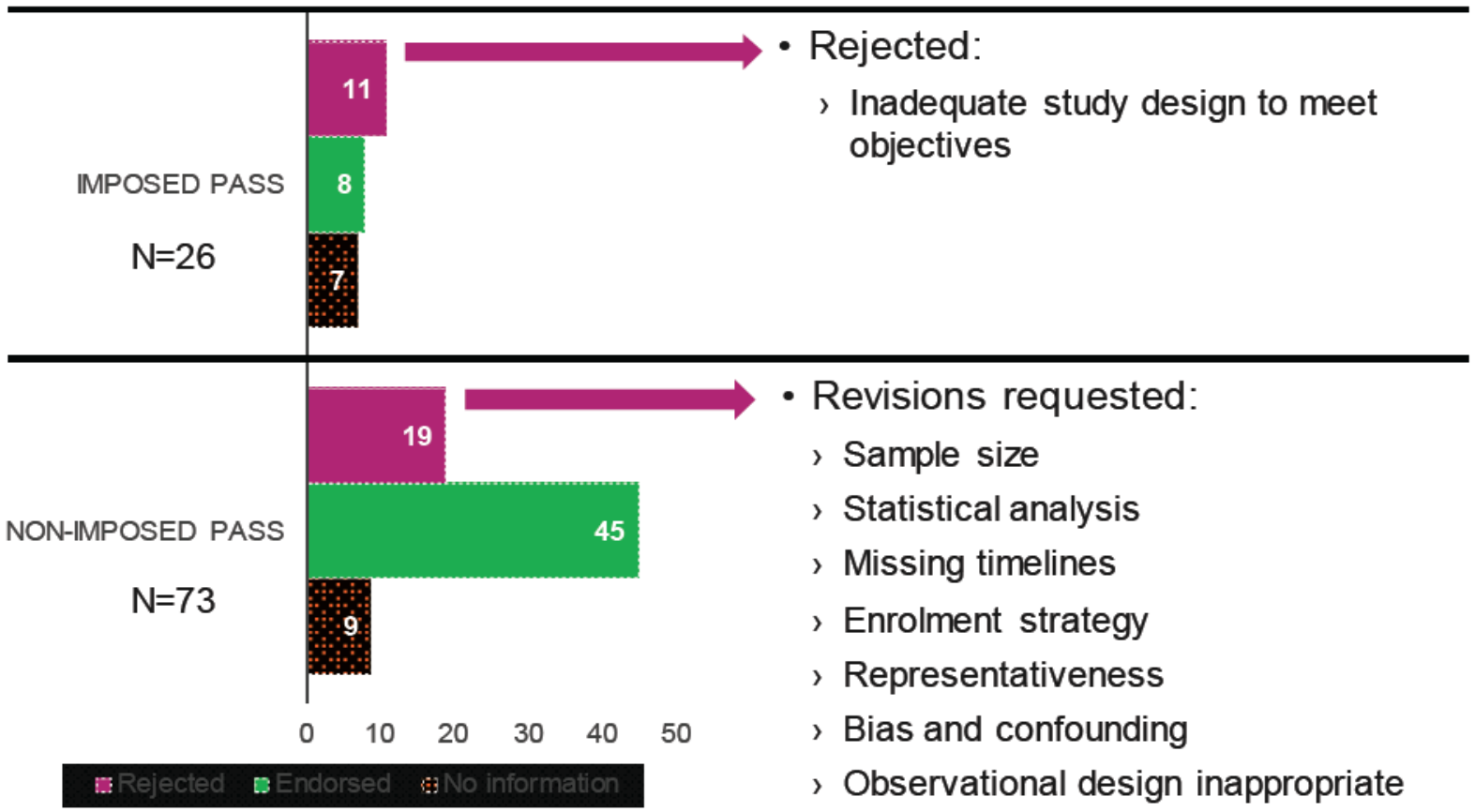
- Study Protocol
  - Scientific rationale for the choices of the study design, analysis, conduct and reporting of a research study
  - Aligned to routine clinical practice
  - Allows successful replication of results

- Informed Consent
  - Simpler than RCT
  - including retrospective study

Need scientific study designs !!!

Some facts

Review of first 24 Months of PRAC Oversight from July 2012



- Rejected:
  - Inadequate study design to meet objectives
- Revisions requested:
  - Sample size
  - Statistical analysis
  - Missing timelines
  - Enrolment strategy
  - Representativeness
  - Bias and confounding
  - Observational design inappropriate

Lessons Learned on the Design of European Post Authorisation Safety Studies (PASS). ENCePPPlenary Meeting, 25 November 2014

Statistical Challenges (1/3)

- Validity
- Randomization and confounding
- Not trials!!!

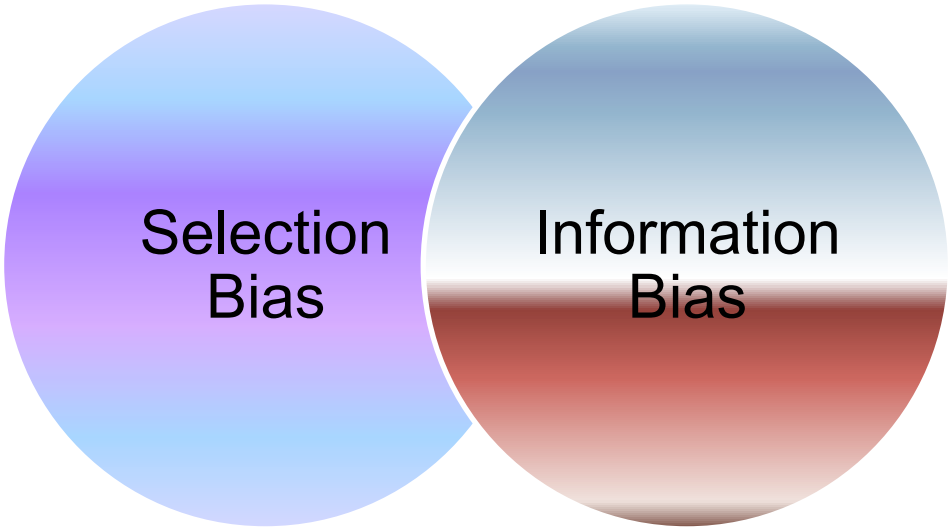
Statistical Challenges (2/3)

- Bias

Selection bias

Information bias

⇒ **Can’t be corrected in analysis**



Statistical Challenges (3/3)

- Handling of missing data
- Sample size determination

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Thanks for your attention☺