EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Opportunities for the use of regulatory data

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Disclaimer

The views expressed in this presentation are the personal views of the speakers and may not be understood or quoted as being made on behalf of or reflecting the position of the EMA or one of its committees or working parties.

Acknowledgements

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Outline

- Key regulatory questions
- Challenges in CNS drug development
- Clinical trial effect
- Opportunities with analysis of individual patient data

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Key regulatory questions

- What is of primary interest to regulators?
  - **Safe and effective** medicinal products available to patients
  - **Protecting patients from harm**
- Thus facilitate efficient and robust drug development
  - More **efficient studies** allowing for **valid and robust conclusions** (e.g. design issues)
  - Increase understanding of data from clinical trials (regulatory assessment/review)

Recent positive developments in CNS

- Existing medicines represent a significant progress from a historical perspective
- Several EMA approvals in 2017 (including for rare diseases and/or conditions with high unmet medical need)

- But
- Still unmet need with high economic and societal impact
- Phase III attrition rate higher in CNS than in other areas
- Need to develop drugs for early stages of disease / partial responders / benign safety profile

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Challenges in CNS drug development

https://www.nature.com/articles/nrd.2016.237.pdf
Butlen-Ducuing, Florence, et al. "Regulatory watch: challenges in drug development for central nervous system disorders: a European Medicines Agency perspective." (2016): 813.

- Butlen-Ducuing et al, 2016: Challenges in drug development for central nervous system disorders: a European Medicines Agency perspective
- Study conducted on evaluation files to understand the **main determinants of the outcome of a regulatory application**
  - The evaluation of a dossier in Europe foresees that all issues identified as raised as Objections to Applicant.
  - **Major Objections** are assumed to reflect the critical points of a medicinal product development.

Data

- All applications for **Initial Marketing Authorisation or Extension of Indication** for Neurological and Psychiatric Conditions
- *Ab urbe condita* up to December 2014

By Indication	By procedure	By Outcome
46 Psychiatry	70 Initials	74 Positive
57 Neurology	33 Extensions	29 Negative

- Submitted dossier not a random sample of drug development programmes (EMA submissions, not at national level)

Outcome variable for the analysis

- Outcome of an application → three levels
- 1) **Approval** of the **full indication** as applied for by the applicant
- 2) **Approval** with **restricted indication** as compared to the one it was applied for
  - e.g. application for two conditions but only one approved
  - or restricted to a subset of the targeted population
- 3) **Refusal**

Main exposure variable for the analysis

- Content analysis to classify objections in **18 categories**
- Across **5 domains**: early phase, planning of confirmatory studies, efficacy, safety, clinical relevance

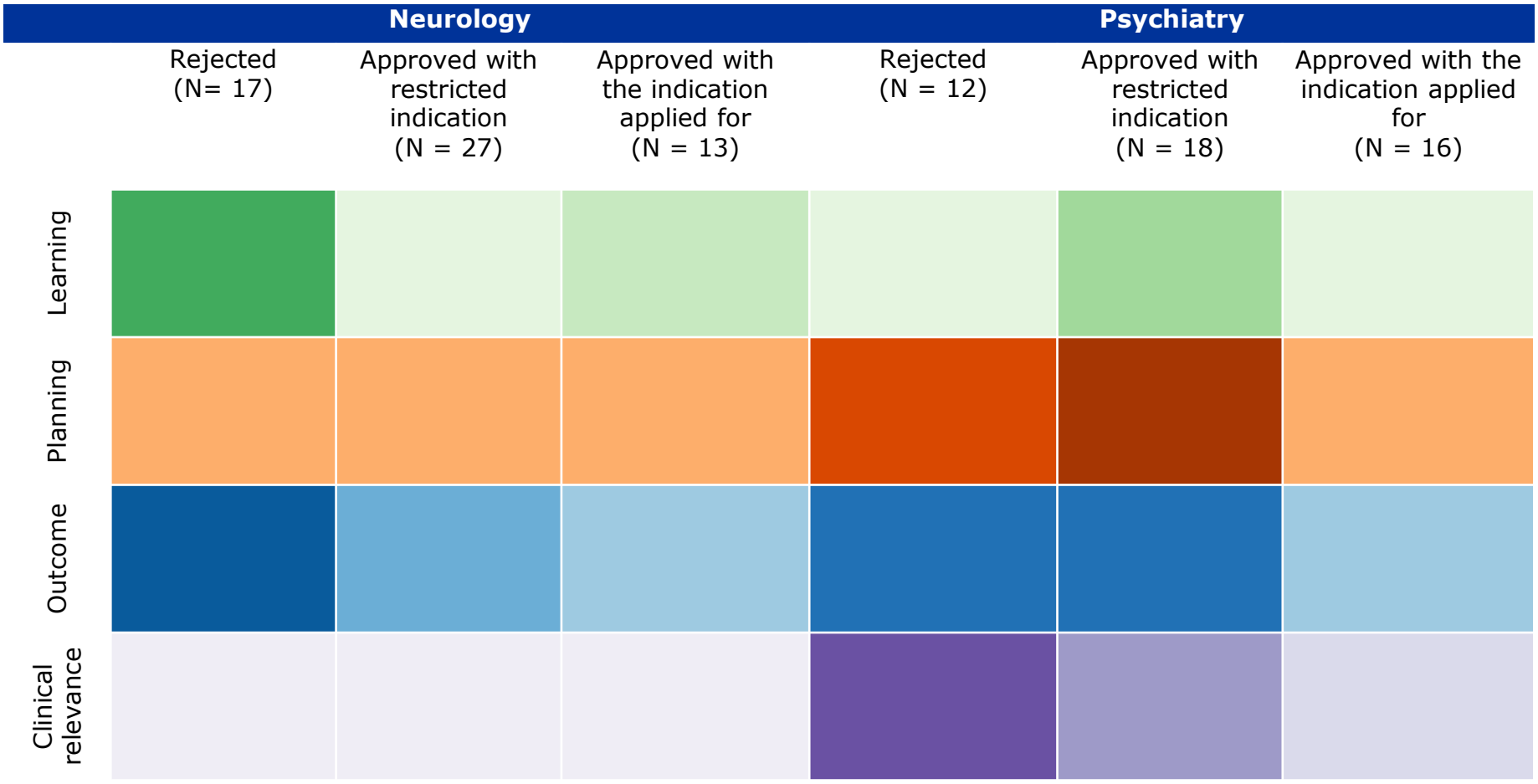
Examples		
Variable name	Description	Raised (Y/N)
Insufficient justification of the dose	Dose finding for confirmatory studies missing or not properly performed	
Choice of comparator	Objections concerning the choice, the dose or the lack of comparator	

Method of the main analysis

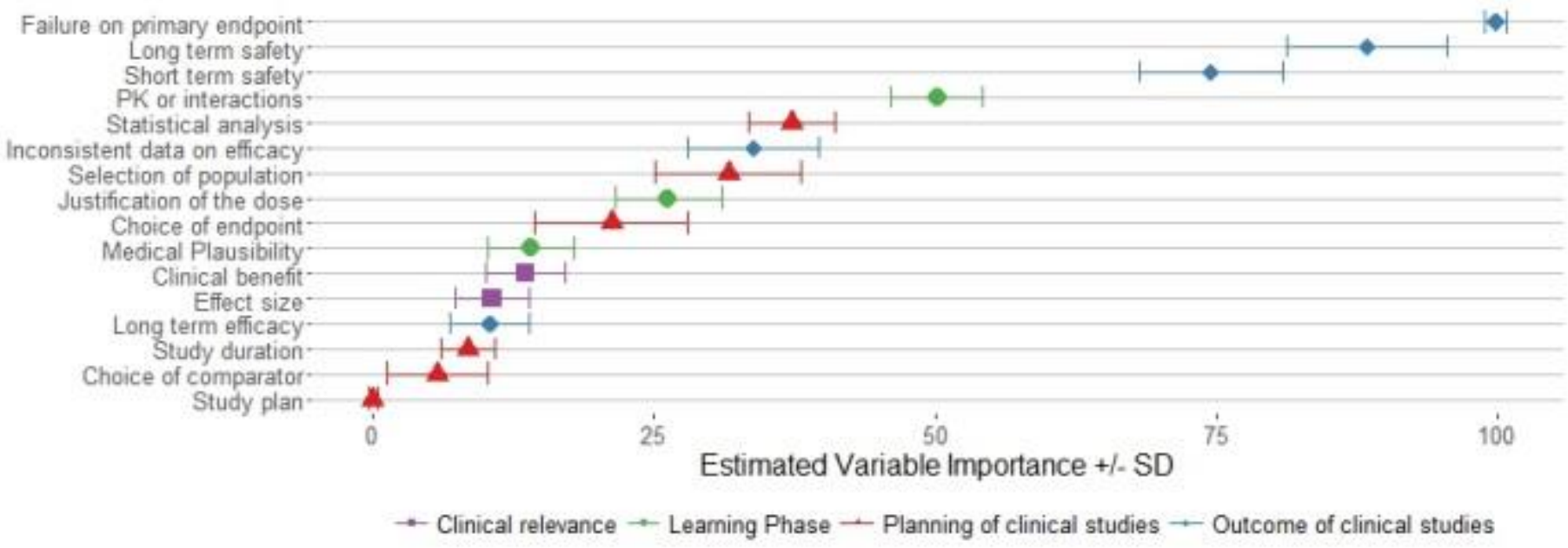
- Main model: **Random Forest** (Breiman, 2002)
  - "Variable importance" of the categories of Objections as predictors of outcome as indicator of the "importance" of each pitfall identified in the clinical developments.
  - Average and variability from 1000 "random forests".
  - Model chosen due to no overfitting despite many predictors and limited dataset.
- We also did **linear modelling** to confirm the analysis results.

Results: % of objections by domain

Percentage of MOs by TA, domain and outcome shown as proportional to the colour darkness.

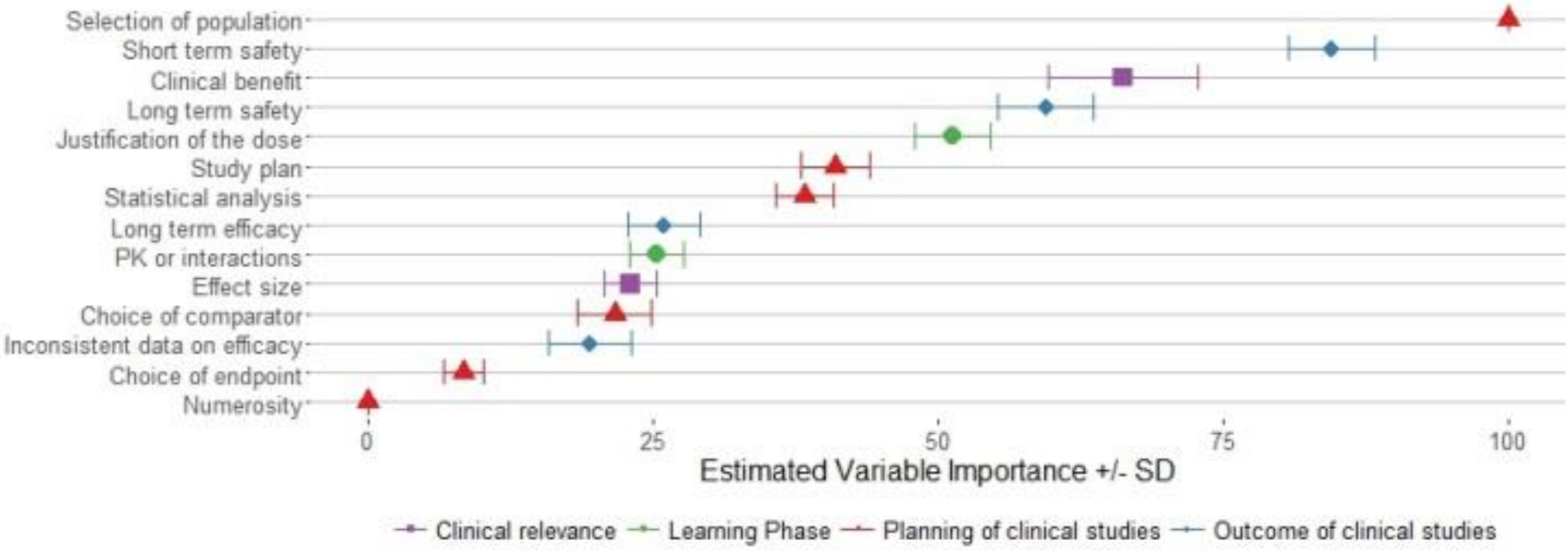


Results – Variable importance in Neurology



- Issues with strongest impact on the outcome of applications in neurology: **failure to reach the primary end point**, **safety** and lack of properly conducted specific **PK/PD studies**.

Results - Variable importance in Psychiatry



- Issues with strongest impact on the outcome of applications in neurology: **selection of the population, safety, clinical benefit** and lack of proper **justification of the dose**.

Main findings on challenges for CNS drug dev.

- The evaluation of dossiers in **Psychiatry** often detects issues in **planning of confirmatory studies** and **clinical relevance** of results.
- On the other hand, **Neurology** evaluations focus on **outcome of confirmatory studies**.
- For **both** Neurology and Psychiatry, the outcome of applications does not only depend on safety and efficacy results but also on elements of the **learning phase** (e.g. PK and dose finding).

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Placebo effect in depression and schizophrenia

- High number of **failed clinical developments** over past 20 years in major depressive disorder and schizophrenia
- **Known factors**: lack of knowledge of the pathophysiology, lack of biomarkers, lack of well-validated preclinical models, and…
- **Response to placebo**
  - In the context of a randomised parallel placebo-controlled trial
  - What are the determinants of change in the placebo arm?
  - Investigational treatment may actually not be efficacious or trial may be inefficient

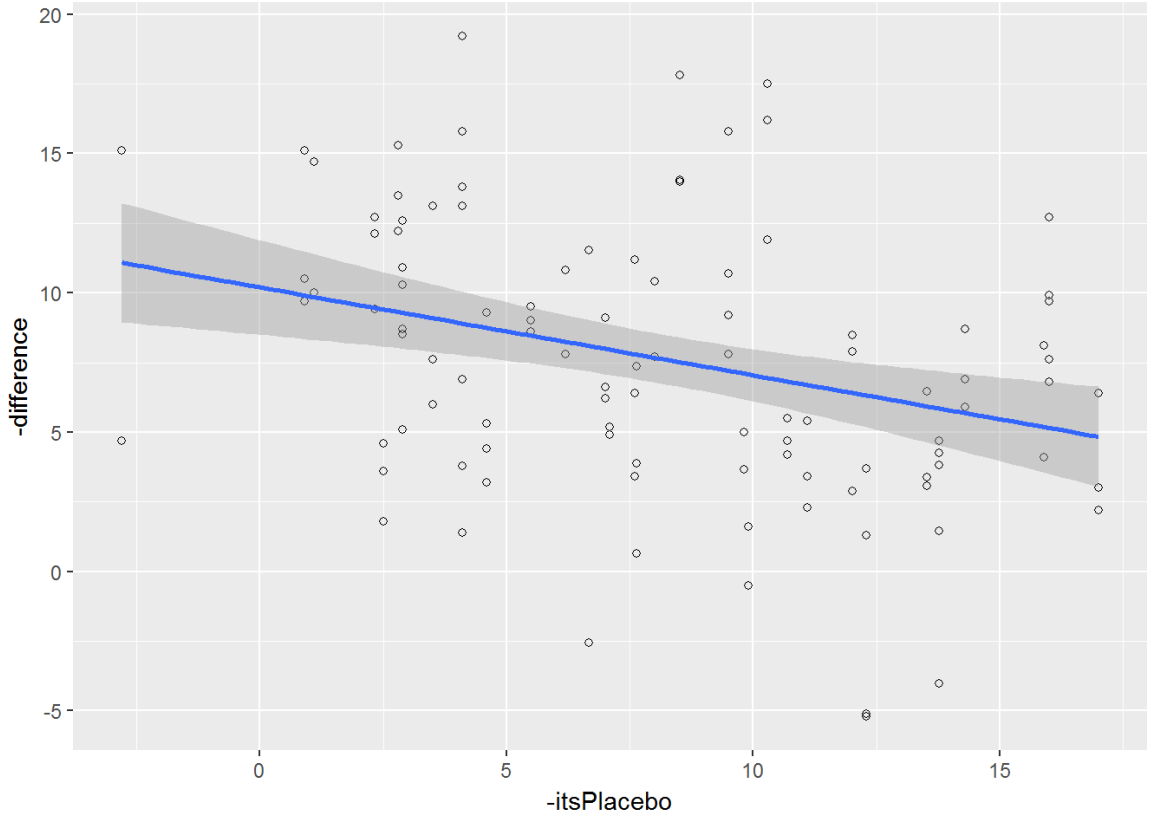
Placebo effect or clinical trial effect?

- **Positive expectancy** with regard to the non-specific effects of a treatment attributable to factors other than specific active components.
  - e.g., health care setting, medical rituals, and engagement with health care professionals
  - confirmed in a number of meta-analyses in psychiatry
- Effect occurs among **all patients** - randomly assigned to receive placebo and active treatment
- Magnitude of placebo effect so large that **trial fails to distinguish effect** of active treatment vs. placebo **OR effect is absent**

Data and outcome measure

- Parallel, **short-term**, randomised double-blind placebo-controlled clinical trials submitted to EMA for regulatory approval; major depressive disorder and schizophrenia
- Baseline and final values, or change from baseline
  - **HAMD-17** for MDD and **PANSS** for SCZ
- Mean difference:
  - Not a standardised mean difference
  - Not a standardised scale

An additive effect?



- Difference between treatment and placebo **vs.** change from baseline in the placebo arm
- Decrease in the difference between treatment and placebo:
- Non-fully **additive effect**?
- **Artefact** of the data?
- Is the correlation between these two factors caused by other **confounders**?

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Access to individual–patient data: an obvious added value?

Main determinants of the outcome of a regulatory application

- IPD is not relevant to research based on regulatory data

Clinical trial effect

- In theory, it should help, but…
  - Data management issues (e.g. inconsistent data standards)
  - Meta-analysis based on aggregate data sometimes as useful as IPD meta-analysis
  - Added value is for specific questions only, e.g. missing data, effect driven in subgroups, individual baseline value vs. inclusion criterion.

IPD – further ideas for methodology research

- **Methodological research**: adequacy of the design, statistical analysis methods…
- **Typical factors to study**: baseline predictors, post-baseline predictors, item change in scales, variability in scales…

Caveat with regulatory databases

- Submitted dossier not a random sample of drug development programmes; EMA does not have **access to data from failed programmes**.
- EMA piloted an **initiative in Alzheimer's Disease** inviting companies to discuss with the Agency **developments that did not lead to a submission**.
- **Important learnings for the Agency** – highlighting the value of sharing data from negative trials – with the Agencies but even better with the public.

Thank you for your attention

Acknowledgements: Lorenzo Guizzaro, Florence Butlen-Ducuing, Manuel Haas, Norbert Benda

Further information

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