# Exploring regulatory perspectives on Bayesian statistics in assessment and decision making

Kit Roes

Radboudumc & Chair EMA Methodology Working Party

The views expressed are **personal views** and not necessarily the views of CBG-MEB or EMA.

Radboudumc

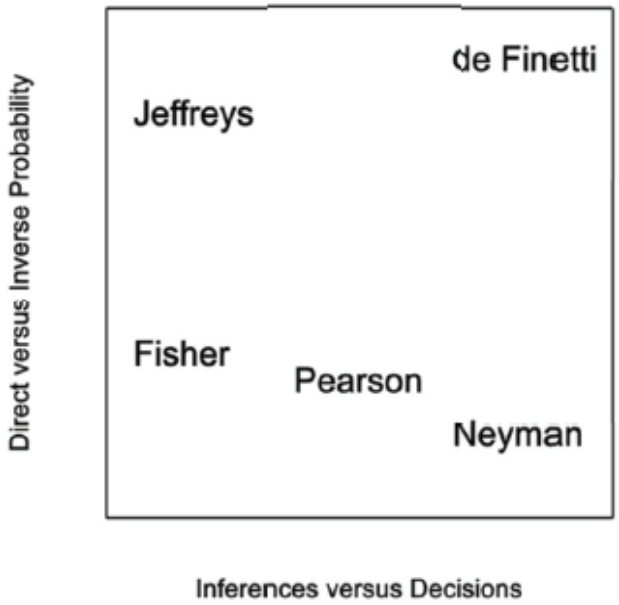
# Preliminaries

*RMM Vol. 2, 2011, 48–66*
*Special Topic: Statistical Science and Philosophy of Science*
*Edited by Deborah G. Mayo, Aris Spanos and Kent W. Staley*
*http://www.rmm-journal.de/*

*Stephen Senn*

**You May Believe You Are a Bayesian But You Are Probably Wrong**

# Preliminaries




- There is no universally superior system of statistical inference (yet).
- *Eclectic,* or: statistical inferential approach *fit for the (research) question* (D.R. Cox).
- In regulatory (confirmatory) driven thinking, emphasis has typically been on Neyman-Pearson based *"Decisions".*

# Preliminaries

Regulatory decision making requires *scientific inference,* of which statistical inference is a part, however significant.

Regulatory *decisions*: totality of evidence.

Phase III trial succes ≠ Regulatory decision.

Type 1 error (control) ≠ error in decision making.
Instrument for consistent statistical inference at the experiment level.
*Secondary assessment given* efficacy can be concluded.

**Article 26**
The marketing authorisation shall be refused if,….., it is clear that:

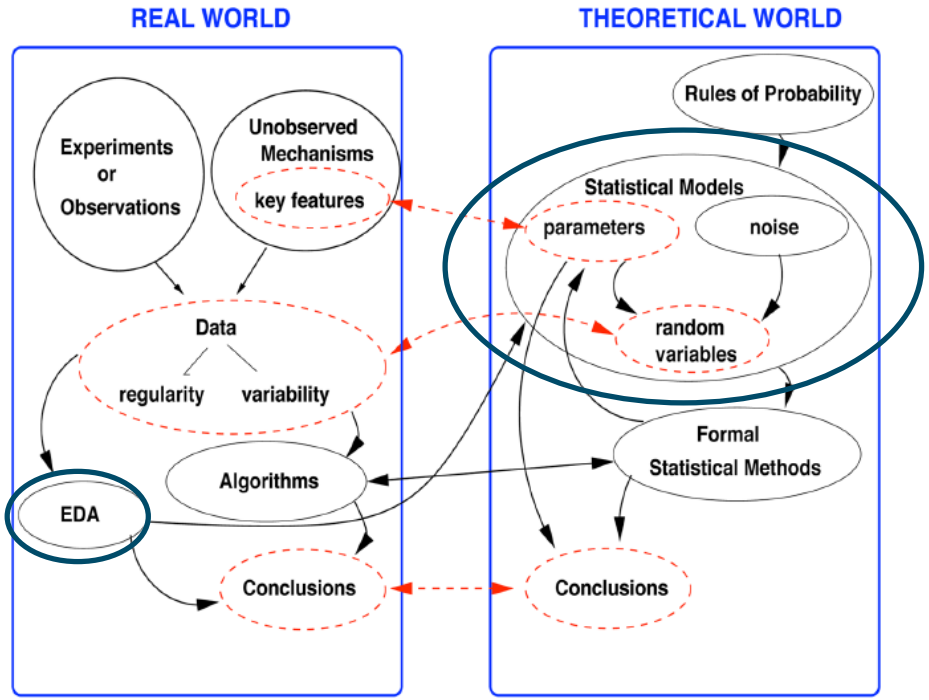
(a) the risk-benefit balance is not considered to be favourable; or

(b) its therapeutic efficacy is insufficiently substantiated by the applicant; or

(c) its qualitative and quantitative composition is not as declared.

# Preliminaries

- Data are modelled through probability distributions.
- Data serve to reveal characteristics of underlying system that generated the data (**data generating mechanism**).
- Formal inference serves to draw *conclusions* about the unknown parameters.

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**Statistical Inference: The Big Picture**

**Robert E. Kass**[*][Professor]
Robert E. Kass: kass@stat.cmu.edu

# Points for today

- Regulatory guidance (in development) & reflections.
- Confirmatory clinical trials
- Areas to further develop
- Concluding remarks

# Regulatory guidance in development

| | | |
|---|---|---|
| EMA | Concept paper on Bayesian statistics | |
| | Reflection paper on “platform trials” | |
| ICH | E11A | – Pediatric extrapolation (Step 2b) |
| | E20 | – Adaptive designs |
| | M15 | – Model Informed Drug Development |

Fundamental concepts need to be discussed / developed / understood, e.g.:

- What constitutes a study / experiment?
- At which level do operational characteristics need to be understood / controlled?
- Credibility of models used.

# Reflections

- Pediatric extrapolation.
  - Efficacy well established in adult population.
  - Strong priors can be reasonable and bayesian methods fit the research question(s): door clearly open.
- Modeling and simulation
  - Use of bayesian approaches prevalent and (proven) useful.

**Credibility of model(s) for *the data generating mechanism* central.**

WHITE PAPER

**Scientific and regulatory evaluation of mechanistic *in silico* drug and disease models in drug development: Building model credibility**

Flora T. Musuamba[1,2,3] | Ine Skottheim Rusten[1,4] | Raphaëlle Lesage[5,6] | Giulia Russo[7] | Roberta Bursi[8] | Luca Emili[8] | Gaby Wangorsch[1,9] | Efthymios Manolis[1,10] | Kristin E. Karlsson[1,11] | Alexander Kulesza[12] | Eulalie Courcelles[12] | Jean-Pierre Boissel[12] | Cécile F. Rousseau[13] | Emmanuelle M. Voisin[13] | Rossana Alessandrello[14] | Nuno Curado[15] | Enrico Dall'ara[16] | Blanca Rodriguez[17] | Francesco Pappalardo[7] | Liesbet Geris[5,6,18]

# Reflections

(Adaptive) clinical trial designs.

- “Operationally bayesian”: bayesian approach to interim decisions, but no borrowing (through prior or external data) and operational characteristics well understood based on DGM for data from the trial.

- Incorporation of external information / data, or informative prior (borrowing).*
  - Arguably the area with largest potential impact on drug development (e.g., in rare diseases).

* I restrict myself to borrowing & priors that are based on data.

# Confirmatory clinical trials


*Confirmation* and *replication* are cornerstones of *scientific inference*.

Replication

- *Robustness* across settings and environments.
- “Exact” copy of the same trial may not really differ from 1 trial.

# Clinical trials with borrowing

Scientific inference (not only statistical) on the primary efficacy outcomes:

- New trial to add value: prior to be “moved” with reasonable data from new trial.
- What level of borrowing puts a confirmatory nature at risk?
- Replication (non-sequential, and not exact copies): consistent approach possible, when it is not reasonable to use the same priors/external data?

# Clinical trials with borrowing

Within an (R)CT many aspects of the *data generating mechanism* are controlled.

Borrowing typically based on more complex modelling *for trial and external data*.

- Credibility of the data generating model, esp. for the external data.
- Properties (operational characteristics) may not be derived analytically.
- Assessment of consistency with prior data more impactful than exact type 1 error control.

Robustness and credibility both important and challenging.

- Largest gain expected when sample sizes are small.

Case by case: Many aspects of design and context relevant.

# Areas to further develop

Primary and secondary assessment of data: A viewpoint.

- Definition of *trial success criteria* (if not fully met, efficacy cannot be considered confirmed). Reflected in design (sample size).

- Assessment of properties, *given that efficacy is confirmed*.
    - Secondary endpoints.
    - Subgroup consistency / heterogeneity.
    - Safety to inform risk – benefit.
    - ……..

# Areas to further develop

Secondary endpoints.

- Current: Uncertainty controlled / expressed based on multiplicity (type 1 error) control.
- Bayesian alternatives worth considering.
- Borrowing from external data: consistency across enpdoints a potential issue.

Subgroup evaluation (if not part of trial succes criteria).

- In a substantial number of cases licensing decision adapted based on subgroup findings.
- Additional analyses (beyond exploring heterogeneity) can add value.
- Borrowing from external data: consistency a potential issue.

# Areas to further develop: Safety to inform B-R

General

- Relies on much broader assessment then within a trial.
- Statistical analysis typically (still) not that advanced at all.
- Nature of data (rare events, relevant information across many sources) suited for bayesian approaches.

Within trials

- Preferably risk & benefit estimated, comparatively, for the same population.
- In case of borrowing for efficacy from external data, it might be unclear if that is achievable.

# Concluding remarks

- Bayesian statistics has a place in regulatory assessment and decision making.

- Use in design, assessment and decision making requires: Attention / standards for credibility of more complex models – over and above type 1 error control.

- Multidisciplinary EMA Methodology Working Party

*I do not believe I am a Bayesian, but for complete information I do not believe I am a Fisherian (or….) either.*