Clinical trials in rare diseases: There is no magic potion.

Results and way forward from the Asterix project.

Kit Roes
UMC Utrecht

Armin Koch, Martin Posch, Ferran Torres, Hanneke vd Lee, Cor Oosterwijk, Egbert Biesheuvel, Caroline van Baal and all the researchers of the Asterix consortium

(The views expressed are personal and not necessarily those of the CBG-MEB)

The Asterix project

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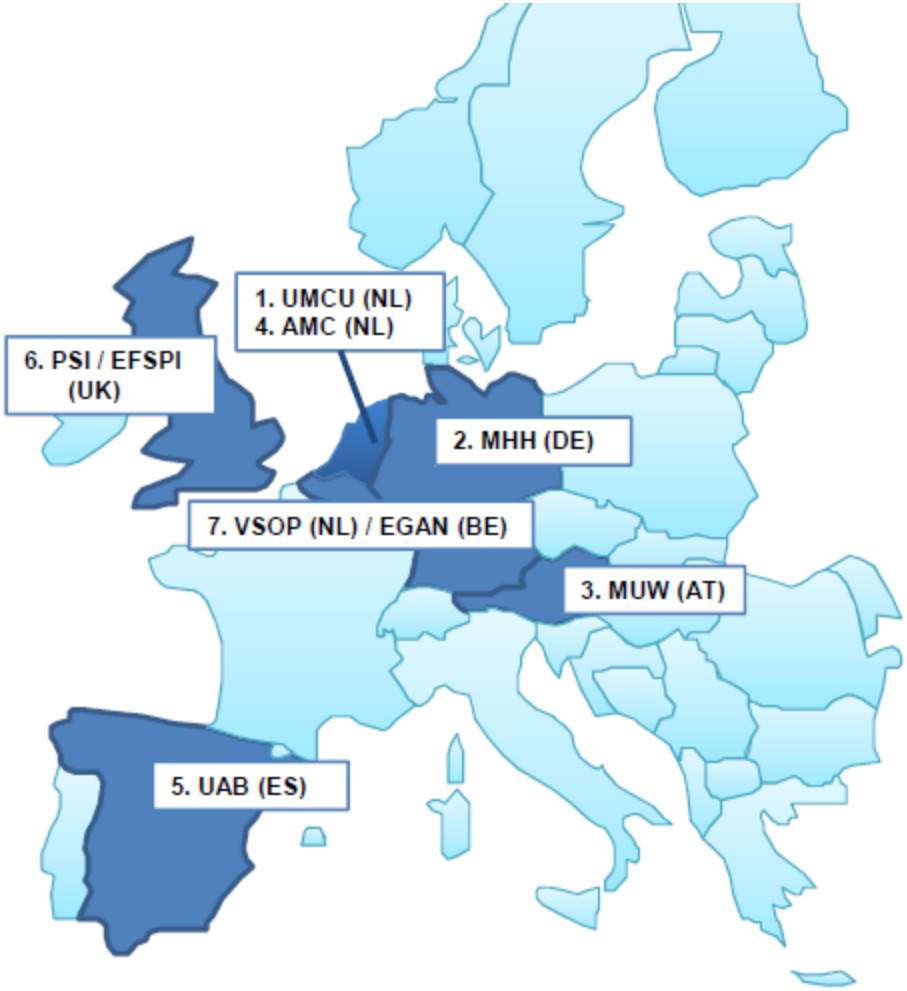
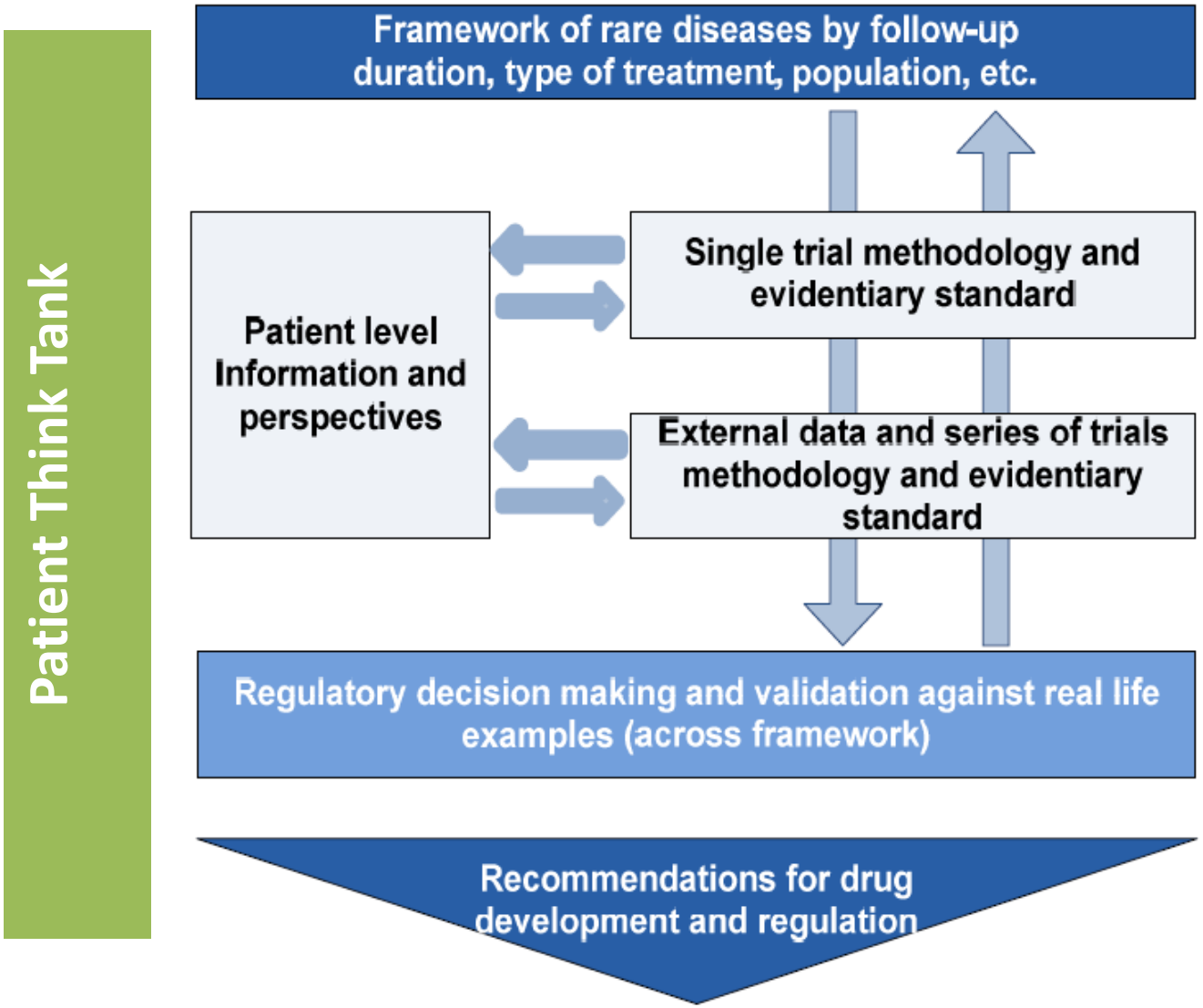


UMCU	Kit Roes
AMC	Hanneke van der Lee
MUW	Martin Posch, Hannover
MHH	Armin Koch
UAB	Ferran Torres, Caridad Pontes
VSOP	Cor Oosterwijk
PSI/EFSPI	Egbert Biesheuvel

The Asterix project



Focus on statistical methodology for rare diseases.

- More often an area of high medical need (no treatment)
- Rare disease with large heterogeneity between patients in disease course.
- In (very) rare disease a relatively large fraction of the population to treat could be included in clinical trials (finite “patient horizon”).
- Challenge of appropriate (clinical) endpoints and biomarkers.
- Evidence synthesis more challenging (replication of trials, between study heterogeneity).

Individual trials

- Progress in methodology
  - More efficient procedures for co-primary endpoints.
  - Multi-armed sequential trials with simultaneous stopping rule.
  - Optimal sequential design subject to maximum sample size.
  - Basket trial design for first in human studies
  - Optimal tests for multiple binary outcomes
  - Sample size re-assessment using power priors

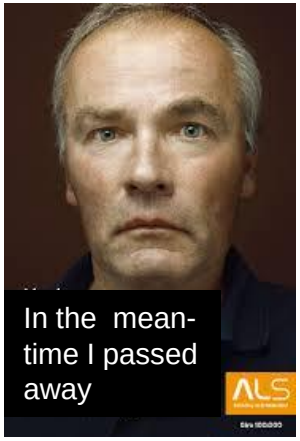
External data and series of trials

- Progress in methodology
  - Decision making for studies with two strata with and without heterogeneity
  - Dynamic borrowing (from controlled trials) through emprirical power priors
  - Robust choice of prior in Bayesian meta-analysis of small number of trials and sparse events

Evidentiary standard

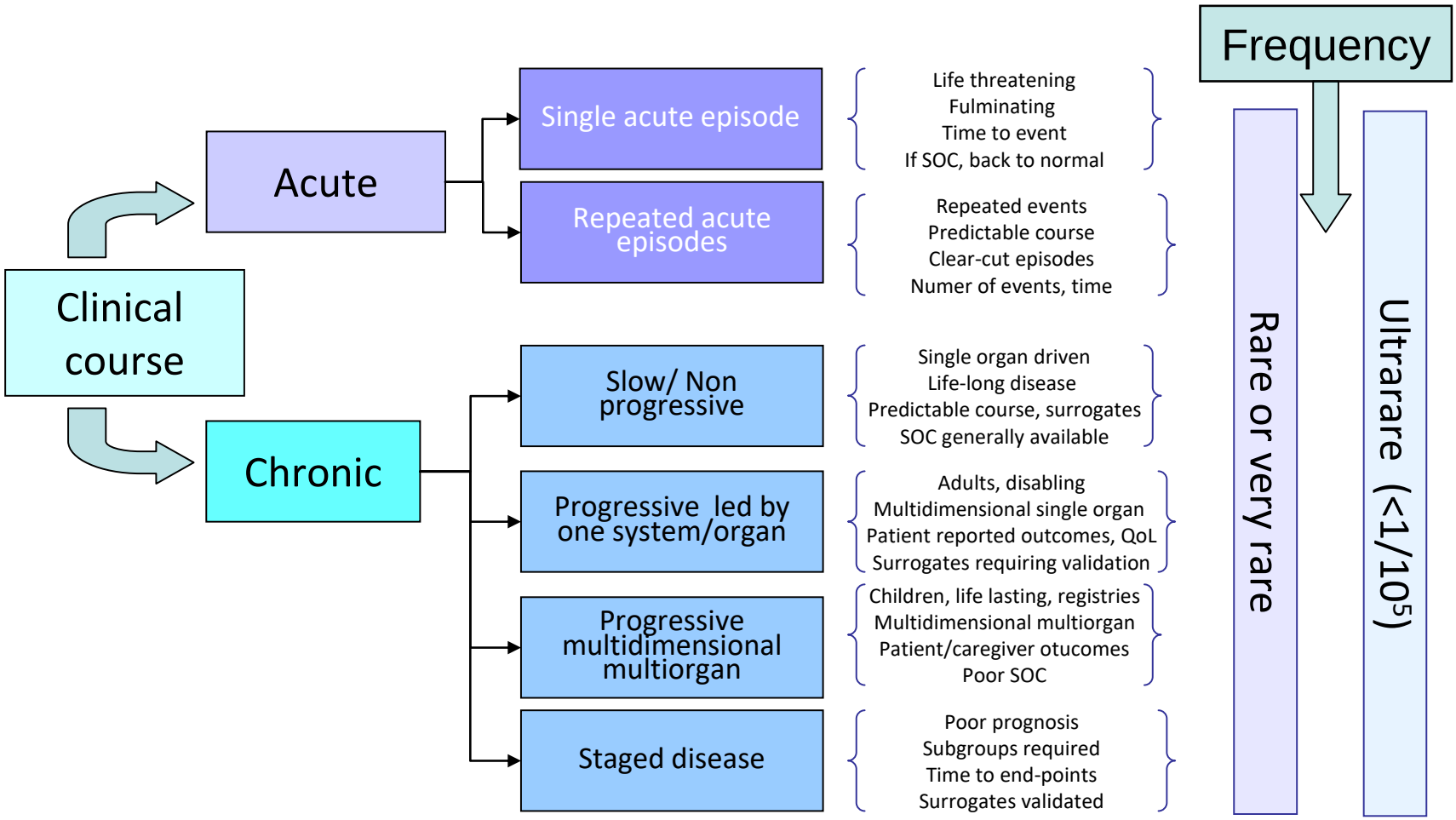
- Progress in methodology
  - Randomised vs non-randomised evidence & bias
  - Evidence, eminence & extrapoation: rational weighting of prior information to reduce sample size in vulnerable (small) populations)
  - Evaluation of Benefit – Risk assessment in European Public Assessment Reports (EPARs)
  - Ongoing: Patient horizon and rational link to type 1 / type 2 error choices.

Patient Centered



- Progress in methodology
  - Development (concept, statistical, validation plan) for Goal Attainment Scaling – Novel approach to deal with heterogeneity. To be submitted for EMA Qualification.
  - POWER Model to include patient perspectives in trial design
  - Ethical Framework for rare disease clinical trials
  - Patient centered leaflets on clinical trial methodology

Framework & guidance



Framework & guidance

- Ongoing
  - Evaluation of all methodology against European Public Assessment Reports.
  - To provide more specific guidance at the disease cluster level.
  - To understand more specific the evidence base of regulatory decisions.

Progress put into context (1)

- Broader results
  - Large network of scientists and trained PhD students.
  - Impact on new trials in rare diseases.
  - Increased understanding of clinical trials in general.
  - Increased understanding of role (and opportunities) of clinical evidence in regulatory decision making for orphan drugs.
  - Increased patient centeredness of our own profession.

Progress put into context (2)

- Rare diseases pose more fundamental dillema's:
  - Due to limited possibility of replication, bias (e.g. historical data) more difficult to assess: Randomisation even more important.
  - Heterogeneity (between trials, between strata, between…) instrinsically more diffcult to assess.
  - Challenge rational basis for evidentiary standards (such as those for significance).

Progress put into context (3)

"…..patients suffering from rare conditions should be entitled to the same quality of treatment as other patients."

Median 538 patients enrolled in orphan drug trials, 1588 in non-orphan.

New methods strongly focus on efficiency: more information from limited (new) data (which is not unique for small populations).

Progress in more rational evidentiary standards needed.

- Join us in Zaandam

  September 18 & 19

- Visit our website: www.asterix-fp7.eu