# **Trial design for rare diseases**: Examples of progress from the Asterix project

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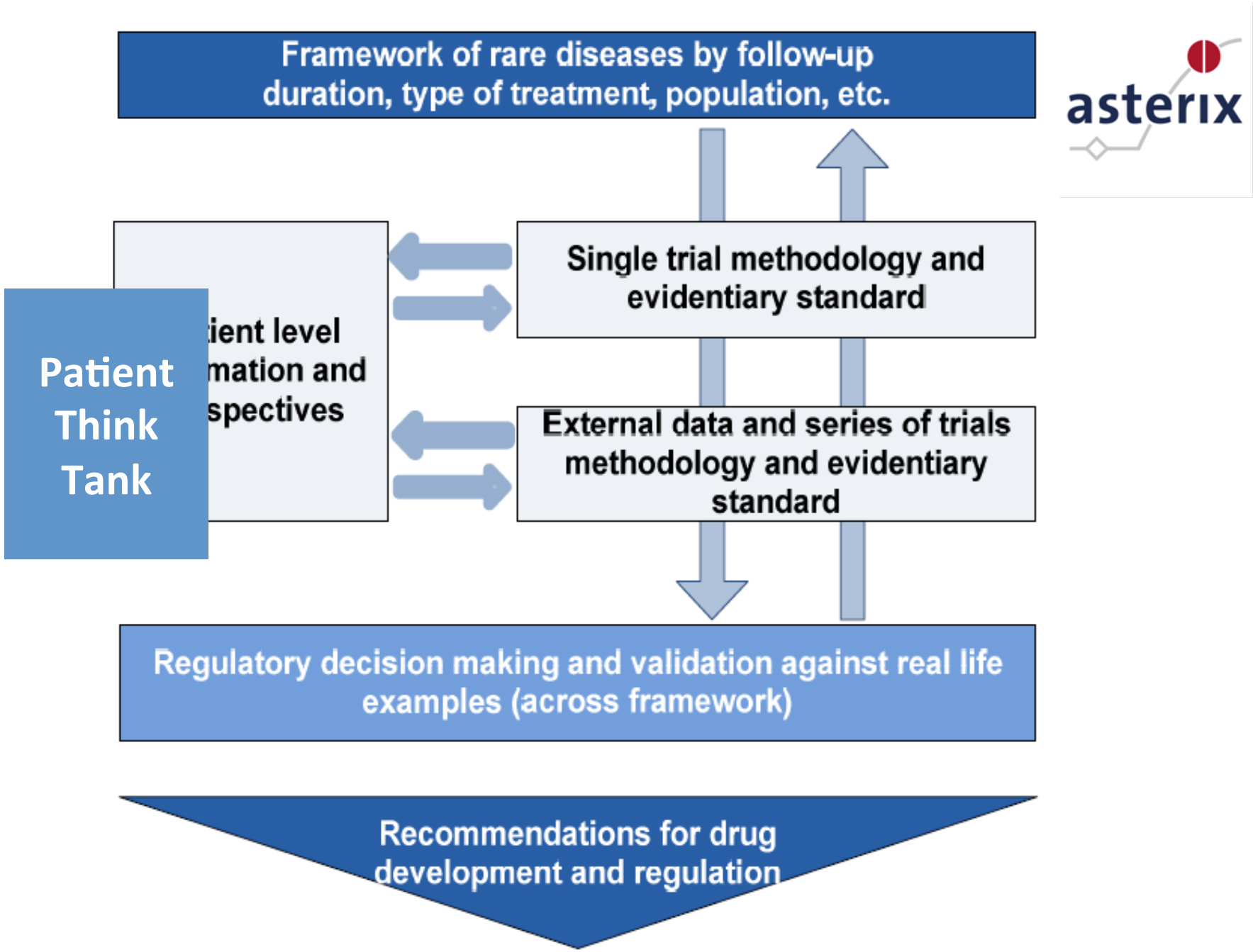
Framework of rare diseases by follow-up duration, type of treatment, population, etc.
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Patient Think Tank
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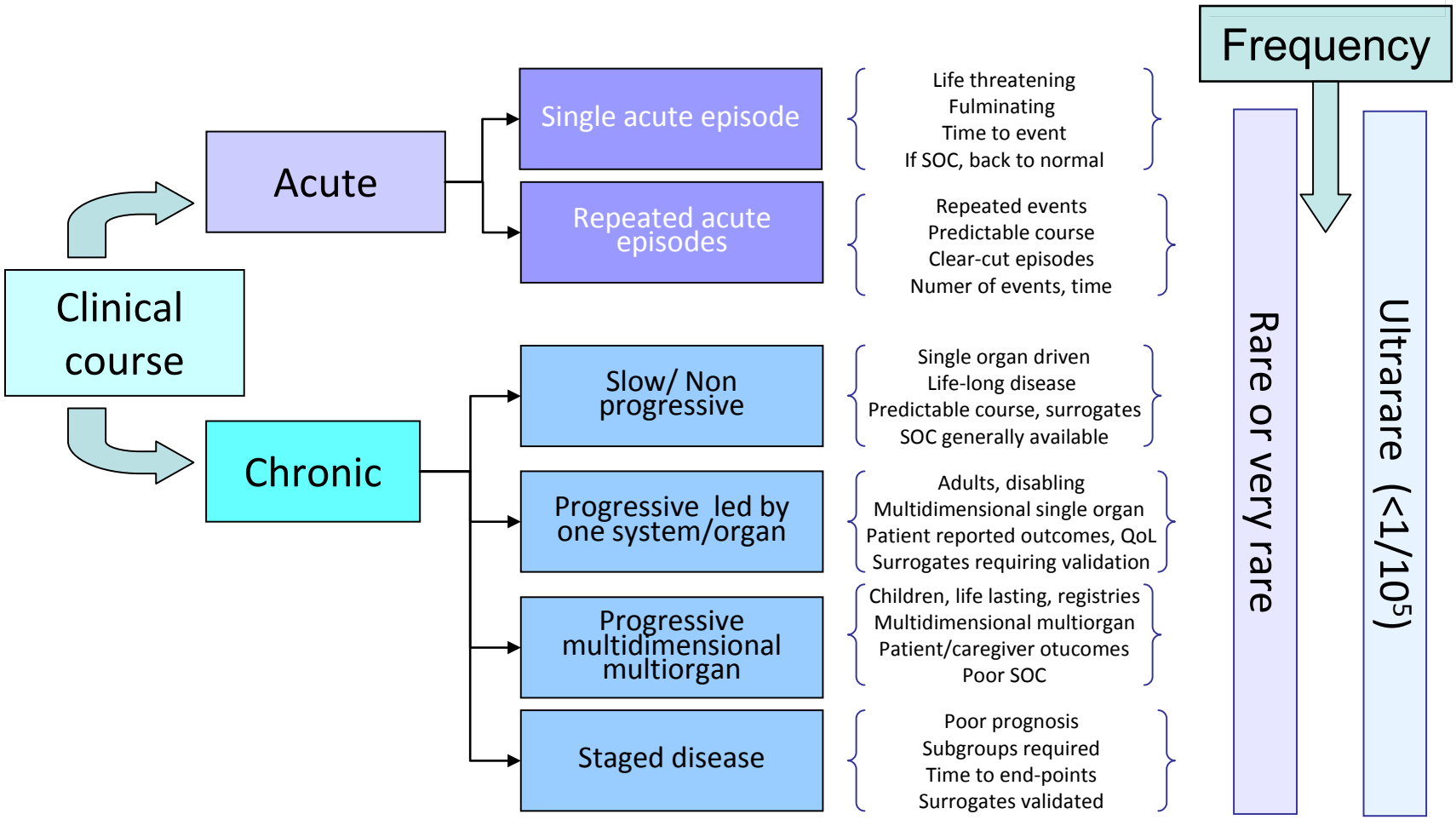
spectives
Single trial methodology and evidentiary standard
External data and series of trials methodology and evidentiary standard
Regulatory decision making and validation against real life examples (across framework)
Recommendations for drug development and regulation

# Framework for guidance

- Guidance on design at disease level no longer practical (over 8000 rare diseases).
- One general document (at present) may not provide sufficient guidance.
- Framework with intermediate approach, driven by key characteristics of disease and treatment.
- Developed (in part) statistically, based on about 100 EMA dossiers.

# Proposed framework



# Single trial methodology: Sequential study design

- Alternative for rare diseases
  - A priori known limited achievable sample size (Nmax)
  - Include interim analyses to allow early stopping (number, spacing)
  - Take small sample size into account in calculations:
    - Sequential t-tests (complicated, software), or
    - Replace boundaries:

      Instead of $c_k$ test against $c'_k = t(n_k-2;1-\phi(c_k))$

# Sequential study design

A GSD with a combination of the above (Nmax, number, spacing) has an Inflation Factor (IF)

- IF ↑, ASN ↓, Power ↓

Optimise the design:

- Balance expected sample size (ASN) and power
- But with present level of evidence (type I error), power loss inevitable

# Results

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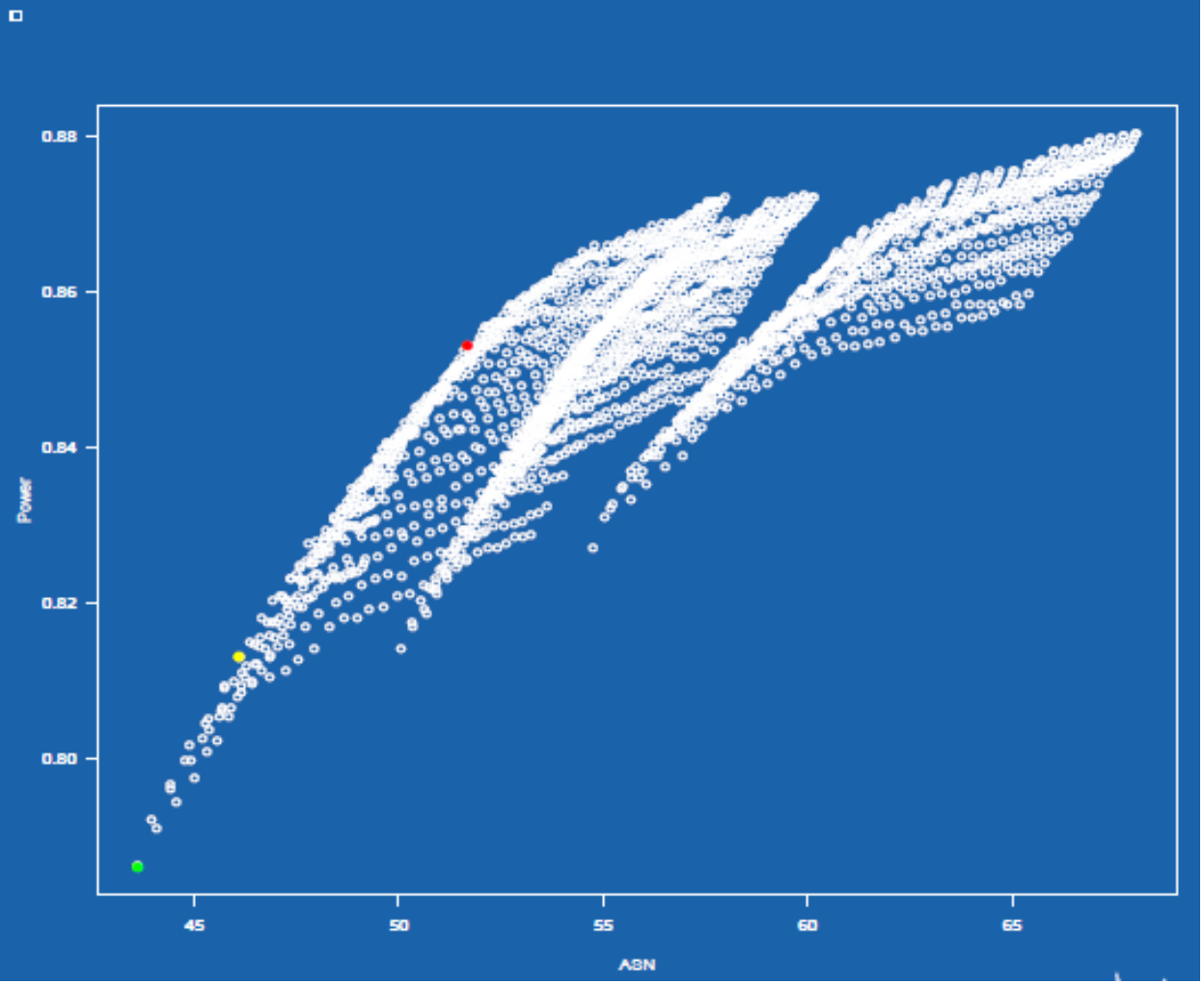
$(ASN_i / N_{max} * P_{fix} / P_i)$

$(ASN_i / N_{max} + P_{fix} / P_i)$

$\sqrt{(ASN_i / N_{max})^2 + (P_{fix} / P_i)^2}$



# Series of trials methodology

- In drug development for rare diseases, synthesis through meta-analysis might improve robustness of (regulatory) assesment

- (Sequential) Meta-analysis can improve efficiency of drug development plans

- Facilitating adaptive licensing

# Series of trials methodology

Initial idea:

- Bayesian methods for extrapolation in rare disease
- Reduce the burden for formal proof of efficacy.

Impact on decision making needs to be fully understood.

- Frequentist and Bayesian strategies are compared from a decision making perspective.
- In case of 2 (completed) trials: (1) full (fixed/random effects) meta-analysis, (2) one trial as prior for the other, (3) down-weighing the first trial

# Series of trials: findings

Fixed-Effect model

- Levels out evidence of both sources
- Retrospective and prospective analysis lead to the same results
- Credible intervals point to existing treatment effect

Random-Effects model

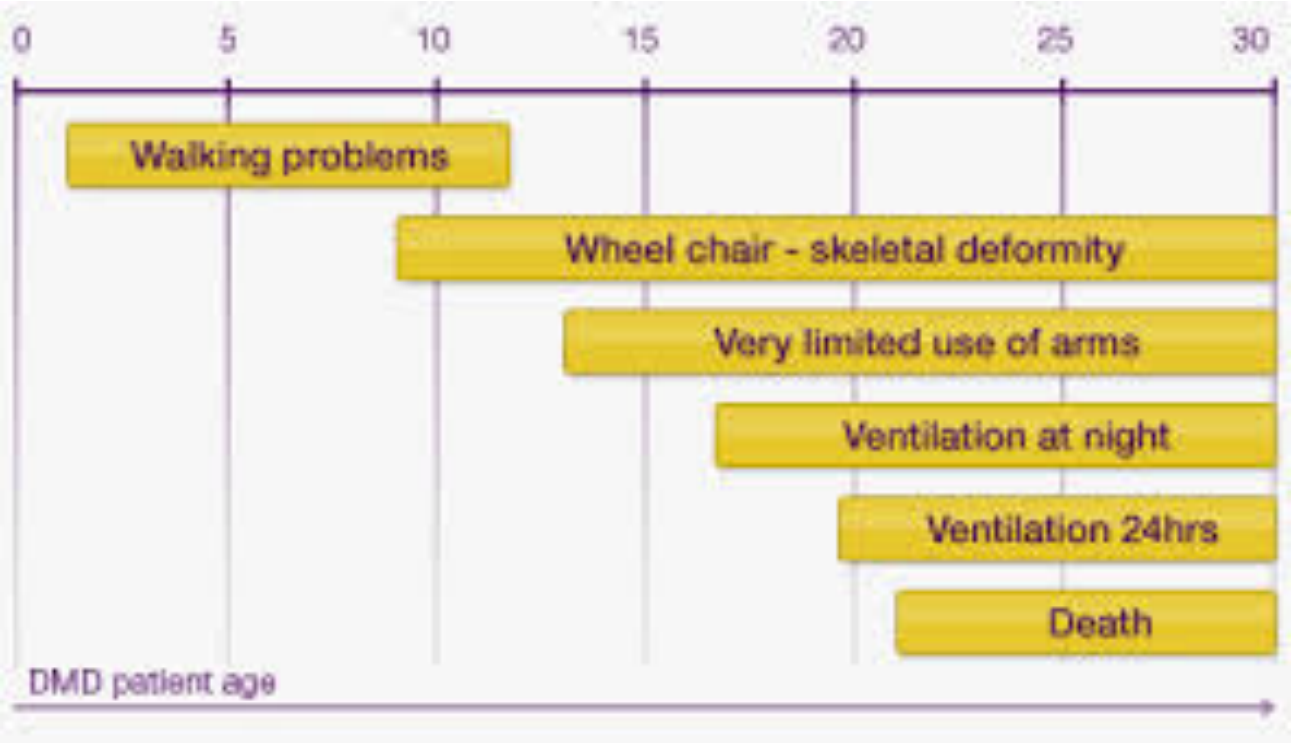
- "Dynamic borrowing" (Viele et al. [2013])
- Existing information has in general lower weight
- Credible Intervals point to existing or unclear treatment effect depending on the (informative) prior distribution of the heterogeneity parameter and the chronological trial order

Power prior approach

- Existing evidence is always downweighted
- Conclusions on the treatment effect are depending on the amount of borrowed data and the trial sequence

# Patient level information and perspectives

- Rare diseases often subject to large heterogeneity in disease course/manifestation
- Duchenne as an example



# Patient level information and perspectives

Need to come up with new approaches (for late stage clinical development):

- Outcomes individualized to patients' objectives

- *Goal Attainment Scaling* is an example:
  - Scaling individual current level and objective on standardized scale (e.g., -3, -2, -1, 0, 1, 2)
  - Combine accross patients
  - Furthher research needed on validity and match with the same treatment mechanism.
  - Review completed, exploring pilot application

# Concluding

- Formal combination (bayesian, meta-analysis) of evidence  to increase robustness of decision making
- Serious reconsideration of level of evidence needed, in concert with new models of decision making
- Framework will help to provide guidance in the heterogenous world of rare diseases
- Including patients and patients' perspectives is an enrichment