Advances in **S**mall **T**rials d**E**sign for **R**egulatory **I**nnovation and e**X**cellence

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SEVENTH FRAMEWORK PROGRAMME

Outline

- Perspectives, Patients and Evidence
- Concept and objectives of **Asterix**
- Examples of patient involvement
- Status / conclusions

Perspectives, Patients and Evidence

- Depending on definitions : ± 8000 rare diseases
- 30 M (6-8%) of population in EU suffer from rare disease
- Roughly 80% suffers from one of 100 of these
- Many genetic, many affecting children

Perspectives, Patients and Evidence

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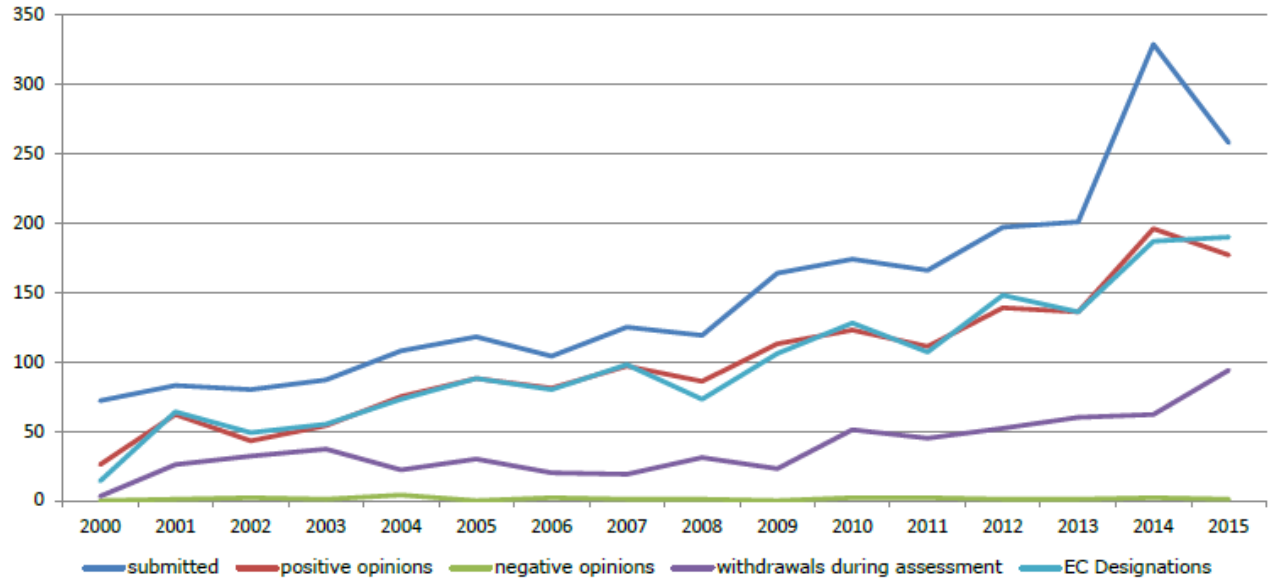
More than 1500 new therapies designated as orphan



EMA Orphan medicines figures 2000-2015

90 orphan medicines authorised (11 in 2013, 17 in 2014)

Authorised does *not* automatically lead to *available* ***for patients***

www.ema.europa.eu/docs/en_GB/document_library/Other/2015/04/WC500185766.pdf

Perspectives, Patients and Evidence

Perspective of treating physician

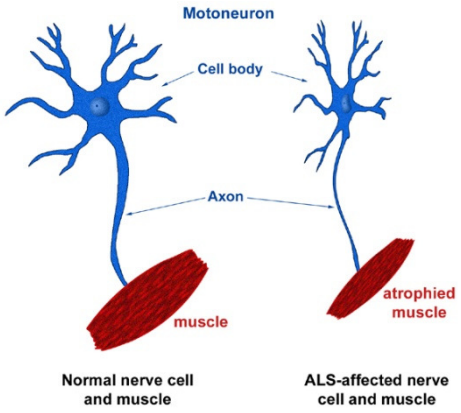
Evidence based decision for the (next) patients to treat, selecting from the available treatment options

Perspective of market authorisation of a new drug

Evidence based decision of allowing physicians to add a new drug to their treatment options

Provide information to guide the prescribing physician

Perspectives, **Patients** and Evidence



e-Patient Dave de Bronkhart

e-Patient Dave

A voice of patient engagement

Home Courses Schedule Media For Patients Pt. Communities For Providers Videos Boards & Awards Testimonials Books About Contact

- Stage IV, grade 4 Renal Cell Carcinoma

- Advice and evidence through community
  - An uncommon disease
  - Get to a hospital that does a lot of cases
  - There's no cure, but HDIL-2 sometimes works
  - When it does, about half the time it's permanent
  - The side effects are severe
  - Don't let them give you anything else first

TEDxMaastricht - Dave deBronkart - aka e-Patient Dave: "Let patients help!"

Perspectives, Patients and **Evidence**

The European legislation on orphan medicinal products [Regulation (EC) No 141/2000] emphasises that patients suffering from rare conditions should be

- “entitled to the same quality of treatment as other patients.”
- Current rationale is to present evidence at the same confidence levels
- Small populations guidance does stimulate alternatives for design and analyses
- Careful case-by-case decisions are made, that essentially may “relax” level of evidence

Context

- Unmet need for drugs to treat rare diseases
- Difficulty to establish efficient and reliable evidence from **clinical trials in small populations**
- Absence of methods to include **patients and patient perspectives** to generate results that matter to patients
- Uncertainty in **regulatory decision making** on new treatments

Context - FP7 Projects

FP7 Call – HEALTH.2013.4.2-3

New methodologies for clinical trials for small population groups

Three projects are funded:

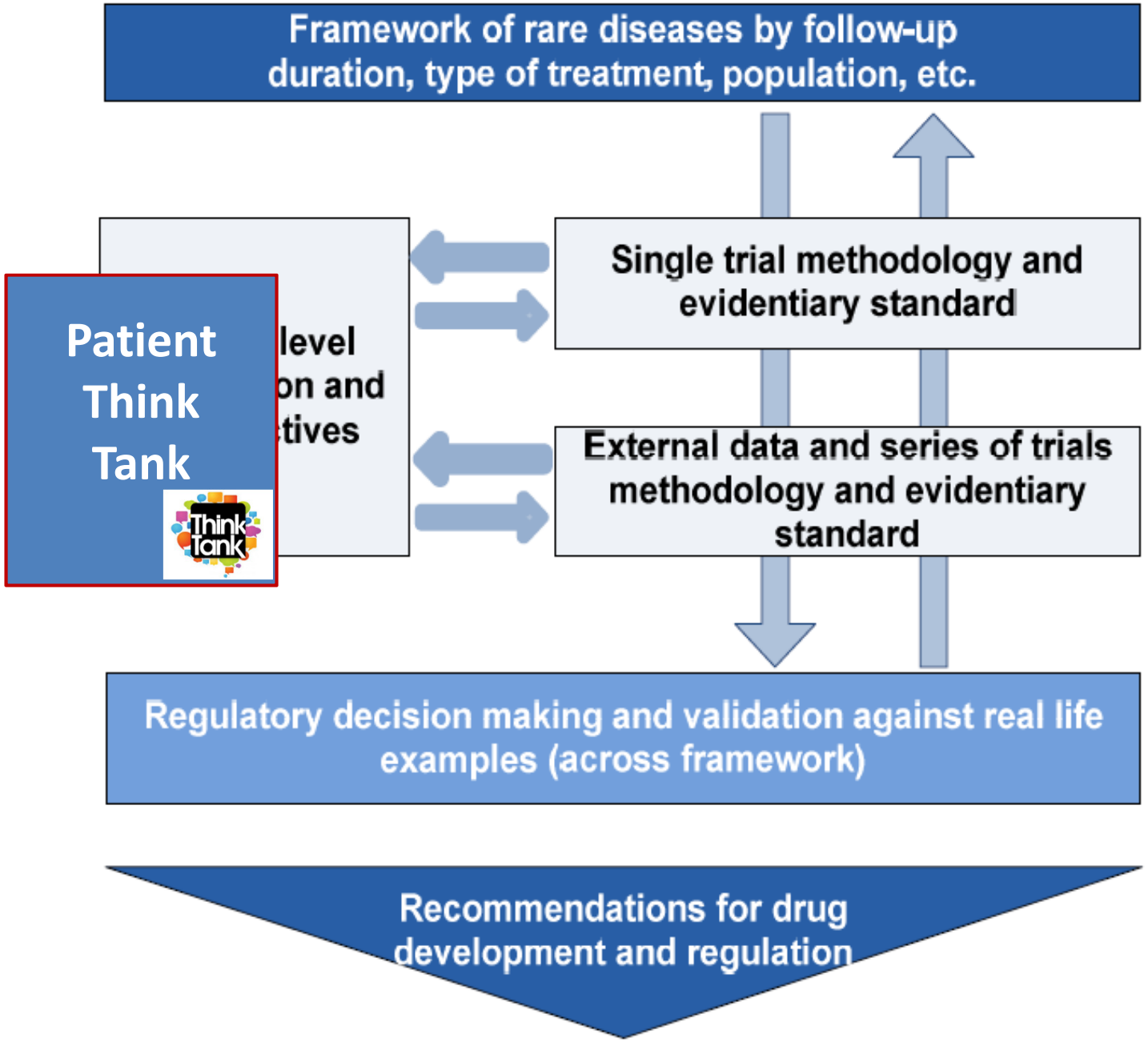
- **ASTERIX**
  Advances in Small Trials dEsign for Regulatory Innovation and eXcellence

- **IDeAl**
  Integrated Design and AnaLysis of small population group trials

- **InSPiRe**
  Innovative methodology for small population research

Concept and Objectives

- statistical design **innovations** in **individual** and **series of trials**
- **clinically based clustering** to guide design and analysis
- include **patient level info & perspectives** in design and decision making throughout the clinical trial process
- re-consider the scientific basis for levels of evidence to support **decision making** at the **regulatory level**
- validation of new methods against real life data and regulatory decisions


Framework of rare diseases by follow-up duration, type of treatment, population, etc.
Patient Think Tank
Think Tank
level
on and
tives
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

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Patient Think Tank

- Systematic involvement of patients and their perspectives
- PTT comprises of 12 members
- Collaborate and provide constant feedback

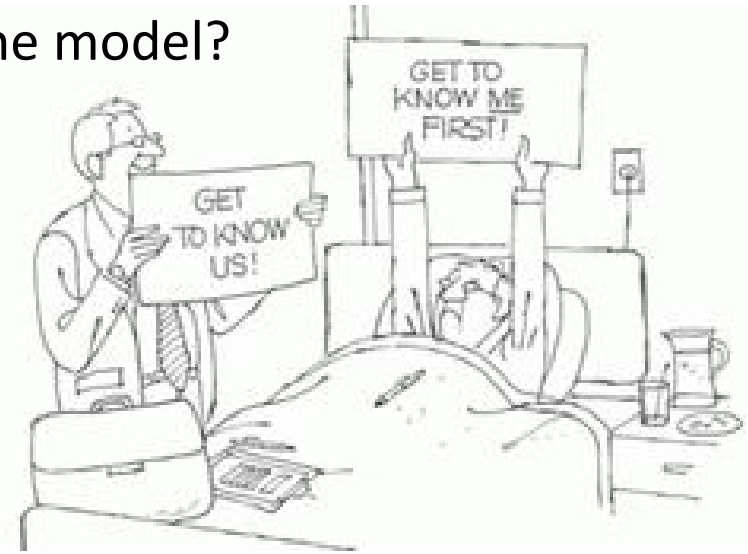
Provide input in the development of methods to

1. include patient opinions on **novel trial designs**
2. include **patients preferences** in the weighting of outcomes and patient focused outcomes
3. optimize use of info in **patient registries** to decide on trial design

PTT – input in trial designs

- 1st F-2-F meeting in October 2014 A'dam on adaptive designs and weighing of outcomes
  - \+ Important to involve patients
  - \- Why involve patients only for limited questions?
  - \- Where are the other stakeholders in the model?

we changed our approach …



- Open interviews with patients in 2015 which will result in a qualitative paper

PTT – involvement

- 2nd F-2-F meeting in October 2015 Barcelona on clustering framework
  - + Welcome for whole 2-day meeting
  - + Interactive break-out sessions

- **True interaction and learning experience** for all of us

Topics discussed by PhD students

Presentations by statisticians:

- Methods on combining series of trials
- Interpreting multiple endpoints
- Clinical Trial Methodology for small samples
- Stratified randomization in comparative clinical trials in small populations
- Heterogeneity in meta-analyses
- Group sequential designs
- Critical appraisal of designs proposed as alternative to the parallel randomized controlled design in the field of rare diseases
- Use of already available information with Bayesian analysis

Topics brought up by patients

- **Involvement of patients**
  - Patients want to be kept informed
  - They have the legal right to know the design of the trial they are enrolled in
  - They want to have a larger role besides just a source for recruitment

- **Different conditions and safety rules** for rare disease research vs ‘regular’ large trials
  - Shift of acceptable type I error

Topics brought up by patients

- Patients want to be involved in the **choice of outcome measures**

- **Role of placebo**
  - Placebo should be reduced
  - Patients want to be in experimental arm (especially in progressive diseases)
  - Compare new treatment with existing treatment
  - Try different doses instead of placebo arm
  - Re-using placebo group?

Example: Goal Attainment Scaling

How is Goal Attainment Scaling[1] useful in rare disease patients?

Imagine 3 boys with Duchenne disease:

-2 Adam is unable to walk
-1 Adam can make 3 steps
0 Adam is able to walk for 5 minutes
1 Adam can walk for 15 minutes
2 Adam can walk longer distances

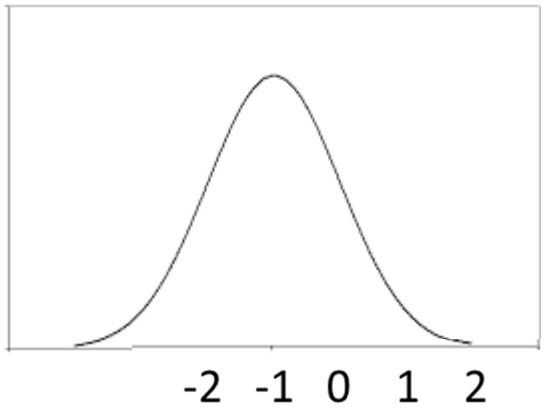
-2 Brad is unable to eat alone
-1 Brad can use a spoon for 5 minutes
0 Brad can use a spoon during a meal
1 Brad can use a knife and fork
2 Brad can cut and eat his own food

-2 Chris is unable to breathe by himself
-1 Chris can breathe for 10 minutes
0 Chris can breathe for one hour
1 Chris can breathe for two hours
2 Chris can breathe for five hours

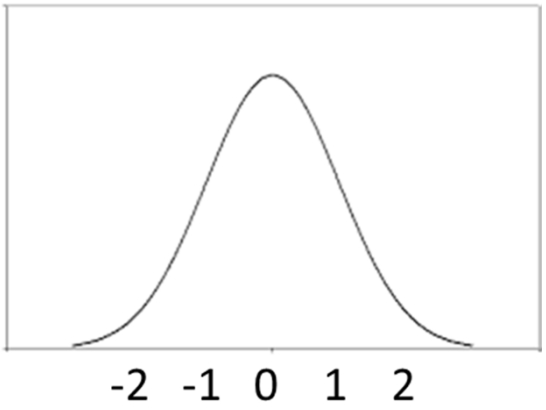
Example: Goal Attainment Scaling

MODEL

Before treatment



After treatment



We want to test whether this ‘shift’ in the underlying variable is significant

Example: Goal Attainment Scaling

Research Question

$$T = 50 + \frac{10\,\Sigma w_i x_i}{\sqrt{(1-\rho)\Sigma w_i^2 + \rho(\Sigma w_i)^2}}$$

T = *GAS score*

x_i = *Original score*

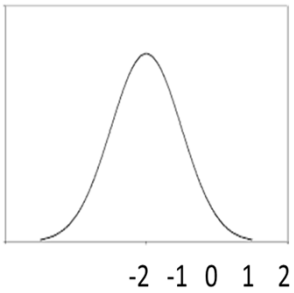
w_i = *Weight given to the original score*

ρ = *Intercorrelation among goal scores (estimated at 0.3)*

Example: Goal Attainment Scaling

WEIGHTS

- Based on **difficulty**: the more difficult, the higher the weight?
  - the instrument becomes less sensitive when the chosen goal is more difficult!



- Based on **importance**: makes it more relevant for the patient
  - but.. Is the most relevant goal also the goal that is closest to the underlying ability?

Example: Goal Attainment Scaling

- Is there value of using GAS in rare disease trials?
- Systematic review on the use of GAS in drug trials
  - Validation is mainly done in geriatrics/rehabilitation
  - Usually in non-drug trials
- Statistical background of GAS
- Validation of GAS in an existing trial

Patient registries

- Develop recommendations for the design of patient registries to:
  optimize the info for trial design in small populations

For example:

- *When can it be used as a historical control group, to reduce the use of placebo?*
- *Can it be used for sample size calculations?*

Patient registries

- Interviews (>10)
  - Mainly coordinators of rare disease registries, like Lysosomal storage disease, progressive brain tumor in children, Cystic Fybrosis, ALS and group of some ultra-rare inherited disorders.
- Interview topics
  - Reasons for registry set-up
  - Collaboration
  - Choice of variables
  - Organization of data
  - Use of registry in research
  - Recommendations for future coordinators

  - Recruitment
  - Natural course/more information about disease
  - Historical control group

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- Interview topics
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- Recruitment tool for RCT
- Data collection tool for RCT
- Sample size calculation
- Historical controls in non-randomized studies
- Extension of indication

Patient registries

First Results

- Registries are important, not only for trial design, but also for trial efficiency
- Not all coordinators are aware of possibilities of registry

Next Steps

- Additional interviews and alignment within Asterix
- Finalize reports, write paper and recommendations

Status - concluding

- Patient involvement is essential … and possible
- We have started and making progress …..

"learn to think *like* the patient, not *for* the patient"

"talk *with* the patient, not *to* the patient"

www.asterix-fp7.eu