Promoting clinical development for patients with rare diseases

an overview of new methodology by the ASTERIX project

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Outline

- Concept and objectives of **asterix**

- Patient level information and perspectives
  - Patient registries to inform trial design
  - Patient involvement in trial design
  - Patient involvement in weighing outcomes
  - Patient focused outcomes

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

On behalf of Kit Roes, Armin Koch, Martin Posch,
Ferran Torres, Cor Oosterwijk, Egbert Biesheuvel,
Caroline van Baal and
all the researchers of the Asterix consortium

SEVENTH FRAMEWORK PROGRAMME

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

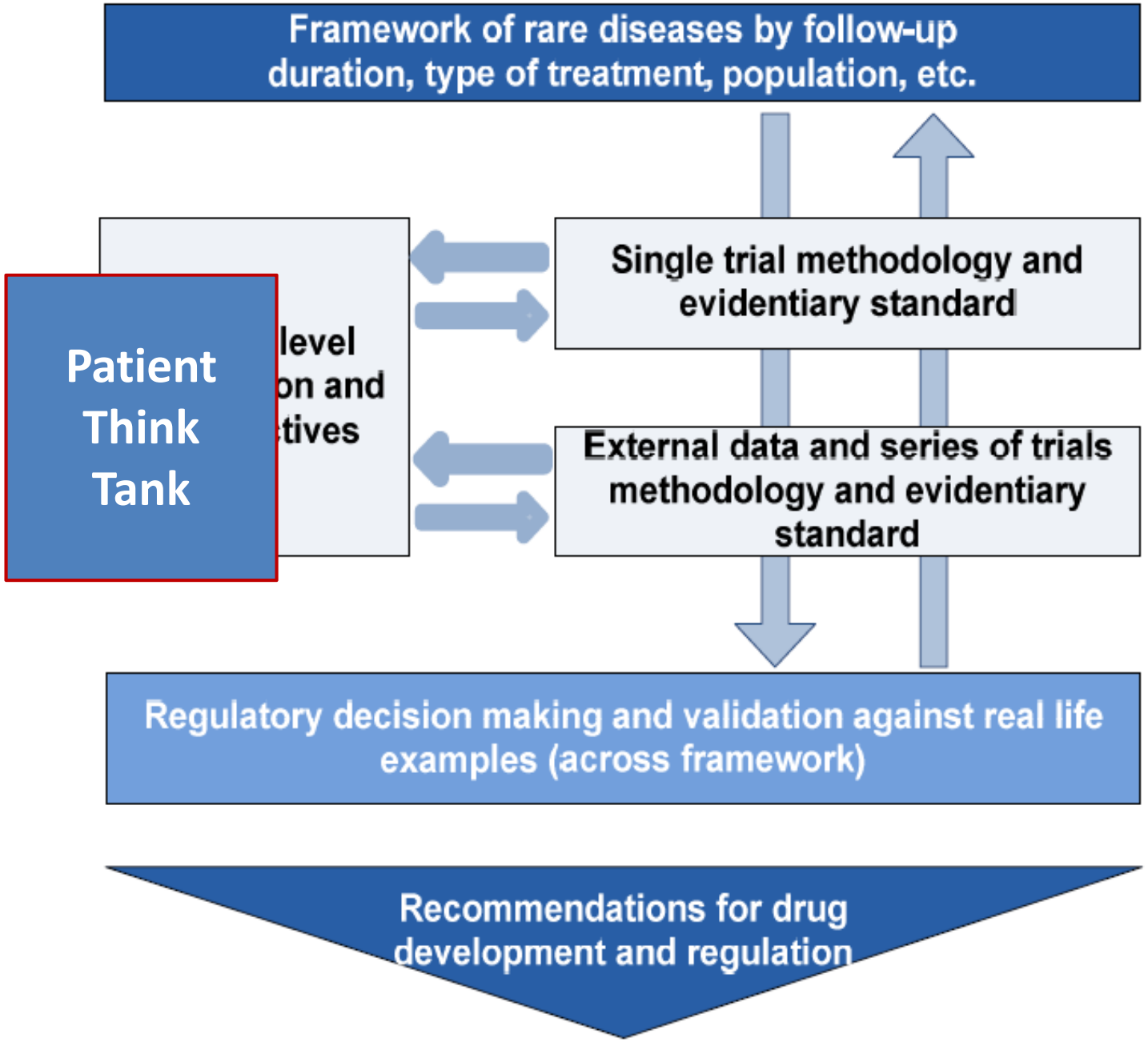
- **IDeAl**
  Integrated Design and AnaLysis of small population group trials

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

Key Objectives

Design and analysis methods for single trials and series of trials

- Clinically based clustering to guide design and analysis
- Appropriate new standards of statistical evidence for small target populations
- Improve design in single trials:
  - Randomisation and alternatives
  - Multiple endpoints
  - Adaptive approaches
  - Individualised patient outcomes
- Improve design & analysis of series of studies:
  - Including different designs (controlled / uncontrolled)
  - Including improvements in methods for single trials
  - Link to adaptive licensing strategies


Framework of rare diseases by follow-up duration, type of treatment, population, etc.
Patient 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

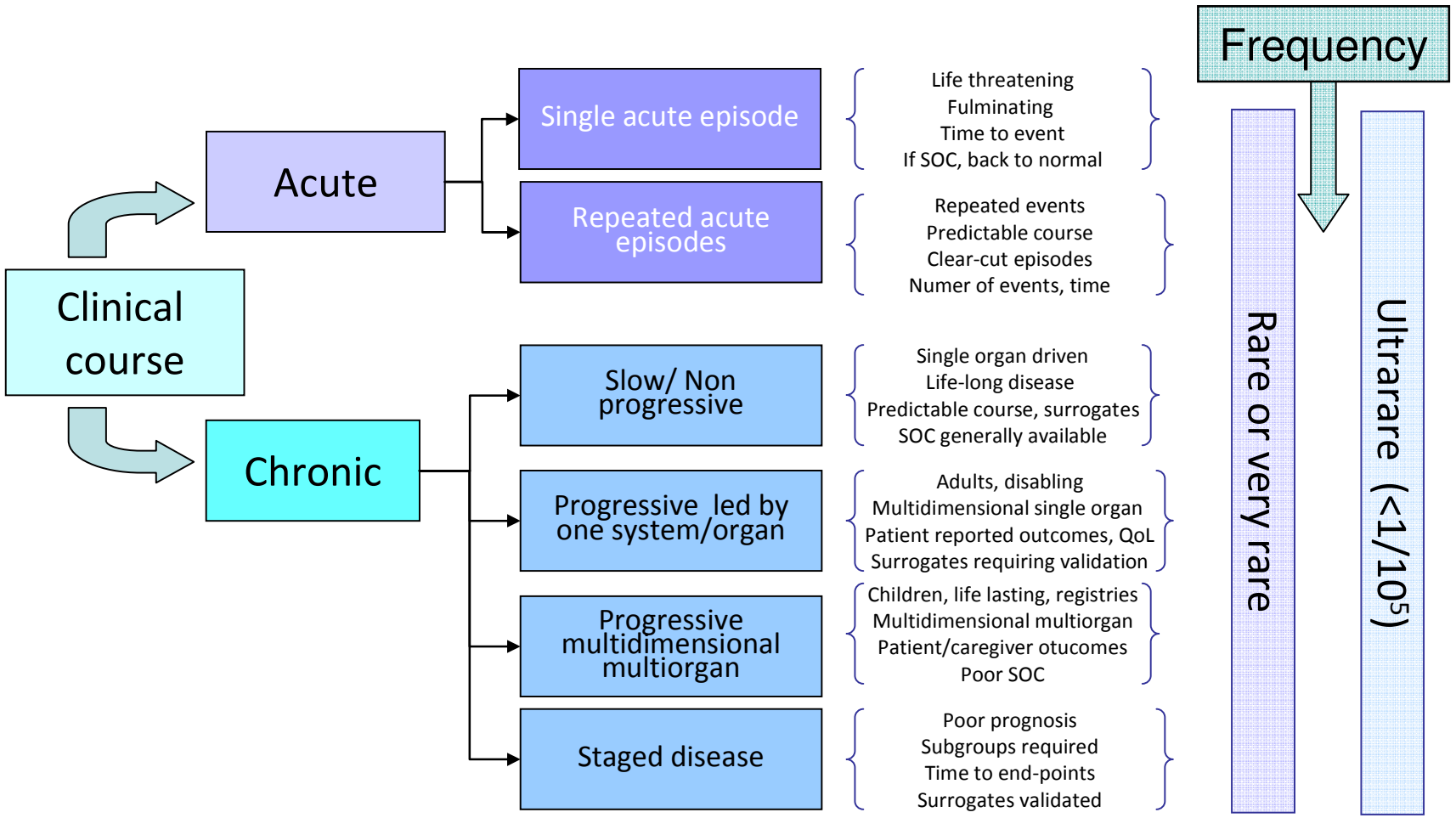
- Systematic involvement of patients and their perspectives
- 10 members
- PTT helps setting the research agenda
- Statisticians need to explain methods
- PTT collaborates and provides feedback

Example: 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 condition and treatment

Caridad Pontes, Ferran Torres, Josep Torrent et al.

Proposed framework for conditions clustering



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Patient registries to inform trial design
Methods

Interviews with coordinators of rare disease registries:

- why this registry?
- how does it work?
- what would you advise others?

Interviews with statisticians working on methods for clinical trials in small populations:

- what information should a registry contain?

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Patient registries to inform trial design
Results (1)

Reasons to start a registry

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

Use of registry in clinical trial

- Recruitment tool for RCT
- Data collection tool for RCT
- Historical controls in non-randomized studies

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Patient registries to inform trial design
Results (2)

Useful information for a statistician:

- Potential primary outcome measure
- “Nuisance parameters” for sample size calculations

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Patient registries to inform trial design
Conclusions

Registries are important, not only for trial design, but also for trial efficiency

Not all registry coordinators are aware of all possibilities

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Patient involvement in trial design

- 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
  - Patient organisations want to have a larger role besides just being a source for recruitment

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Topics brought up by patients (1)

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

Topics brought up by patients (2)

- Use of registries:
  - Use of historical data in trials
  - Reduction of placebo use

Topics brought up by patients (3)

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

Topics brought up by patients (4)

- Role of placebo:
  - Placebo use should be minimal
  - 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?

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How to involve patients in weighing outcome measures?

POWER model

Patient participation in
Outcome **M**easure **WE**ighing
for **R**are diseases

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Patient focused outcomes

- Generic outcome measures usually not responsive
- Development and validation of disease-specific outcome measures in rare diseases problematic
- Heterogeneity among rare disease trial participants
- Looking for an individual outcome measure: Goal Attainment Scaling (GAS)

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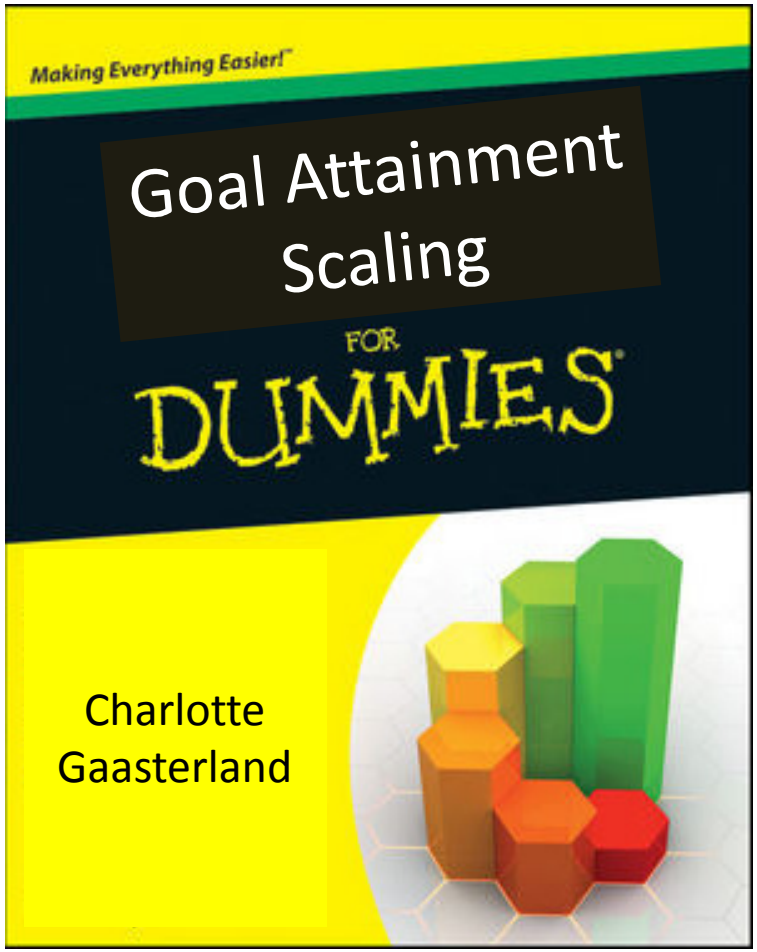
GAS…?


Making Everything Easier!™
Goal Attainment Scaling
FOR
DUMMIES
Charlotte Gaasterland

Imagine 3 boys with Duchenne disease:

‘I want to walk’

‘I want to eat independently’

‘I want to breathe independently’

How do we measure improvement?

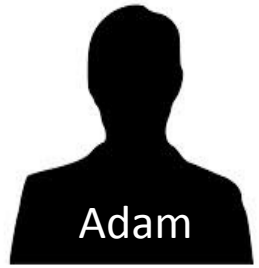
-2 Adam is unable to walk

-1 Adam can take 3 steps

0 Adam can walk for 5 minutes

1 Adam can walk for 15 minutes

2 Adam can walk longer distances



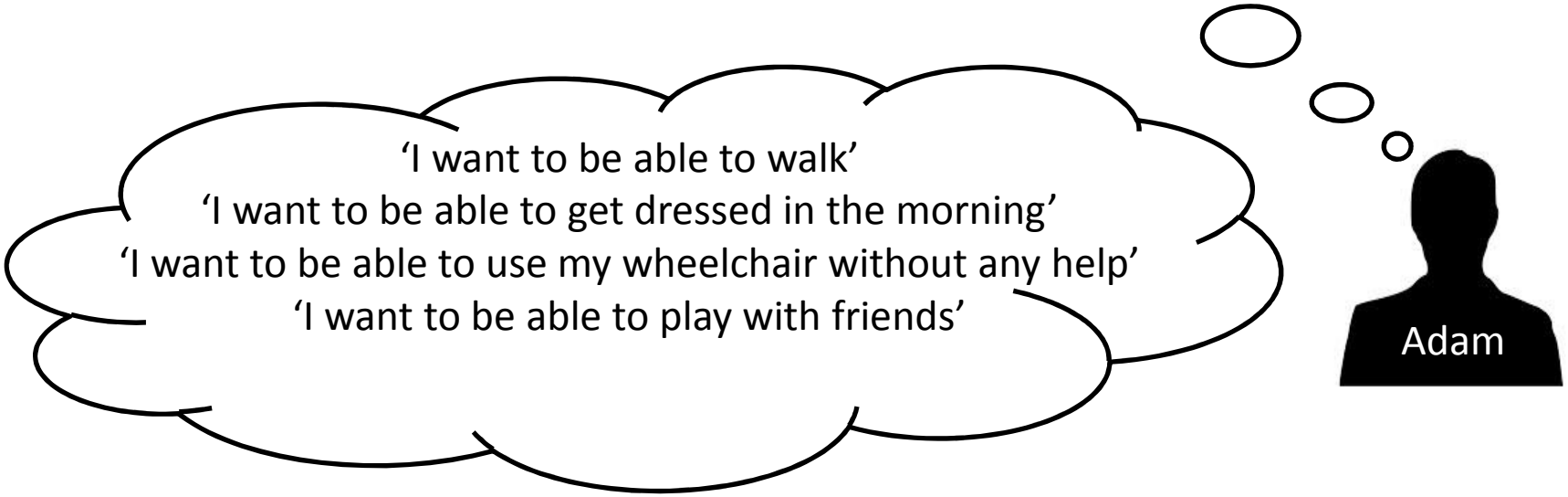
-2 Chris is unable to breathe independently

-1 Chris can breathe for 10 minutes

0 Chris can breathe for one hour

1 Chris can breathe for two hours

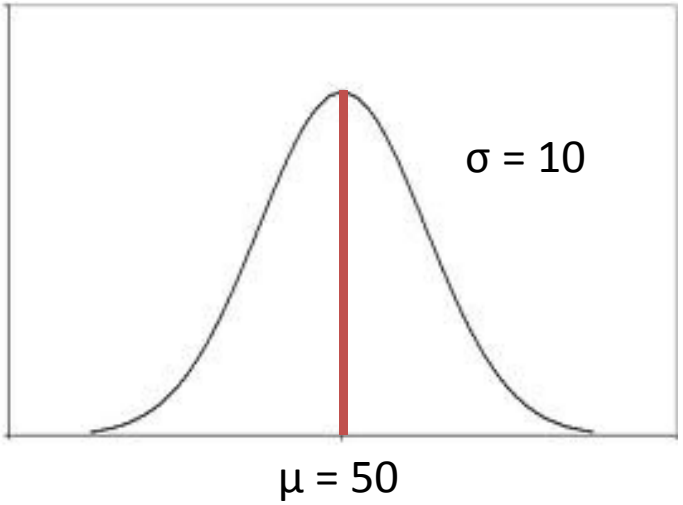
2 Chris can breathe for at least three hours



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

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

T	=	*GAS score*
x_i	=	*Original score*
w_i	=	*Weight given to the original score*
ρ	=	*Intercorrelation among goal scores (estimated at 0.3)*



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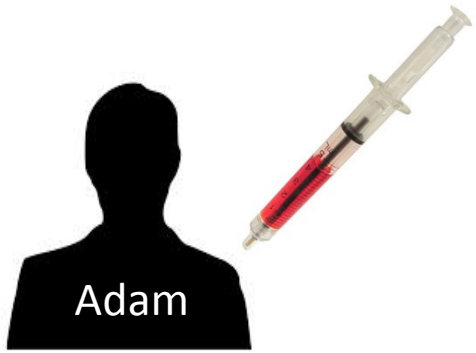
1. What are your goals, defined in 5 levels of attainment?
2. Which goals are most important to you?
3. *Intervention*
4. Have you attained your goals?



Gaasterland et al. BMC Medical Research Methodology (2016) 16:99
DOI 10.1186/s12874-016-0205-4

BMC Medical Research Methodology

RESEARCH ARTICLE Open Access

A systematic review to investigate the measurement properties of goal attainment scaling, towards use in drug trials

Charlotte M. W. Gaasterland[1*], Marijke C. Jansen-van der Weide[1], Stephanie S. Weinreich[1,2] and Johanna H. van der Lee[1]

Abstract

Background: One of the main challenges for drug evaluation in rare diseases is the often heterogeneous course of these diseases. Traditional outcome measures may not be applicable for all patients, when they are in different stages of their disease. For instance, in Duchenne Muscular Dystrophy, the Six Minute Walk Test is often used to evaluate potential new treatments, whereas this outcome is irrelevant for patients who are already in a wheelchair. A measurement instrument such as Goal Attainment Scaling (GAS) can evaluate the effect of an intervention on an individual basis, and may be able to include patients even when they are in different stages of their disease. It allows patients to set individual goals, together with their treating professional. However, the validity of GAS as a measurement instrument in drug studies has never been systematically reviewed. Therefore, we have performed a systematic review to answer two questions: 1. Has GAS been used as a measurement instrument in drug studies? 2: What is known of the validity, responsiveness and inter- and intra-rater reliability of GAS, particularly in drug trials?

Methods: We set up a sensitive search that yielded 3818 abstracts. After careful screening, data-extraction was executed for 58 selected articles.

Results: Of the 58 selected articles, 38 articles described drug studies where GAS was used as an outcome measure, and 20 articles described measurement properties of GAS in other settings. The results show that

Conclusions

Asterix is one of three European consortia developing methods for clinical trials in small populations

Involvement of patients is crucial

Results and recommendations will be widely communicated

Your input is appreciated

www.asterix-fp7.eu

Thank you!

- Kit Roes

- Egbert Biesheuvel

- Charlotte Gaasterland

- Martine Jansen-van der Weide