Applicability of novel methods WP5

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ASTERIX End Symposium

Novel methods developed within ASTERIX

Orphan conditions studies and EPARs

WP5 objective

- Determine **applicability, advantages & disadvantages**
  - **added value** of novel methods

- Provide **recommendations on methodology per cluster** of conditions

- Determine the
drug developm

d

Six condition clusters

1. Acute, single episodes
2. Acute, recurrent episodes
3. Chronic, stable/slow progression
4. Chronic, progressive, one system/organ
5. Chronic, progressive multiple systems/organs
6. Chronic, staged conditions

Methods included

- Innovative trial designs
- Study endpoints & statistical analysis
  - **Patient perspective: Goal attainment scaling (GAS)**
- Meta-analysis
- Level of evidence

Methods

- 6 clusters 14 methods 26 EPARs

		Level of evidence (A)	Meta-analysis (B)			Innovative trial designs C				
Cluster/topic	OMP	Long-short outcomes	Heterogeneity estimators	Prior distributions for variance parameters in sparse-event MA	Delayed-start randomisation	Sample size reassessment and hypothesis testing in adaptive survival trials Phase II/III (seamless)	Multi-arm group sequential designs with a simultaneous stopping rule UMW	Sequential designs for small samples	Bayesian sample size re-estimation using power priors	Dynamic borrowing through empirical power priors that control type I error
Cluster A Acute: single episodes	Savene									
	Pedea									
	Defitelio									
	Sirturo									
Cluster B Acute: recurrent episodes	Ilaris									
	Cayston									
	Xyrem									
	Diacomit									
	Sicklos									
	Tracleer									
Cluster C Chronic: stable/slow progression	Revestive									
	Plenadren									
	Xagrid									
	Glybera									
Cluster D Chronic: progressive, one system/organ	Soliris									
	Wilzin									
	Orphacol									
	Glivec									
Cluster E Chronic: progressive, multiple systems/organs	Fabrazyme									
	Kalydeco									
	Vyndaqel									
	Zavesca									
Cluster F Chronic: staged disease	Afinitor									
	Opsumit									
	Litak									
	Revlimid									

Testing direct applicability

Testing applicability modifications allowed

Criteria list and pre-requisites

		Essential/Critical pre-requisites	All below if applicable to current practice, otherwise NA and not mention/list
a.1. Multi-arm group sequential designs with a simultaneous stopping rule		SPECIFIC	Context
	a.1.1.	>= 3 arms including control (placebo)	number of arms in main trial(s)
	a.1.2.	>=1 interim analysis	Interim analysis done Y/N, If so, reason: stopping for futility, overwhelming evidence of efficacy, safety.
	a.1.3.	developed for continuous endpoints, transportable to other types (i.e	Type of endpoint (primary EP) (binary, continuous) Composite? Time to event?
	a.1.3.'		Type of (major) secondary endpoints (fill in as above)
	a.1.4.		Adaptive randomisation
	a.1.6.	>1 (time to outcome faster than accrual rate)	Delta time= recruitment - assessment (delay) /immediate or delayed response a.2.5.
	a.1.7.		Recruitment rate
	a.1.8.		Seamless design?
	a.1.9.		Adaptive design?
	a.1.10.		Allocation ratio
	a.1.11.		Did they allow dropping of arms
	a.1.12.		What was the control group?
	a.1.13.		MRCT? Multicentric? If Y, then how many?
	a.1.14.		Summary of models used in planning (e.g., disease progression, dropout, dose–response)

Study characteristics

- No of studies
- Type of (co-)primary endpoints/key secondary endpoints
- Recruitment pattern
- Time to outcome measurement
- Controlled or not
- Number of arms (if single arm: why?)
- Cross-over or not
- Acute or chronic condition

Example - Fabrazyme EPAR

- Cluster E: chronic, progressive, multiple systems/organs
- Fabry disease (ultra-rare): enzyme deficiency → accumulation of GL3

- Enzyme replacement therapy (exceptional circumstances 2001)

- Drug development:
  - Primary endpoint: reduction of GL3 accumulation (dichotomous)

  - Key secondary:
    - Change in GL3 in endothelium of kidney, skin and heart
    - Score of kidney tissue and urinary GL3 levels

  - 58 randomised patients

Methods' pre-requisites

Multi-arm multi-stage trial with simultaneous stopping rule

1. Time recruitment : Time outcome >1/>>1
2. >=1 interim analysis
2. Continuous outcomes (ideally, but transportable to binary)
3. >=3 arms (at least 2 experimental arms + 1 placebo)

Group sequential design for small samples

1. Time recruitment : Time outcome >1/>>1
2. Continuous outcomes (ideally, but transportable to binary)
3. Exactly 2 arms (treatment + control)

Method evaluation: 2-step approach

Step 1

Step 2

- NO adjustments

With adjustments
(reasonable)

Methods' pre-requisites – Step 1

Multi-arm multi-stage trial with simultaneous stopping rule

1. Time recruitment : Time outcome >1/>>1 ✓
2. >=1 interim analysis ✓
3. Continuous/binary outcomes ✓
4. >=3 arms (at least 2 experimental treatments + 1 placebo) ✗

Group sequential design for small samples

1. T recruitment : T outcome >1/>>1 ✓
2. Continuous/binary outcomes ✓
3. Exactly 2 arms (treatment + control) ✓

Methods' pre-requisites – Step 2

Multi-arm multi-stage trial with simultaneous stopping rule

1. Time recruitment : Time outcome >1/>>1 ✓
2. >=1 interim analysis ✓
3. Continuous/binary outcomes ✓
4. >=3 arms (at least 2 experimental treatments + 1 placebo) ✓

Group sequential design for small samples

1. T recruitment : T outcome >1/>>1 ✓
2. Continuous/binary outcomes ✓
3. Exactly 2 arms (treatment + control) ✓

Match method - study

Step 1:

- Group sequential design for small samples could be applicable immediately (Primary endpoint dichotomised from continuous) ✓
- Multi-arm multi-stage trial with simultaneous stopping rule not applicable (only 2 arms) ✗

Step 2:

- If we choose the continuous form of the primary endpoint (or e.g. urinary level of GL3 [1]) strongly applicable ✓
- Previous *phase I/II study explored multiple doses* for short-term only *but no optimal dose for longer term*, hence **multiple treatment regimens could have been tested in a MAMS** ✓

1. Thurberg BL, Rennke H, Colvin RB, Dikman S, Gordon RE, Collins AB, et al.
Globotriaosylceramide accumulation in the Fabry kidney is cleared from multiple cell types after enzyme replacement therapy. Kidney Int. 2002 Dec;62(6):1933–46.

Fabrazyme – potential impact

Potential advantages

- Quicker results
- Decreased placebo and non-inferior treatment exposure
- Control of type I error, maintaining power
- Increased precision for rejection boundaries
- Optimised use of available information

Potential disadvantages

- Increased logistic complexity
- Increased administrative and economic burden
- Sufficient evidence but not overwhelming
- Extra patients in case of effect size overestimation

Adjustments and reasons (1)

- Continuous endpoints preferred over binary
- Some rare conditions are rare versions of non-rare conditions
  - E.g. Tuberculosis – Sirturo
- Rare versions of cancer/tumor conditions
- Use hepatic or pancreatic biomarkers

Adjustments and reasons (2)

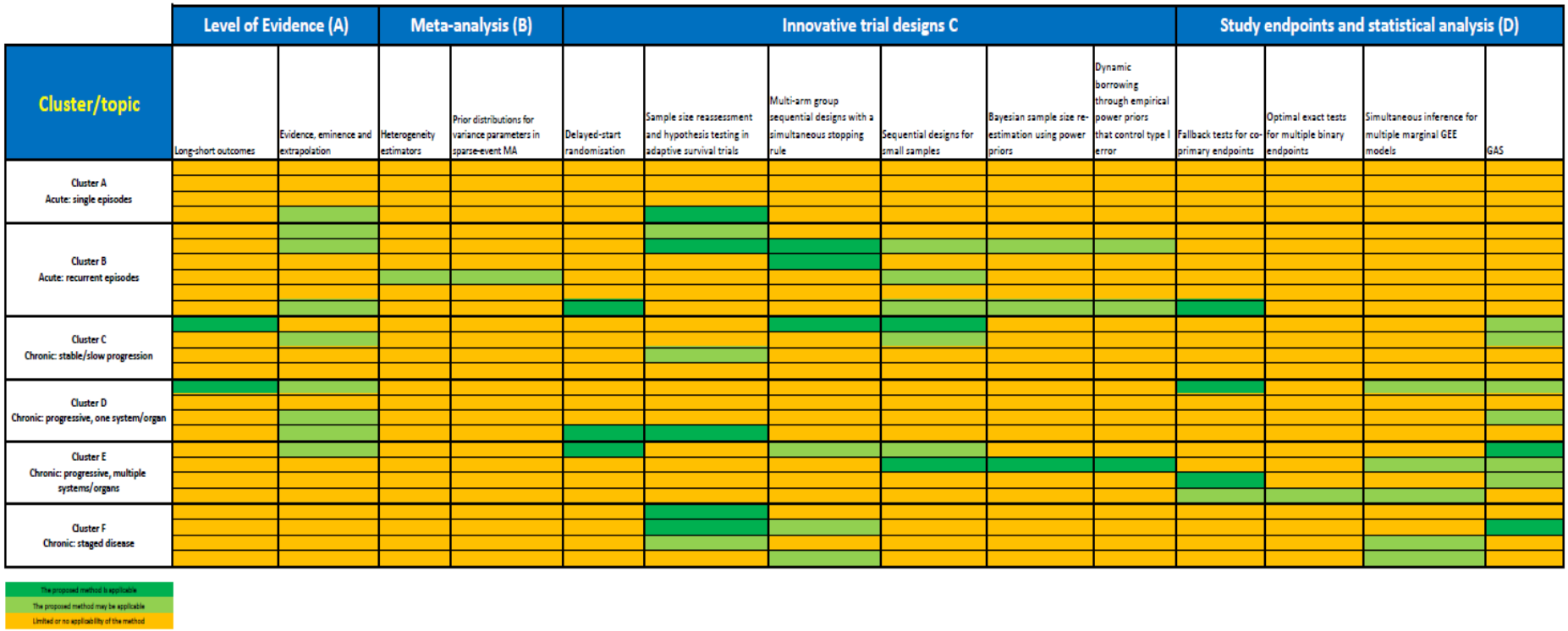
- For repurposed drugs a MAMS with a simultaneous stopping rule could be used (NSAIDs for patent ductus arteriosus)
- Multiple endpoints used to capture full clinical efficacy array
- Key secondary endpoints could be used as primary instead of secondary (6MWT/6MWD)

Heatmap of applicability


Heatmap Step 1


Heatmap Step 2

Step 1 - No adjustments



Step 2 - With adjustments

Cluster/topic	Level of Evidence (A)		Meta-analysis (B)		Innovative trial designs C						Study endpoints and statistical analysis (D)			
	Long-short outcomes	Evidence, eminence and extrapolation	Heterogeneity estimators	Prior distributions for variance parameters in sparse-event MA	Delayed-start randomisation	Sample size reassessment and hypothesis testing in adaptive survival trials	Multi-arm group sequential designs with a simultaneous stopping rule	Sequential designs for small samples	Bayesian sample size re-estimation using power priors	Dynamic borrowing through empirical power priors that control type I error	Fallback tests for co-primary endpoints	Optimal exact tests for multiple binary endpoints	Simultaneous inference for multiple marginal GEE models	GAS
Cluster A Acute: single episodes														
Cluster B Acute: recurrent episodes														
Cluster C Chronic: stable/slow progression														
Cluster D Chronic: progressive, one system/organ														
Cluster E Chronic: progressive, multiple systems/organs														
Cluster F Chronic: staged disease														

The proposed method is applicable

The proposed method may be applicable

Limited or no applicability of the method

Application of methods
Evaluation exercise summary

- First step – some immediate applicability
- Second step - exercise ***flexibility*** – gain applicability + advantages
- There is room for the novel methods to improve the designs for small populations trials
- Recommendations by cluster of conditions

What's next?

Katrien Oude Rengerink

London, 27 July 2006

GUIDELINE ON CLINICAL TRIALS IN SMALL POPULATIONS

TABLE OF CONTENTS

Update?

What can we add to the guideline?

- Updated, more specific guidance including novel methods
  - Including literature since 2006
    - ASTERIX
    - IDEAL
    - Inspire

- Use clustering to tailor guidance

London, 27 July 2006

GUIDELINE ON CLINICAL TRIALS IN SMALL POPULATIONS

TABLE OF CONTENTS

Methodological and statistical considerations

Paragraphs

6.1. Design stage

6.2. Data analysis

6.3. Reporting

Sequential designs

Sequential designs – with a goal to demonstrate 'statistical significance' if a treatment is genuinely superior to control - generally reduce the required sample size. There can be several different types of sequential design – all providing valid statistical conclusions but each tailored to specific balances of expected outcomes and patient availability. Some designs are 'open-ended' and (in theory) continue to recruit patients until a reliable positive or negative conclusion about the treatments can be made

Sequential designs, as with response-adaptive designs, require treatment outcomes to be available quickly (relative to the patient recruitment rate). This will almost never be the case if we are looking for long-term survival data, for example, but may be the case if we are looking at shorter term clinical or surrogate/bio-markers

slow because patients are so rare; hence such methods may have more of a place in these situations than in more common diseases. Ultimately, however, the extent to which the sample size can be reduced depends on the size of the effect. Variations on sequential methods are the, so-called, group-sequential methods and adaptive designs. See also draft guidance on adaptive designs (CHMP/2459/02).

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	Orphacol			Added value?
	Tracleer			
	Zavesca			
Cluster F Chronic: staged disease	Afinitor			
	Opsumit			
	Litak			
	Revlimid			

Limitations

- Few EPARs evaluated per cluster
  - If no applicability in heatmap: not impossible
  - If applicable in all cases: not always possible

  → Necessary to combine heatmap with methods pre-requisites

- Clustering helpful, still heterogeneity within clusters

Dis

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Thanks for all input:
"It takes a village to raise a child"
African proverb