



Clustering of rare medical conditons based on applicability of methods and designs for clinical trials

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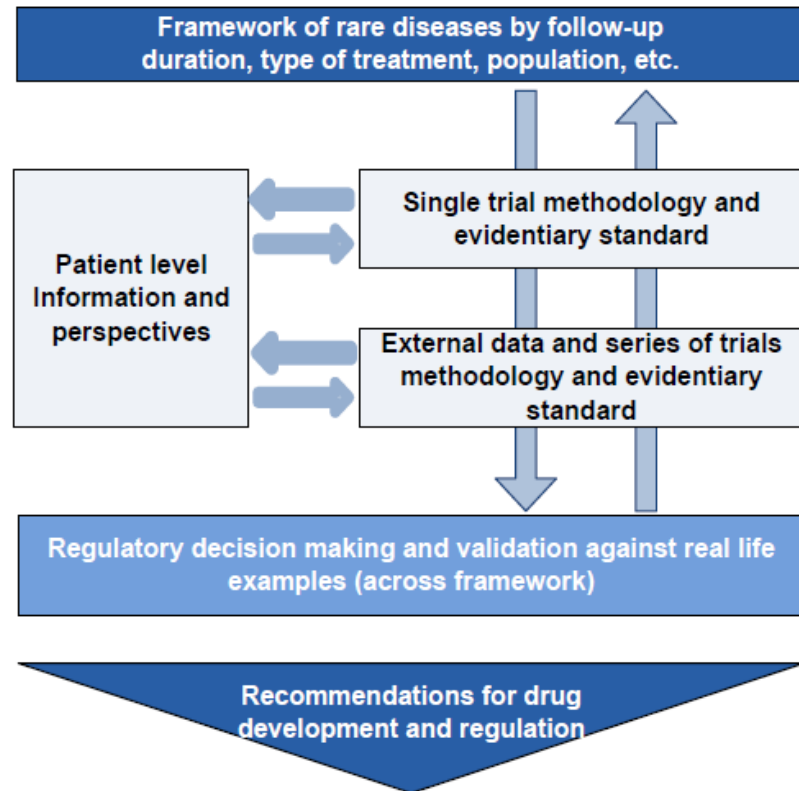
Objectives

1. Asterix clustering

2. Regulatory standard

3. Simulations

4. Recommendations





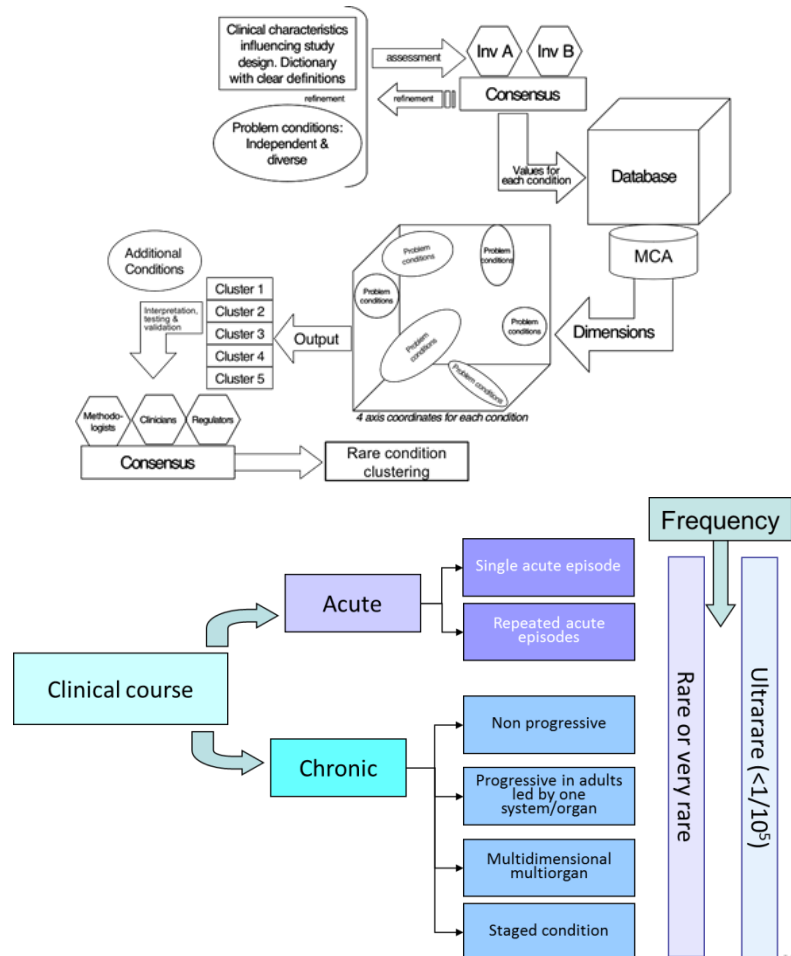
1. The ASTERIX clustering

» Grouping of conditions

- 1 general document, 8000 conditions, need something in between
- Improving decision on **where** to apply **what** methods
- Thus based on items we use to decide methods
- Tool for creating scenarios: clustering analysis
- Consensus rounds until final product agreed

» Asterix clustering of conditions

- *Monica Gómez-Valent PhD dissertation 7th July 2017*





Clustering of rare medical conditions

- » Grouping of medical conditions
 - Defined by both the clinical disease and the indication of the new treatment
 - According to requirements for applicability of methodologies and designs of clinical studies.
- » Medical condition \neq disease
 - One disease may hold different conditions depending on the therapeutic approach
 - *Cystic fibrosis*
 - *Treatment of acute pulmonary exacerbations*
 - *Correction of defective chloride channels.*

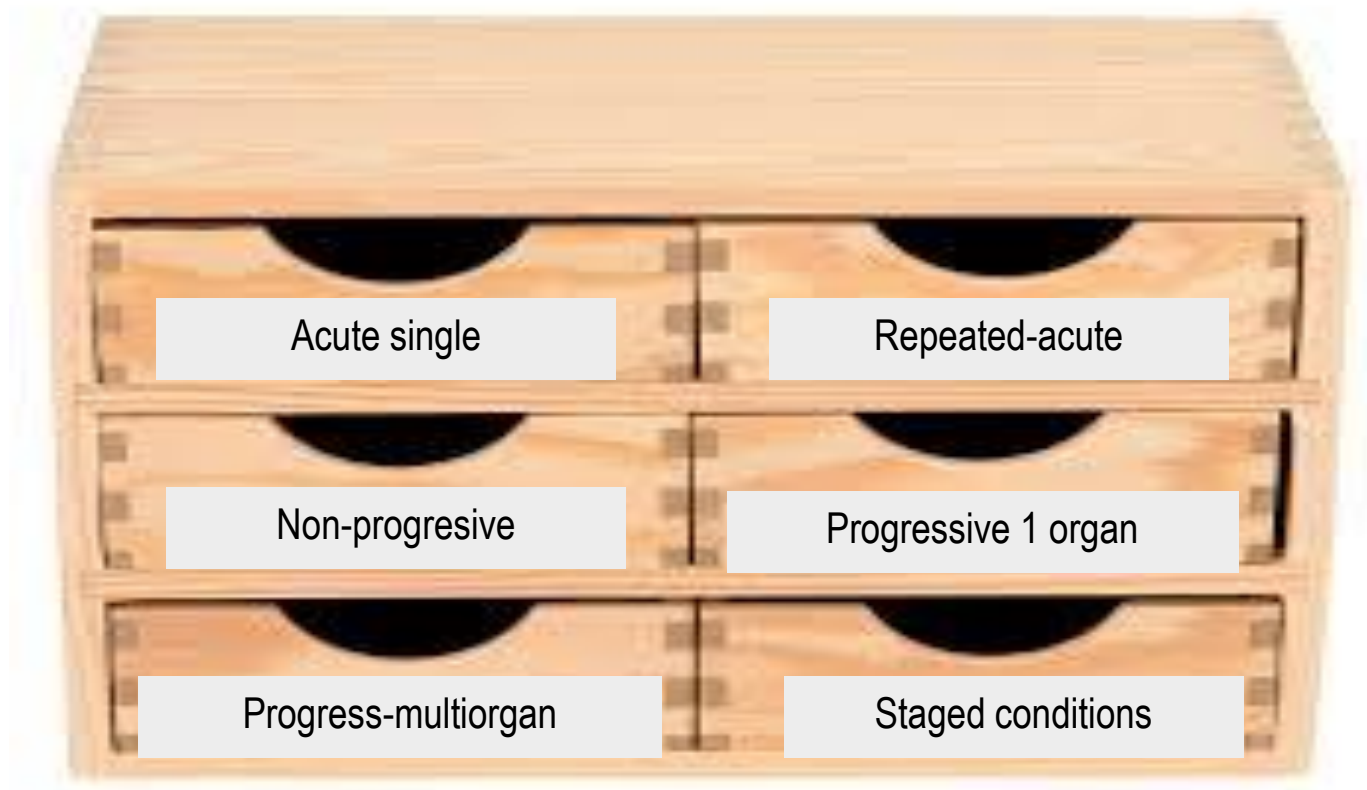


Key determinants

- » **Clinical course:** relevant to the overall study setting and type of control, and to the ability to use acquired information in an ongoing basis;
- » **Specificity of the impairment:** determining the type and number of variables that may be used to measure efficacy;
- » **Severity of the impairment:** determining control group, and type and source of efficacy information;
- » **Heterogeneity** of the condition and/or concurrent treatments, relevant to the need to foresee subgroups and to the approach for measurement of efficacy;
- » **Ethiology, standard of care and reversibility** of the condition, determining ethical aspects and the sequence of designs.



Clustering of rare medical conditions





asterix Clustering of rare medical conditions

Cluster 1: Single acute episode

Incident cases with single acute episode, with rapid onset and rapid endpoint.

Well-known and predictable course in absence of treatment, often serious or life-threatening. Recovery generally returns to baseline health status with or without sequels.

Comparison if an effective SOC exists, add-on designs. Generally single hard objective and clinically relevant end-point, often binary.

Cluster 2: Repeated acute episodes

Prevalent subjects who suffer clear-cut repeated episodes separated by relatively healthy periods.

Well known predictable clinical course, generally due to a single biological or physiological abnormality which - if severe or immunological- may derive into multiorgan impairment. Baseline status may deteriorate along years due to repeated episodes.

Generally there are clinically relevant time-related end-points, number of episodes by time. If mild, variables may be based on patient reported outcomes. If serious, then binary clinical end-points.

Cluster 3: Chronic non-progressive

Prevalent subjects who suffer life-long disease of mainly a single system/organ, with constitutive activity due to deficiency or impairment of function and a predictable well-known clinical course.

May be adult or both pediatric and adult. Does not rapidly deteriorate the subject function or life-expectancy with current standard of care, but further deterioration may occur in years.

There are available surrogates that directly measure the underlying defect or deficiency.



Clustering of rare medical conditions

Cluster 4: Chronic progressive led by one system-organ

Initial impairment of one system/organ, clinical course is longer than acute conditions, usually year(s). Progressively reducing life quality and/or quantity of life, seriously disabling. Current standard of care generally symptomatic or supportive, but not curative. Frequent heterogeneity in clinical expression. Variables often rely on PROM, and patient perceptions on the disease; disability and QoL are relevant for decision-making.

Cluster 5: Chronic progressive multidimensional

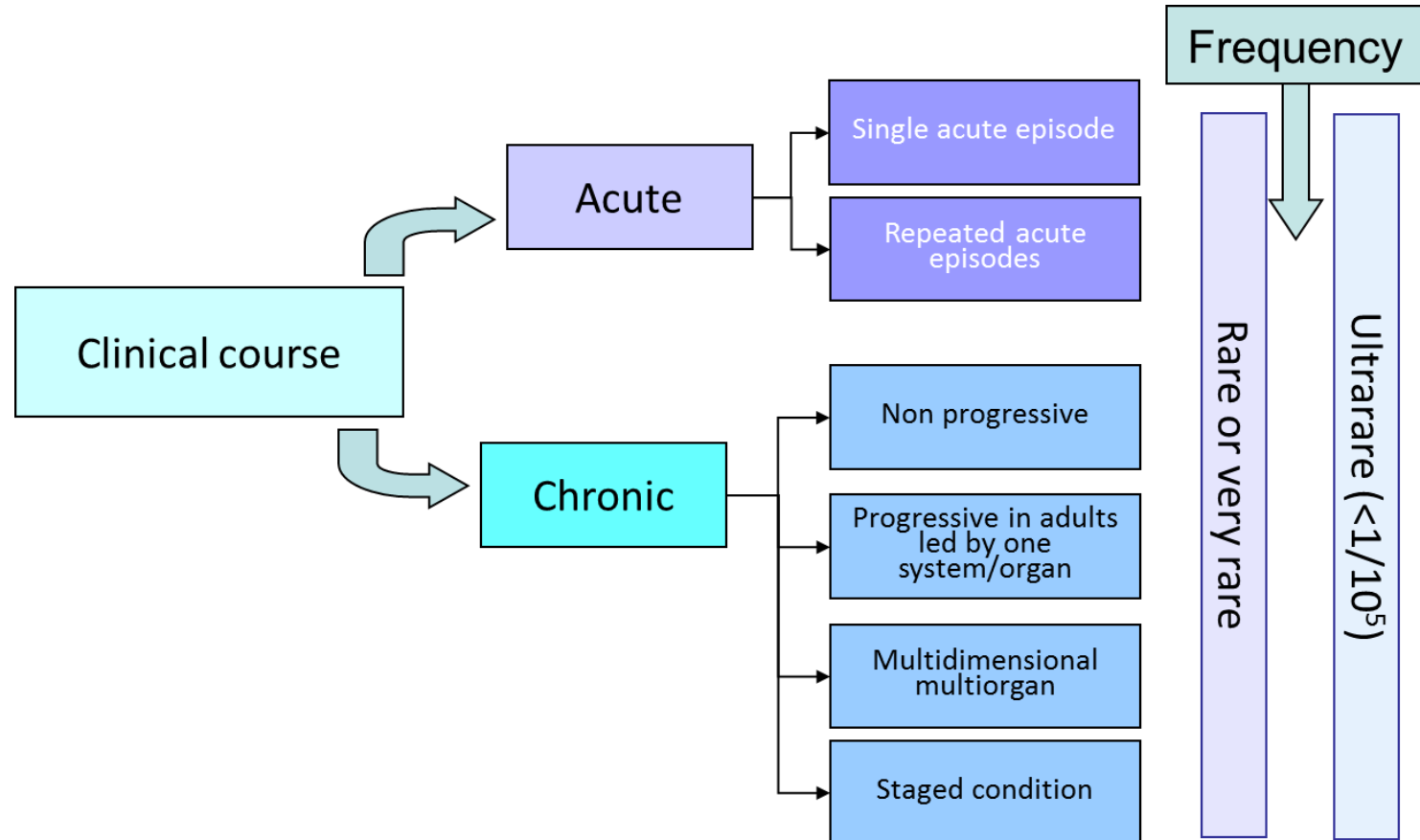
Mainly prevalent cases. Life-lasting diseases, often inherited starting as paediatric and, if mild or available SOC, affecting (young) adults. Often SOC poor or not available. Highly variable clinical course, with impact in multiple system/organs, requiring multidimensional assessment. Clinical or functional status and QoL assessed by caregivers/patients. Previous data on event/response rate or variance often available. If not rapidly life-threatening, prospective registries often feasible and available. If inherited, known physiopathology, options for targeted therapies and genetic approaches.

Cluster 6: Staged conditions

The condition progresses/expands into other system/organs, with defined clinical stages with different SOC. Prognosis and treatment approaches depend on disease extension. Disease burden is a key variable, either time dependent or not. For those neoplastic, imaging is preferred method for staging; haematological conditions also assess tumour burden, and non-malignant conditions generally measure subject function. Quality of life relevant for all. Outcomes referred to progression, stagnation or reversal of the condition, with time in each stage as a relevant measure of disease. If reversal is not feasible, late stages have poor (fatal) prognosis.



Clustering of rare medical conditions





2. The regulatory standard

- » Description of current regulatory decision making for OMP in EU
 - 125 EPARs until Dec 2014
 - Basis for OMP approval
 - Detailed description of each EPAR
 - Summaries by cluster
- » Regulatory standard for OMP
 - Manel Fontanet PhD dissertation 14th Sept 2017

		Acute single episodes (N=27)	Chronic slow or non- progressive condition (N=24)	Progressive conditions led by one organ-system (N=29)	Progressive multidimensional condition (N=21)	Recurrent acute episodes (N=13)	Staged condition (N=45)	All trials (N = 159)						
Double blind	8	29.6%	12	50.0%	7	24.1%	15	71.4%	12	92.3%	26	57.8%	80	50.3%
Single blind	1	3.7%		0.0%		0.0%		0.0%	1	2.2%	2	1.3%		
Open label	18	66.7%	10	41.7%	22	75.9%	6	28.6%	1	7.7%	18	40.0%	75	47.2%
NA		0.0%	2	8.3%		0.0%		0.0%		0.0%		0.0%	2	1.3%
Randomized	14	51.9%	17	70.8%	10	34.5%	18	85.7%	13	100.0%	37	82.2%	109	68.6%
Placebo controlled	7	25.9%	12	50.0%	5	17.2%	14	66.7%	12	92.3%	25	55.6%	75	47.2%
Active controlled	3	11.1%	4	16.7%	3	10.3%	2	9.5%	1	7.7%	8	17.8%	21	13.2%
Not controlled	12	44.4%	8	33.3%	20	69.0%	4	19.0%		0.0%	9	20.0%	53	33.3%
Other	5	18.5%	0	0.0%	1	3.4%	1	4.8%	0	0.0%	3	6.7%	10	6.3%
1 arm	12	44.4%	7	29.2%	17	58.6%	3	14.3%		0.0%	8	17.8%	47	29.6%
2 arms	14	51.9%	13	54.2%	10	34.5%	16	76.2%	11	84.6%	20	44.4%	84	52.8%
3 arms	1	3.7%	3	12.5%	2	6.9%	2	9.5%		0.0%	14	31.1%	22	13.8%
4 arms		0.0%	1	4.2%		0.0%		0.0%	2	15.4%	3	6.7%	6	3.8%
Parallel groups	14	51.9%	15	62.5%	12	41.4%	17	81.0%	11	84.6%	37	82.2%	106	66.7%
Single arm	12	44.4%	7	29.2%	17	58.6%	3	14.3%		0.0%	8	17.8%	47	29.6%
Crossover		0.0%	2	8.3%		0.0%	1	4.8%		0.0%		0.0%	3	1.9%
Randomised withdrawal		0.0%		0.0%		0.0%		0.0%	2	15.4%		0.0%	2	1.3%
Historical control	1	3.7%		0.0%		0.0%		0.0%		0.0%		0.0%	1	0.6%
Final variable	12	44.4%	3	12.5%	1	3.4%	4	19.0%	11	84.6%	9	20.0%	40	25.2%
Intermediate variable	15	55.6%	21	87.5%	28	96.6%	17	81.0%	2	15.4%	36	80.0%	119	74.8%
Single variable	21	77.8%	18	75.0%	24	82.8%	17	81.0%	11	84.6%	31	68.9%	122	76.7%
Composite variable	1	3.7%		0.0%		0.0%	1	4.8%		0.0%	13	28.9%	15	9.4%
Co-primary variables	2	7.4%	2	8.3%	4	13.8%	2	9.5%	2	15.4%	1	2.2%	13	8.2%
Multiple end- points	3	11.1%	4	16.7%	1	3.4%	1	4.8%		0.0%		0.0%	9	5.7%
Continuous		0.0%	11	45.8%	5	17.2%	13	61.9%	8	61.5%	13	28.9%	50	31.4%
Discrete	20	74.1%	10	41.7%	21	72.4%	6	28.6%	3	23.1%	11	24.4%	71	44.7%
Both	1	3.7%	3	12.5%	2	6.9%	1	4.8%	1	7.7%		0.0%	8	5.0%
Time variable	6	22.2%		0.0%	1	3.4%	1	4.8%	1	7.7%	21	46.7%	30	18.9%
Includes biomarkers	19	70.4%	16	66.7%	24	82.8%	17	81.0%	6	46.2%	27	60.0%	109	68.6%
Superiority	13	48.1%	14	58.3%	8	27.6%	16	76.2%	12	92.3%	36	80.0%	99	62.3%
Value estimation	12	44.4%	8	33.3%	21	72.4%	3	14.3%		0.0%	9	20.0%	53	33.3%
Non-inferiority	1	3.7%	1	4.2%		0.0%	2	9.5%	1	7.7%		0.0%	5	3.1%
NA	1	3.7%	1	4.2%		0.0%		0.0%		0.0%		0.0%	2	1.3%



2. Analysis of the standard

Lack of clinical trials in MAA	<ul style="list-style-type: none">• 12% of all OMP MAA without evidence coming from clinical trials• Most unavoidable: summary of data on products already available.• Retrospective studies have a low level of evidence, source of uncertainty for decision making.
Lack of 2 pivotal trials in MAA	<ul style="list-style-type: none">• Only 30% of MAA based on at least 2 pivotal trials.• Lower control of the type 1 error due to lack of replication• Higher proportion of MAA with 1 single trial in staged, progressive multidimensional, and acute single episodes.
Negative trials as the only basis for pivotal regulatory assessment	<ul style="list-style-type: none">• 10% of MAA based on clinical trials have negative trials as the only basis for approval; 15% in the acute single episodes cluster.



2. Analysis of the standard

Low level of evidence of pivotal data	<ul style="list-style-type: none">• Low potential to conclude causality in a substantial proportion of trials• Only half of the pivotal trials in MAA were double blind• Open label single arm trials frequent, especially in progressive conditions lead by one organ.• Most trials used intermediate primary variables, except in acute conditions.
Overestimation of results	<ul style="list-style-type: none">• Single arm, open-label, non-controlled and non-randomized trials more likely to meet their main objective• Studies using composite variables, intermediate end-points and discrete variables had positive results more often.
Conclusions based on subgroups	<ul style="list-style-type: none">• 16.3% of MAA with at least one pivotal trial concluding based on subgroups; some post-hoc.
Small extent of population exposure to assess clinical safety	<ul style="list-style-type: none">• average size of the safety population always smaller than that recommended by ICH E1• This was much lower amongst ultrarare conditions, with less than 100 patients in most cases.



2. Areas for improvement

Lack of clinical trials in MAA

- Well established therapeutic uses can be summarised by applying metanalytical techniques to the published studies.
- Prospective registries and compassionate programs may allow to obtain structured and complete information to design trials, and on postmarketing effectiveness and safety, although not comparative.

Lack of 2 pivotal trials in MAA

- Strategies aimed to manage the type 1 error may help, especially in the clusters where one single trial MAA is frequent (staged conditions, progressive multidimensional conditions and acute single episodes).

Negative trials as the only basis for pivotal regulatory assessment

- Reduce the chances of negative trials.
- Strategies aimed to refine designs by leveraging prior information
- Enrichment strategies to maximize differences and effect size
- Fallback testing to manage uncertainty in choice of variables
- Strategies to adapt parameters of the study design, such as choice of groups, variables, assumptions for sample size, by using using information as acquired, Bayesian approaches, other



2. Areas for improvement

Low level of evidence of pivotal data	<ul style="list-style-type: none">• Alternative methods to maximize the inferential value of data• Maintain or improve the acceptability of trial participation from the ethical point of view may increase feasibility and robustness of designs.
Overestimation of results	<ul style="list-style-type: none">• Alternative methods may increase the robustness of designs and minimise the potential for bias.
Conclusions based on post-hoc analyses	<ul style="list-style-type: none">• Pre-planned subgroup analysis and methods to account for heterogeneity such as stratification, dynamic randomization
Small extent of population exposure to assess clinical safety	<ul style="list-style-type: none">• Uncertainties at MAA are difficult to manage• Disease registries and natural history series may be useful to separate disease from adverse events• Post-marketing commitments on long-term studies and registries as options to complement the data that cannot be obtained at the time of confirmation of efficacy.• Extrapolation from other populations may be an option when the drug is used for other indications.



3. Applicability and simulations

» Which designs and methods can be applied to each cluster?

- Novel Asterix designs
- Already known alternative designs

» Application

- Theoretical and qualitative

» Application testing

- Testing models by cluster
- Novel and known methods
- On the way

Next speakers



4. Recommendations

- » By clusters
- » Recommendations for regulatory development based on applicability
 - Alternative known methods
 - Novel methods
- » Advantages and disadvantages
 - Compared to current regulatory standard for each cluster

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JOY IN THE STORM (Winning Expert's Choice photo - EURORDIS Photo Contest 2016)

Thank you