Clinical Trials in Rare Diseases Methodological Issues

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Trials in Rare diseases: 2 settings -1st-

IF

- Condition with a very homogeneous clinical course (rapidly progressive/stable disability)

AND

- Treatment aim is cure or dramatic improvement

Trials in Rare diseases: 2 settings -1st-

IF

- Condition with a very homogeneous clinical course (rapidly progressive/stable disability)

AND

- Treatment aim is cure/dramatic improvement

Any success (e.g. 1 case of cure) can be attributed to therapy

Examples

- Insulin for Type I diabetes
- Heart transplantation for terminal stage heart failure
- (Gene) Therapies in hereditary metabolic disorders
- *'Lazarus' effects in advanced cancer patients?*

If any success can be unequivocally attributed to therapy

Small, uncontrolled clinical trials

may provide evidence making further RCT's

- Not necessary
- **Unethical**
- **Unfeasible (informed consent)**

Methodological requirements?

Trials in Rare diseases: 2 settings -2nd-

IF

- Chronic progressive diseases with variable clinical course

OR

- Treatment aim is **NOT** cure (e.g. palliation)

Examples

- Autoimmune diseases (e.g. Rheumatic)
- Rare infectious diseases
- Hereditary neuropathies
- **Rare Tumors**

Trials in Rare diseases: 2 settings -2nd-

IF

- Chronic progressive diseases with variable clinical course

OR

- Treatment aim is **NOT** cure (e.g. palliation)

No individual outcome can be attributed to therapy

If no outcome can be unequivocally attributed to therapy

Type of error

- Bias

- Chance

If no outcome can be unequivocally attributed to therapy

Type of error	**Solution**
• Bias	• **Well conducted RCT** (Prospective studies?)

If no outcome can be unequivocally attributed to therapy

Type of error	**Solution**
• *Bias*	• *Well conducted RCT (Prosp. studies?)*
• **Chance**	• **Large size**

Available Evidence on treatments for Rare Diseases

- Case Reports
- Small Studies
- Uncontrolled (Phase II?) Trials
- Low quality trials (protocol, selection criteria, assessment of endpoints, exclusions, GCP, etc.)

INADEQUATE EVIDENCE

Available Evidence on treatments for Rare Diseases

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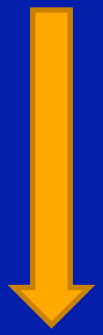
CLINICAL GUIDELINES?

Available Evidence on treatments for Rare Diseases

INADEQUATE EVIDENCE

CLINICAL GUIDELINES?



CLINICAL DECISION?

Available Evidence on treatments for Rare Diseases

- Small Studies } Statistical error

Available Evidence on treatments for Rare Diseases

- *Small Studies*

- Uncontrolled Trials
- Low quality trials

} Bias

Statistical error and Conventional statistical reasoning

Conventional Statistical Reasoning

1. Starting hypothesis (null hyp., H0):

   new treatment = standard one

Conventional Statistical Reasoning

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2. To demonstrate: new treatment >> standard,
   reject null hypothesis (p<0.05)

Conventional Statistical Reasoning

1. *Starting hypothesis (H0):*

   new treatment = standard one

2. *To demonstrate: new treatment >> standard, reject null hypothesis ($p<0.05$)*
3. To reject null Hypothesis: **Large Sample Size**

Conventional Statistical Reasoning

1. *Starting hypothesis (H0):*

   new treatment = standard one

2. *To demonstrate: new treatment >> standard, reject null hypothesis ($p<0.05$)*
3. *To reject null Hypothesis: Large Sample Size*
4. **Only information collected within the experiment used in interpretation of study results**

Example

		Mortality
Tumor X	**Nil vs A**	**15% vs 12.5%**
N=12000		**P = 0.0007**

H0 Rejected: A is effective in X

Example

		Mortality
Tumor X	*Nil vs A*	*15% vs 12.5%*
N=12000		*P = 0.0007*
Tumor Y	**Nil vs A**	**15% vs 7.5%**
N= 240		**P=0.066**

H0 not rejected: A not shown effective in Y

Conventional Rules for study design

- A study **must** have an adequate size

Conventional Statistical Rules

- *A study **must** have an adequate size*
- Required Size, based on:
  - Significance level (usually 5%)
  - Minimal clinically worthwhile difference
  - Power (usually 80-90%)

Conventional Statistical Rules

- *A study **must** have an adequate size*
- *Required Size, based on:*
  - *Significance level (usually 5%)*
  - *Minimal clinically worthwhile difference*
  - *Power (usually 80-90%)*
- Results: Test of significance
  - $P<0.05$ = Positive Study
  - $P>0.05$ = Negative Study

Adequate size

- Test of significance

  To have a good chance to reject the null hypothesis when wrong (= power) large sample size or large difference

- Point Estimates +/- 95% CI's

  To reduce uncertainty, large sample size

How large? – Needed number of events

Rel. Reduct. Event Rate	Needed number of events
50%	71
40%	**125**
30%	**252**
20%	**635**
10%	2830

α=0.05, power = 80%

Required sample size in cancer clinical trials

In trials in early disease, cumulative mortality from 10% to 70%: **500-5000** pts

In trials in advanced disease, cumulative mortality from 50% to 90%: 3**00-1000** pts

Selection criteria for a given trial

Site, Histology, Stage

- Patients characteristics (age, sex)
- Previous treatments
- **Biology, Genetics**

Frequency of specific CLINICAL CONDITIONS

Implication

If , in a given clinical condition,

Implication

If , in a given clinical condition,

- it is not possible to assemble (in a reasonable time) an adequate number of patients (hundreds or thousands),

Implication

If , in a given clinical condition,

- it is not possible to assemble (in a reasonable time) an adequate number of patients,
- **and the efficacy of a new treatment is not outstanding,**

Implication

If , in a given clinical condition,

- it is not possible to assemble (in a reasonable time) an adequate number of patients,
- and the efficacy of a new treatment is not outstanding,

this efficacy CANNOT be demonstrated (or ruled out)

Consequence

For the large majority of rare diseases, there are **no** treatments of proven efficacy

(according to standard EBM criteria)

No magic solutions!

- In rare diseases, the evidence available for clinical guidelines and decisions is necessarily going to be less...

in terms of

- Quantity?
- Quality?

Quality vs Quantity (of evidence)

- Quantity = Statistical precision (number of studies, size of studies)

Quality vs Quantity (of evidence)

- Quantity

- **Quality ?**
  - Study Design
  - Quality of data
  - Statistical Plan
  - Endpoints
  - (Randomization)

Quality vs Quantity (of evidence)

In rare diseases, difficulties in assembling adequate amount of evidence (**quantity**), should not be used to justify **low-quality** studies

Quantity of evidence
Common Solutions

Quantity of evidence
Common Solutions

- National, European, worldwide cooperations
- *(Prolonged accrual ?)*
- *(Prolonged follow-up ?)*

National, European, worldwide cooperations

Examples of **very successful** cooperations

- Paediatric Rheumatology INternational Trials Organisation (PRINTO) for paediatric rheumatic disorders
- European Neuroblastoma Study Group
- Children's Oncology Group (CCG)

International Cooperations

In several rare diseases, necessary/sufficient to answer relevant clinical questions

Problems

- Sponsor/Funds

International Cooperations

In several rare diseases, necessary/sufficient to answer relevant clinical questions

Problems

- *Sponsor/Funds*

- Relevant clinical questions?

Need of preclinical studies and hypothesis-generating trials

International Cooperations

In many rare conditions with very low incidence

International Cooperation: <50 cases/year = Insufficient

Even with prolonged accrual/follow-up

Journal of Clinical Oncology, Vol 21, Issue 5 (March), **2003**: 793-798

Treatment of Children With Nonmetastatic Paratesticular Rhabdomyosarcoma: Results of the Malignant Mesenchymal Tumors Studies (MMT 84 and MMT 89) of the International Society of Pediatric Oncology

Patients and Methods: **From 1984 to 1994, 96 males were treated** in SIOP protocols. …

Results:. .. At 5 years, the overall survival (OS) rate was 92%, with an event-free survival (EFS) rate of 82%. OS and EFS were significantly worse for males with tumors greater than 5 cm and for males older than 10 years at diagnosis.

Conclusion: Males with paratesticular RMS have an excellent prognosis except for a selected group of patients older than 10 years or with tumor greater than 5 cm. **Intensified chemotherapy incorporating alkylating agents for this subgroup may be preferred to the use of systematic lymphadenectomy to improve survival while minimizing the burden of therapy.**

10+10 years, 10 countries

Other solutions

- **Uncontrolled trials**
- Relaxed alfa error
- Surrogate endpoints

Uncontrolled trials

Marginal gains: 50% less patients

VALIDITY/RELIABILITY:
OVERWHELMING EVIDENCE AGAINST

Acceptable only for paradigm-changing treatments

Relaxed alfa error

- Risk of false positive results
- Precision of the estimates

- Marginal gains

  For alfa = 0.1 (e.g. 1-sided tests)

  22% less patients are needed (78 instead of 100)

Surrogate endpoints (SES)

- Potentially substantial gains !

  e.g.

  let's assume that Objective resp. doubles survival (in responders),

  To detect an increase in Objective Response from 30% to 60%: **100 pts**

  To detect this effect on Survival (Initial Hazard Ratio≈0.82) > **800 events**

Problems with SES

- Validation: Large RCT or meta-analysis, statistical problems (demonstration of no difference)
- Extrapolations: Different diseases, different treatments
- Few validated SES are available, **none for rare diseases**

What can be done?

Reconsider conventional statistical reasoning!

Conventional Statistical Reasoning

1. **Starting hypothesis (H0):**

   new treatment = standard one

2. *To demonstrate: new treatment >> standard, reject null hypothesis*
3. *To reject null Hypothesis: Large Sample Size*
4. **Only information collected within the experiment used in design and interpretation of study results**

Weakness of conventional approach

The evidence supporting the study rationale is ignored in its design and analysis (H0)

Focus on significance testing (rejection of H0)

Null Hypothesis (H0)?

- Biological rationale
- Evidence of activity
- Efficacy in other diseases with similarities
- Efficacy in other subgroups of patients with the same disease

New (Bayesian) Approach

- Focus on estimates of effect
- Formal, explicit use of prior information

Test of significance

Mortality

Tumor X **Nil vs A** **P = 0.0007**

(N=12.000)

Tumor Y **Nil vs A** **P=0.066**

(N=240)

Test of significance vs Estimates of effect

		Mortality
Tumor X (N=12.000)	**Nil vs A**	**15% vs 12.5%** (P = 0.0007)
Tumor Y (N=240)	**Nil vs A**	**15% vs 7.5%** (P=0.066)

Estimates of effect + **Prior Evidence**

Tumor X 5yrs mortality

Trial 1 **Nil vs A** **15% vs 12.5%**
(adult patients)
N=12000 **P = 0.0007**

Trial 2 **Nil vs A** **15% vs 7.5%**
(pediatric patients)

N= 240 **P=0.066???**

What if A has a molecular target present both in X and Y?

		Mortality
Tumor X	**Nil vs A**	**15% vs 12.5%**
N=12000		**P = 0.0007**
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Prior Evidence and Scientific Evidence

- Prior evidence is a crucial component in the interpretation of any finding (e.g. X-ray)
- Less direct evidence is required for decision when prior evidence is taken into account
- Bayesian statistics allows to conjugate prior evidence with trial results

Prior evidence

Already (implicitly) used in clinical guidelines and decisions in rare diseases

- No explicit criteria in
  - Selection of evidence
  - Weighing of evidence

- Non-quantitative approaches

Proposed (Bayesian) methodology

Prior information ⇒ probability distribution of the likely effect of the experimental treatment

+

Trial results (if necessary and possible)

=

Posterior Probability distribution of the likely effect of the experimental treatment

(range of plausible effects)

Differences between the present and the proposed approach

- Present :
  - Rational but informal integration of the available knowledge
- Proposed
  - Formal, explicit and quantitative integration of the available knowledge
    - Verifiable quantitative methods
    - Sensitivity analyses
    - Focus on summary effect estimates

Advantages

- All available information is fully and explicitly exploited in
  - Clinical Guidelines
  - Shared Decision making
- **<u>Randomised Trials of small size (50-100 pts)</u>** may be sufficient to discard or accept as standard the new treatment

Sources of prior evidence

- Biological Studies
- Preclinical studies
- Case-reports
- Uncontrolled studies
- Studies with surrogate endpoints
- Studies in other similar diseases
- Studies in the same disease (e.g. different age-groups)
- Others?

Prior evidence and clinical trials

Need to develop and validate new (meta-analytic) approaches to summarize prior information in rare diseases

Meta-analyses in rare diseases

- **NEED TO USE INFORMATION FROM STUDIES <100% VALID AND <100% PERTINENT TO THE QUESTION OF INTEREST**, i.e.
- Different diseases, treatments, endpoints

How to use this approach in planning a new RCT

1. Realistic sample size projection (e.g. 50 events)
2. Review of the (pertinent?) literature
3. Construction of the prior
4. Consider possible scenarios for hypothetical results of the trial (e.g optimistic, neutral and pessimistic)
5. Update prior to give hypothetical posterior distributions
6. Examine possible impact of the new trial

How to use this approach in analysing a RCT

1. Summarize study results
2. Combine trial results (likelihood) and prior distribution to obtain posterior probability distribution of treatment effect
3. Decision
   - Adequate evidence against: Stop
   - Adequate evidence in favor: Stop
   - Still large uncertainty: Study Continues

Efficacy trials in rare diseases

- Uncontrolled (phase II) trials making unethical further efficacy (RCT) trials
- Randomized activity trials followed by uncontrolled efficacy trials (with historical controls
- RCT's with surrogate endpoints
- **Small size efficacy RCT's**

Conclusions

1. Flexible methodological approaches are needed to assess therapies in rare diseases

2. Trials in rare diseases should be conducted with high methodological standards (including a strong - though unconventional- statistical rationale)

3. **Small trial size should not be used to justify low quality trials**

Useful readings

- Tan SB, Dear KB, Bruzzi P, Machin D. Strategy for randomised clinical trials in rare cancers. BMJ. 2003 Jul 5;327(7405**):47-9.**

- Behera M, Kumar A, Soares HP, Sokol L, Djulbegovic B. Evidence-based medicine for rare diseases: implications for data interpretation and clinical trial design. Cancer Control. 2007 Apr;14(2):160-6. Review.

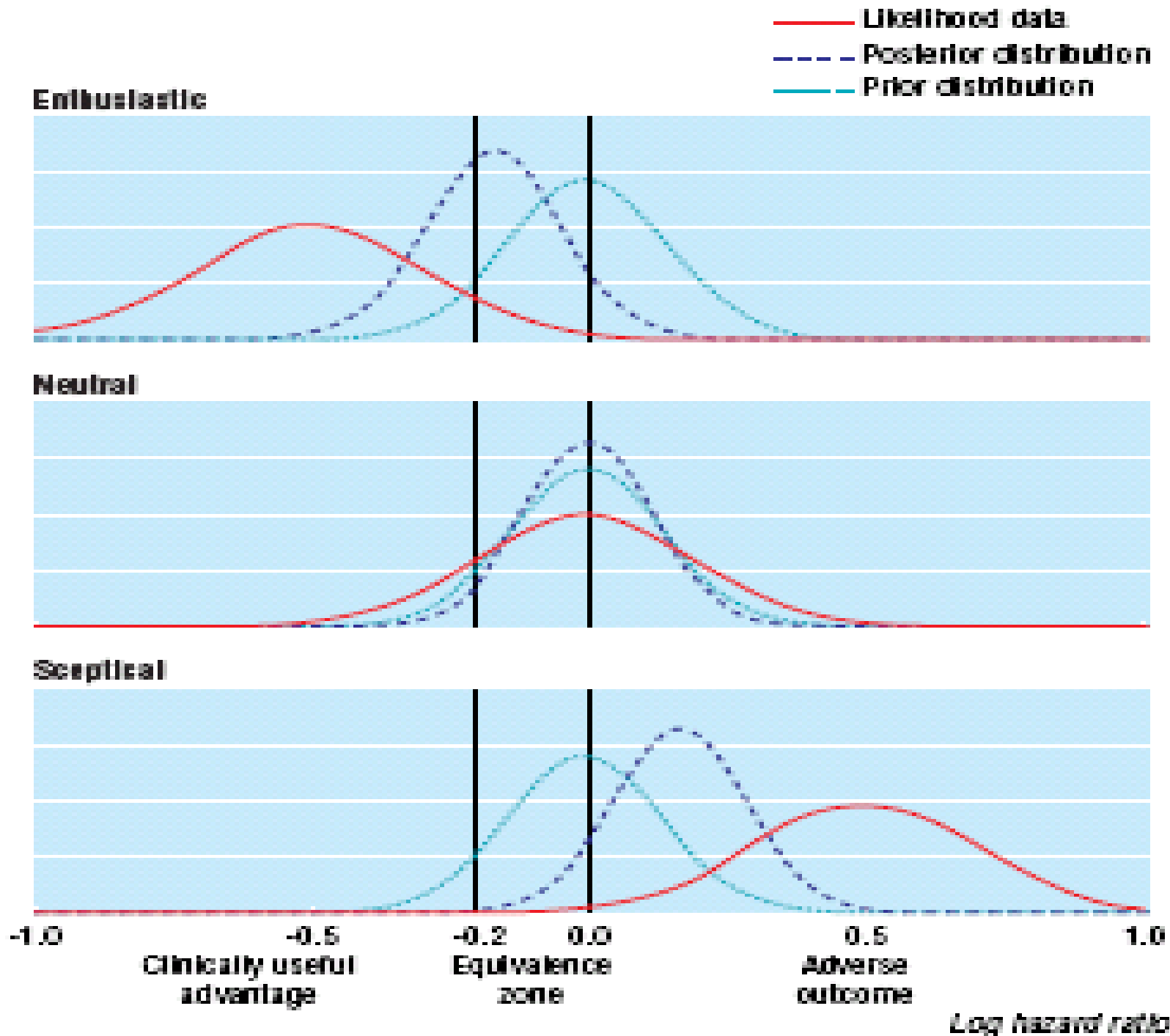
- Spiegelhalter DJ, Freedman LS, Parmar MK Applying Bayesian ideas in drug development and clinical trials. Stat Med. 1993 Aug;12(15-16):1501-11; discussion 1513-7.

Summarizing prior information in rare tumors

- Each piece of information (study) has to be used, weighted according to its:
  - Precision
  - Quality
  - **Pertinence (relevance to the study question)**

Once the available evidence has been summarised, it is possible to estimate the probability that the new treatment, when compared to the standard is:

a) Definitely worse: Stop
b) Much better: RCT not ethical, confirmatory uncontrolled trials (e.g. GIST)
c) **Neither : RCT necessary and ethically justified**


Likelihood data
Posterior distribution
Prior distribution
Enthusiastic
Neutral
Sceptical
-1.0
-0.5
-0.2
0.0
0.5
1.0
Clinically useful advantage
Equivalence zone
Adverse outcome
Log hazard ratio