Challenges in Clinical Study Design in Rare Diseases

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Disclosure of Interests

Company A

Company B

Company C

Company :

Company :

Company Y

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  - Medical Research Council
  - European Commission
  - National Institutes of Health

SOLUTIONS
CHALLENGES IN CLINICAL STUDY DESIGN IN RARE DISEASES

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Questions to address

What are the sample size and study design considerations in a rare disease study?
How do they differ or are they similar to considerations in diseases that are not rare?

Questions to address

Is it justifiable to *combine* etiologically heterogeneous diseases with similar clinical, biochemical and histopathological features in the same study? If so, how would you design such a study?

Given the rarity of these diseases, can or should adults and children with the same disease be *combined* in the same study?

Is it justifiable to *extrapolate* clinical trial results obtained in one disease to other, etiologically and/or phenotypically related conditions in order to obtain broader drug approval? If so, what are the criteria for extrapolation (including consideration of genetic and histopathological information)?

Umbrella studies

Many candidate treatments

One condition

Umbrella studies

Many candidate treatments

One condition

Basket studies

Many conditions

One candidate treatment

Questions to address

combine heterogeneous diseases into the same study?

adults and children in the same study?

extrapolate results from one disease to another?

From a (statistical?) study design perspective – not impossible

But…
Interpretation / conclusions likely to rest substantively on how well we really understand disease biology and mechanism of drug action

Questions to address

What is the value of observational data, (e.g. registries, natural history studies), as supporting information?

My opinion... 100%...

THE COMBINATION OF RANDOMIZED AND HISTORICAL CONTROLS IN CLINICAL TRIALS

STUART J. POCOCK

J Chron Dis 1976, Vol. 29, pp. 175–188. Pergamon Press. Printed in Great Britain

Questions to address

What outcomes should be targeted in clinical studies?

clinical endpoints?

surrogates or other outcome measures?

patient-reported outcomes (not just QoL)

Non-renal manifestations of renal disease:

hypertension outcomes or cardiac outcomes?

what are the important cognitive, psychosocial, and developmental outcomes for adults and children?

- Implications/acceptance by drug regulatory authorities?
- We all want treatments that give *real* benefits to patients
- Treatments may be licensable – but indication wording may be limited

Questions to address

What are some of the ethical challenges in designing clinical trials in rare and ultra-rare diseases, especially in pediatrics?

Role of patient advocacy groups: How can different priorities and perceptions of stakeholders be best negotiated into the design of clinical trials?

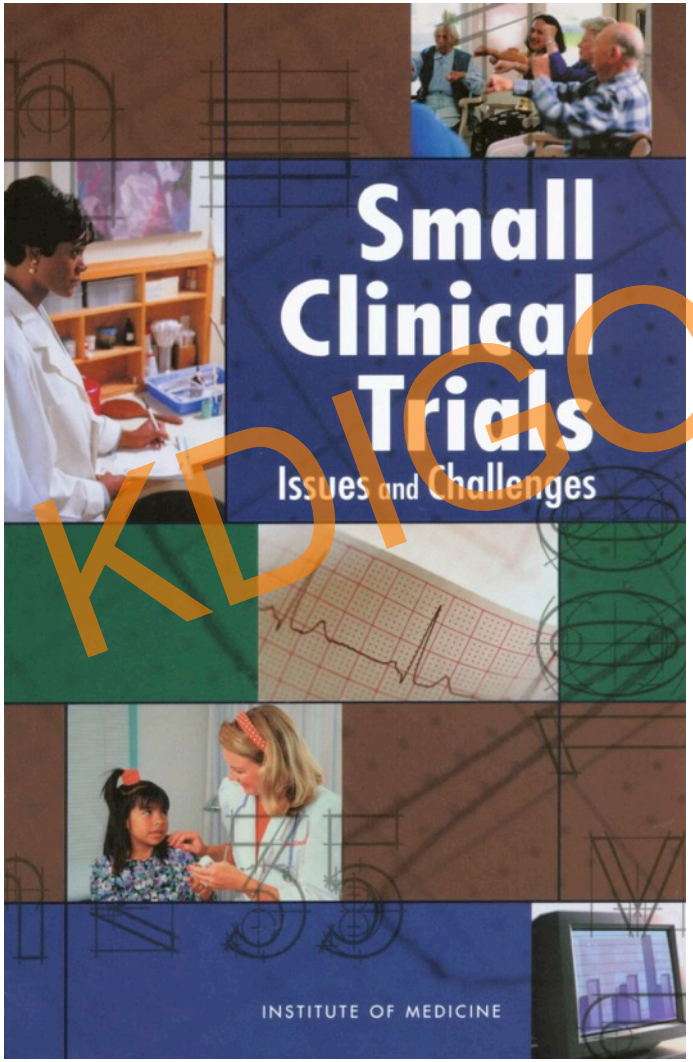
Questions to address

What are the major conceptual differences in clinical study design between academic and industry-driven clinical trials?
Quality, science, organisation, …
Implications?
What's good and what's bad?

Is there a risk that better-funded industry studies may decrease patient availability for academic research?

Role of patient advocacy groups: How can different priorities and perceptions of stakeholders be best negotiated into the design of clinical trials?

We're not alone…



2001

We're not alone…

European Medicines Agency

London, 27 July 2006
Doc. Ref. CHMP/EWP/83561/2005

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON CLINICAL TRIALS IN SMALL POPULATIONS

2006

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Rare Diseases: Common Issues in Drug Development

Guidance for Industry

2009 – 2012(???)

2015

DRAFT GUIDANCE

We're not alone…

CONSULTANTS FORUM

Pharmaceutical Statistics

(wileyonlinelibrary.com) DOI: 10.1002/pst.477

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A guide to the design and analysis of small clinical studies

Farid Kianifard* **and M. Zahur Islam**

Clinical studies, which have a small number of patients, are conducted by pharmaceutical companies and research institutions. Examples of constraints that lead to a small clinical study include a single investigative site with a highly specialized expertise or equipment, rare diseases, and limited time and budget. We consider the following topics, which we believe will be helpful for the investigator and statistician working together on the design and analysis of small clinical studies: definitions of various types of small studies (exploratory, pilot, proof of concept); bias and ways to mitigate the bias; commonly used study designs for randomized and nonrandomized studies, and some less commonly used designs; potential ethical issues associated with small underpowered clinical studies; sample size for small studies; statistical analysis methods for different types of variables and multiplicity issues. We conclude the paper with recommendations made by an Institute of Medicine committee, which was asked to assess the current methodologies and appropriate situations for conducting small clinical studies.

Keywords: exploratory study; pilot study; proof of concept; sample size

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But we're still struggling…