Many rare diseases affect only a few thousand or even fewer than one hundred patients in the EU.

Under such circumstances a trial enrolling several hundred patients may not be practical or possible.

It may be that in conditions with small and very small populations, less conventional and/or less commonly seen methodological approaches may be acceptable.

- Committee on Strategies for Small-Number-Participant Clinical Research Trials
  Small Clinical Trials – Issues and Challenges
  National Academy Press – Washington D.C. 2001

- EMEA - Committee for Medicinal Products for Human Use (CHMP)
  Guideline on Clinical Trials in Small Populations
  Efficacy Working Party (EWP) in joint collaboration with members of the Scientific Advice Working Group (SAWG), the Committee on Orphan Medicinal Products (COMP) and the Paediatric Expert Group (PEG). 2005

- **Methods and examples for small trials**
  - **N-of-1 designs**
  - **Response-adaptive methods**
  - **Analysis of clustered dependent data**
  - **Sequential methods**
  - **Bayesian methods**
  - **Resampling methods (bootstrap)**

There are no special methods for designing, carrying out or analysing clinical trials in small populations. There are, however approaches to increase the efficiency of clinical trials. Further, some methodological approaches, not acceptable in large trials, may be considered acceptable for trials in small and very small populations. The need for statistical efficiency needs to be weighed against the need for clinically interpretable results

Future Work

-compilation of possible methods for the design and analysis in the field of rare diseases

- detailed description of the methods (nontechnical educational kid?)

- comparison of different methods

- software realization (e.g. Macros for SAS, S-Plus)

- collection of exemplary data sets

- funding possibilities

- acceptance by regulatory agencies

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