Clinical trials in small populations

When designing clinical trials in small populations, a balance needs to be made between what is necessary and what is possible to help researchers understand the effects of new medicines under special conditions. The dilemma is to recruit a sufficient number of patients when only a very limited overall number of patients with the disease exist. Organising these studies presents a number of organisational challenges.

It should be recognised there is a difference between small and special populations but they do overlap. There is no common definition of small populations.[1] The term can include, for example:

- groups who have a rare disease including specific sub-types of more common diseases such as rare types of cancers
- children (paediatric patients)
- the elderly (geriatric patients)

Some groups in the general population may require special studies. These groups are defined as special populations, and include patients with impaired excretion, the elderly, pregnant women and breastfeeding women, children, and ethnic sub-groups. This may be because:

- there are particular risks or benefits that need special attention for certain populations;
- a different dose or treatment schedule may be needed.

If there is not already a recognised reference therapy available (standard), a placebo is used as a comparator; however, there are ethical considerations regarding its acceptability to the patient. If not ethically acceptable, a purely observational study or non-controlled trial without

comparator group should be performed, in order to understand the effect of the new treatment in the patient population (non-standard).

When you have limited access to data in patients, it is important to carefully consider information that can be generated in animal models of disease and their predictive value for efficacy and safety in humans.

When collecting data the following factors need to be considered:

- maximising the collection of important information
- keeping study participation burden low
- avoiding loss-to-follow-up

The development strategy for treatment in small populations should be discussed in advance with regulatory authorities through scientific advice/protocol assistance.

Typically, efficacy is measured in terms of:

- Cure
- Survival
- Time to disease progression
- Progression-free survival
- Reversal of organ dysfunction
- Disease stabilisation

In small populations, these classic parameters might not be suitable, as it may be impossible to collect enough information or data to achieve the required confidence level of evidence. The most suitable methodology (endpoint) with which to measure the effect has to be chosen. In some cases, it may only be possible to measure symptom relief, quality of life, or biomarkers; therefore, a combination of measures pointing to the same direction and ’making sense’ has to be considered.

The use of adaptive designs is most relevant for small populations. For instance, it allows researchers to look into the results during the course of the trial and to delete one of the treatment arms if absolutely no effect is seen there. Another option with adaptive design methodology is to combine Phases II and III of the clinical development in one study, and in this way reduce the overall required number of patients for the development of the new treatment.

[glossary_exclude]Further Resources

- European Medicines Agency (2001). *Note for guidance on clinical investigations of medicinal products in the paediatric population.* London: European Medicines Agency. Retrieved 24 June, 2015 from: https://www.ema.europa.eu/en/documents/scientific-guideline/e-11-clinical-investigation-medicinal-products-paediatric-population-step-5_en.pdf [/glossary_exclude]

[glossary_exclude]References

1. European Medicines Agency (2006). *Guideline on clinical trials in small populations*. London: European Medicines Agency. Retrived 24 June, 2015 from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-trials-small-populations_en.pdf[/glossary_exclude]

[glossary_exclude]Attachments

- Presentation: Ethical and Practical Challenges of Organising Clinical Trials in Small Populations.
  Size: 495,286 bytes, Format: .pptx
  A presentation detailing the ethical and practical challenges of organising clinical trials in small

populations.

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