A stratified semi-crossover design used in evaluation of clinical mastitis in dairy cows

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Summary: In a randomised clinical trial comparing homeopathy, placebo and a standard antibiotic treatment of clinical mastitis in dairy cows, three techniques were used to optimalise information from each patient and improve comparability between treatment groups in order to reduce the number of patients needed to detect differences between the treatment groups.

- A three-dimensional semi-crossover design
- Stratification
- Use of score scales in evaluation of outcome after treatment

Introduction: The double blind, randomised clinical trial is claimed to be the most reliable method for evaluation of medical treatment [1]. The randomised clinical trial is interventional, and due to ethical considerations as few patients as possible should be exposed to an experimental situation. When using undocumented therapies or placebo in clinical trials, an essential part of the study population is not given the best, documented treatment. Reduction of sample size by improving study design then becomes particularly important. It may also be important to reduce sample size due to economical and practical limitations.

Material and methods: In the *three-dimensional semi-crossover design* the patients are randomly allocated to one of three treatment regimes. Patients defined as non-responders after a pre-defined period of time are re-randomised to one of the two other treatments. After a second pre-defined period the patients will again be classified as responders or non-responders to the last treatment given. Responders are continued on the treatment, while non-responders are crossed over to the third treatment (Fig 1.)

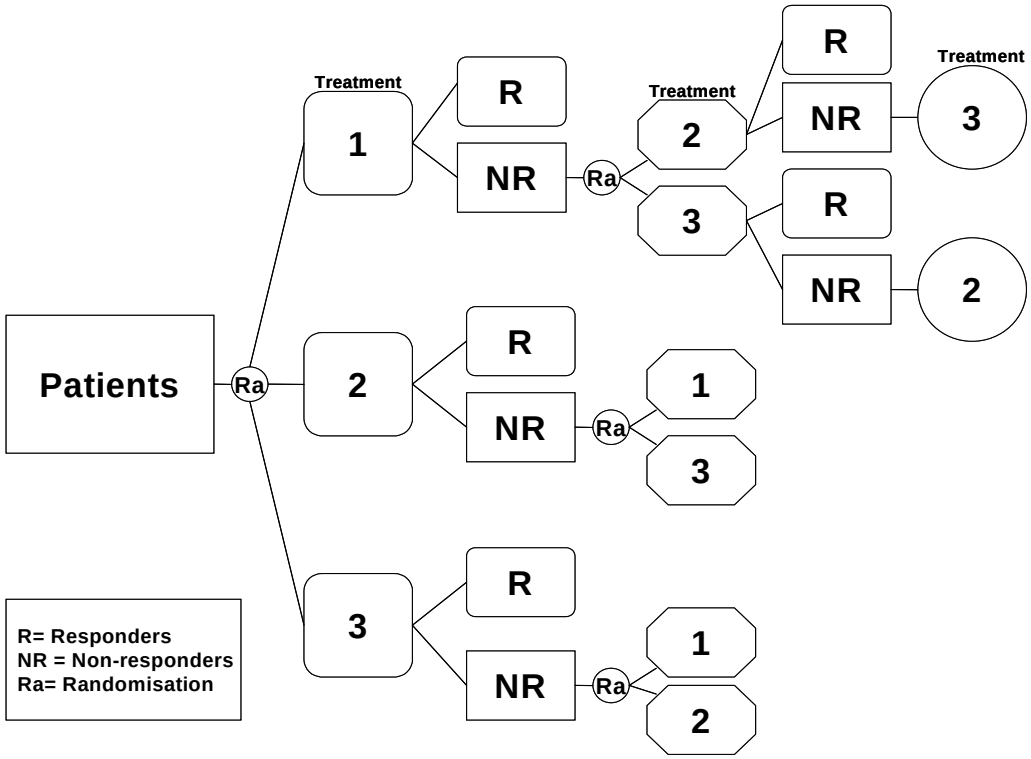

Figure 1.Three-dimensional semi-crossover design. Non-responders to treatment 2 and 3 are re-randomised after same principle as shown for group 1.

Stratification means to make the treatment groups similar with respect to factors regarded as especially important to the outcome. This is achieved by using a separate restricted randomisation list for each of the patient strata [5]. Severity of mastitis, classified as mild, moderate or severe, in accordance with the recommendations given by IDF [4], and lactation number (1.lactation and > 1.lactation) were used as stratification factors. The outcomes in the different strata were compared across treatment, to investigate if these factors really influenced outcome. Additionally, the effect of the factors previous mastitis this lactation, mastitis in previous lactations and bacteriological findings at start of treatment, was investigated. The effect of treatment was adjusted for by using treatment as a covariate in the analysis.
Two *score-scales* were constructed for evaluation of mastitis. Score I, including temperature, appetite, inflammation signs in the affected quarter, changes in milk, CMT and bacteriological findings, was used for evaluation of acute symptoms. Score II, including atrophy, fibrosis, milk production in the affected quarter, changes in milk, CMT and bacteriological findings was used for evaluation of chronic symptoms. Each score-scale includes six parameters, which were scored on a 1-5 scale and added. This gives both score- scales a range from 6 to 30. The score-scales were evaluated from their ability to differentiate between patients classified from clinical criteria as responders and non-responders to treatment.

Results: Significant differences were found between the strata of the factors severity of mastitis, lactation number, bacteriological findings and previous mastitis this lactation. Both score scales were found to differentiate between patients classified as responders and non-responders to treatment based on three different clinical definitions of responders.

Discussion: Use of semi-crossover design in clinical trials can offer an ethically satisfactory way to handle patients not responding to given treatment, and increases the patients´ probability of receiving the best treatment. The frequency of non-responders and the outcome in patients being crossed over to another treatment can be used to compare the therapy regimes.

The factors severity of mastitis, lactation number, bacteriological findings and previous mastitis this lactation influence outcome of treatment significantly, and are relevant as stratification factors in trials of clinical mastitis. However, bacteriological findings are not available at time of randomisation and cannot be used as a stratification factor when including moderate or severe cases.

In evaluation of mastitis treatment binary variables, like clinical or bacteriological cure, are often used [2,6]. These kinds of variables require relatively high numbers of included patients to detect differences between treatments. Score- scales can be handled analytically as continuously distributed variables [3]. The use of such an outcome measure therefore allows a reduction in the number of included patients to detect a difference of the same size.

References

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