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Reducing sample size by combining superiority and non-inferiority for two primary endpoints in the Social Fitness study

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Abstract

Objectives: In randomized controlled trials, two endpoints may be necessary to capture the multidimensional concept of the intervention and the objectives of the study adequately. We show how to calculate sample size when defining success of a trial by combinations of superiority and/or non-inferiority aims for the endpoints.

Study Design and Setting: The randomized controlled trial design of the Social Fitness study uses two primary endpoints, which can be combined into five different scenarios for defining success of the trial. We show how to calculate power and sample size for each scenario and compare these for different settings of power of each endpoint and correlation between them.

Results: Compared to a single primary endpoint, using two primary endpoints often gives more power when success is defined as: improvement in one of the two endpoints and no deterioration in the other. This also gives better power than when success is defined as: improvement in one prespecified endpoint and no deterioration in the remaining endpoint.

Conclusion: When two primary endpoints are equally important, but a positive effect in both simultaneously is not per se required, the objective of having one superior and the other (at least) non-inferior could make sense and reduce sample size.

Keywords: Sample size; Superiority; Non-inferiority; Combined objectives; COPM; Cluster randomized trial

1. Introduction

In randomized controlled trials, the use of one primary endpoint is common when two treatments are compared [1]. However, sometimes, the intervention can only be considered better than the control treatment when multiple objectives are satisfactorily met simultaneously (combined objectives). Such combined objectives may occur when the use of two primary endpoints is clinically relevant and necessary to capture success of the intervention over control adequately [2]. Examples are:

1) Cost of intervention vs. effectiveness dilemma [3].
2) Geriatric physical therapy which aims to improve physical activity both at 3 and at 6 months after start of the intervention [4];
3) Asthma treatment in geriatric patients which aims to improve asthma control and health-related quality of life [5,6];
4) Occupational therapy for older individuals with dementia and their caregivers which aims to improve daily functioning of people with dementia and sense of competence of their caregivers [7];

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The trial which is used as an example in this article (the Social Fitness study) is registered with the Dutch Trial Register (NTR), clinical trial number NTR4347.

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What is new?

Key findings, What this adds to what was known

- Clinical relevance and/or empirical evidence should be leading when selecting criteria for success of an randomized controlled trial with two primary endpoints.
- When using two primary endpoints in an randomized controlled trial, these endpoints can be combined into different scenarios for defining success of the trial, such as improvement (superiority) in both, improvement in one, and no relevant deterioration (non-inferiority) in the other.
- Using two positively correlated primary endpoints with success defined as ''improvement in one of the two endpoints and no deterioration in the other'' gives often more power than using a single primary endpoint.
- Ethical justification implies to strive for reducing sample size. We developed a tool to guide researchers who are planning trials with two endpoints in calculating sample size.

More subtle examples of how two primary endpoints can be used to capture success of a trial arise when intervening on social participation such as in the Social Fitness study. Social participation is an important element of health and well-being [8,9], and it is often reduced in people with cognitive problems [10–14]. Both the target and the target population give raise for using two primary endpoints as we explain below. First, in the Social Fitness study, social participation refers to: one's involvement in social activities in which there is interaction with others in the society which makes one feels valued, attached to the community, and gives meaning to someone's life [15–17]. In our preceding study (H. Donkers et al., 2016 unpublished data), we distinguished two dimensions of social participation: feeling and doing. Feeling refers to the subjective evaluation of satisfaction with one's own social participation, whereas doing refers to the more objective evaluation of the extent to which a person actually performs social activities. Furthermore, not only people with cognitive problems but also their caregivers were targeted in the Social Fitness study. It is know from studies evaluating effects of an Occupational Therapy intervention [7] caregivers play an important role in providing supervision needed to sustain performance of daily activities.

As a result, combined objectives make more sense as explained below.

- Social participation includes two dimensions, related to feeling and doing, detecting changes in social participation therefore requires measurement of both dimensions at the same time through a combined objective.
- As psychosocial interventions generally focus both on the person with cognitive problems and on their primary caregiver [18], referred to as a dyad, success in such interventions can be measured using criteria in which the social participation of the both dyad members improves.
- Another example of the use of combined objectives on patients' social participation includes combining dyad views: a person with cognitive problems can evaluate his or her own social participation, and the primary caregivers can evaluate social participation of the person he or she cares for, as a proxy.

In general, several combined objectives can be formulated for two primary endpoints in terms of improvement (superiority) and no deterioration (non-inferiority):

1) Improvement in one of the endpoints;
2) Improvement in both endpoints;
3) Improvement in the first endpoint and no deterioration in the second endpoint;
4) Improvement in the second endpoint and no deterioration in the first endpoint;
5) Improvement in one of the endpoints and at least no deterioration the other endpoint (i.e., the endpoint that should improve is not specified a priori).

Each of the scenarios above requires a different sample size calculation. The first four situations outlined above were previously discussed [19] for individually randomized trials, but the fifth seems to be new. In this article, we show how to calculate power for all scenarios using two endpoints and extend these to randomized trials where clustering in one or both of the arms is present. We will illustrate this by calculating power for two primary endpoints related to social participation in the Social Fitness study, which is an illustration of scenario 5.

2. Methods

In the Social Fitness trial, the Social Fitness Program (SFP) was compared with care as usual (CAU). The client-centered Canadian Occupational Performance Measurement (COPM) [20,21] was selected as the primary outcome to measure the two dimension of social participation (doing and feeling) at the same time. The COPM includes two domains: (1) perceived performance capacity, which relates to the social participation dimension of doing and (2) satisfaction with performance, which relates to the social participation dimension feeling. After participants formulated goals on social participation during a semistructured interview, they scored their performance and their satisfaction with their own goals. Scores range from 1 to 10, higher scores indicate better performance and more