Editorial

Study Eligibility Criteria: The Perils of Feasibility Based Decision Making

The specification of subject eligibility criteria for any research study is critical to determining the generalizability of results. In randomized trials, eligibility criteria often specify severity for trial entry, which may influence the magnitude of the effect detected.

In this issue of *The Journal,* Goggins, *et al* evaluate the impact of different thresholds for trial eligibility using the Western Ontario and McMaster University Osteoarthritis Index (WOMAC). They identify important considerations in defining trial eligibility[1], including eligibility criteria in an efficacy versus effectiveness trial using a threshold criterion, as well as the need for high sensitivity and specificity of the criterion to prevent misclassification of subjects.

Efficacy trials are intended to determine if an intervention can work under ideal circumstances. As Streiner points out[2], subjects are generally chosen with the intent of showing the largest effect between treatment groups by minimizing the within-subject difference and maximizing the between-group differences. Hence, more severe or symptomatic subjects would be chosen. In an effectiveness trial, where the intent is to have results more generalizable to the clinical population, subjects with a broader range of severity or symptoms may be chosen. While the efficacy approach, by virtue of the narrow selection criteria, limits the number of eligible subjects from the available population, the purpose of the study and the research question are the considerations that should determine the threshold for an eligibility criterion.

Choosing such a threshold is challenging because responders have traditionally been defined based on a measure of change such as an effect size[3]. Subjects with mild severity or symptoms usually have limited potential for change due to the scale range of the measure being used as the outcome. In trials where a large proportion of subjects have mild symptoms, the effect for those with more severe disease will not be detected unless the study is sufficiently powered to perform a stratified analysis based on severity.

The Outcome Measures in Rheumatology Clinical Trials (OMERACT) initiative has presented the concept of low disease activity state (LDAS)[4] based on the premise that LDAS, defined for the outcome of interest (e.g., pain, fatigue) rather than for magnitude of change, defines a responder, thereby determining efficacy or effectiveness of the intervention. As LDAS methodology develops and the approach becomes accepted in trials, the effect on study eligibility based on available samples needs to be evaluated.

The WOMAC pain subscale[5,6], although developed as a disease-specific measure, has low clinical sensitivity and specificity for osteoarthritis of the knee. Questions about pain on activity, as Goggins, *et al*[1] point out, as specified in the WOMAC items, frequently result in reporting of non-OA pathology complaints such as patellofemoral pain. Back and hip pathology can also refer pain to the knee. Additional screening questions and/or tests are required to ensure inclusion of subjects with the disease of interest, thus preventing misclassification.

The challenge of recruiting subjects to randomized clinical trials is such that large pools of eligible subjects often are needed to ensure the feasibility of the trial. However, broadening eligibility criteria while improving feasibility may preclude being able to answer the important research question. As Goggins, *et al*[1] conclude, eligibility criteria need to reflect the patient group targeted for treatment.

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See What WOMAC pain score should make a patient eligible for a trial in knee OA?, *page 540*

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