PATIENT-CENTERED OUTCOMES RESEARCH INSTITUTE

Rare Disease Research Guide for Merit Reviewers

This guide is intended for PCORI merit reviewers to consider when reviewing research applications that deal with rare diseases. This guide provides a list of essential items that the research application should address and that the reviewer should look for.

1. Rare diseases by definition are geographically distributed over wider ranges than more prevalent diseases, and therefore rare disease research projects require more time and/or more sites to enroll patients.
2. Power calculations for rare diseases are problematic since the true incidence of medium rare (less than 1 in 100,000) and ultra-rare (1 in 20,000 up to 100,000) diseases are often approximations, and true numbers are often not available.
    a. Some centers have particular expertise in a rare disease and will have a higher population count than other centers (clustering).
    b. There is a great deal of genetic heterogeneity among rare diseases making phenotypes inconsistent, which can affect power calculations.
    c. Special attention should be paid to the proposals accrual methods. A realistic estimate of **active** and available (seen on routine basis) patients should be provided, and numbers around the appropriate phenotype should be provided. Be aware that reported numbers often include all patients seen by that center over an extended period of time and may also include all patients whether or not they have the appropriate phenotype. Reviewers should be careful not to punish studies that present highly realistic numbers.
3. Statistical methodologies for rare diseases are still somewhat in their infancy. Large effect sizes can be detected, but reviewers should be aware that these are often unknowable before the studies have commenced. A guarantee of a P value below 0.5 can rarely be made in the design of any rare disease.
4. Particular attention in the review should be paid to the documentation for the available pool of patients. The PI should be able to list how many of these patients they have seen in a relevant time frame and that are being followed. The research team should survey patients for their willingness to participate. By in large, rare disease patients are more willing than the general population to participate in research, but reviewers should also consider how many ongoing studies are in that rare disease population, i.e. study fatigue.
5. Applicants should list the number of ongoing studies in the field competing for recruitment of the same patients. Note should be made that some studies will not interfere with each other, and given the limited number of participants, this is probably acceptable.
6. It should be viewed as a benefit that the PI is affiliated or part of a preexisting registry or longitudinal program for that rare disease. This often results in pre identification of potential recruits and can significantly speed ascertainment.

7. Risk benefit calculations and explanations are different in rare diseases since many of them have severe and often rapid outcomes for the patients. The risk factors for the patients from the disease are often significantly higher than those of the general pop (e.g. higher anemic coma VS blood pressure). This should be taken into consideration when evaluating the risk of the study for the potential benefit for the population. Examples from the severe end of the oncology world are probably relevant for this type of situation.