Improving Participation in Clinical Trials of Novel Therapies: Going Back to Basics

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KEYWORDS

• Systemic lupus erythematosus • Randomized clinical trials • Enrollment • Retention

KEY POINTS

- Enrollment in most clinical trials has declined over time.
- Strategies associated with higher enrollment rates are not well studied, in general, and especially in systemic lupus erythematosus.
- Improving outcomes has been replaced by improving the audit trail and documentation.
- Refocusing the "ask," realizing that most participants do not have adequate health literacy, using principles of plain English, and understanding decision-making heuristics could improve efficiency.

BACKGROUND

Since the first published clinical trial in the Book of Daniel,[1] which compared plant and water with meat and wine and their effect on physical appearance, the randomized controlled clinical trial has become the gold standard of clinical research. Their number, size, oversight, time to completion, and costs have increased logarithmically even as their power and influence have eroded[2] and the calls for reform are mounting.[3]

One disturbing sign is that more than 81% of recent clinical trials experience delays from poor recruitment.[4] One of 5 subjects recruited never show up for screening; one of 20 subjects enrolled do not complete the trial.[5] Both recruitment and enrollment rates seem to be getting worse. The rate of enrollment was 75% between 1999 and 2002 and 59% in 2003 and 2006; retention was 69% between 1999 and 2002 and

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decreased to 48% between 2003 and 2006.[5] Delayed enrollment of more than a month is experienced in 70% of the trials in the United States,[4] causing delays in completion of the trials and higher costs.[5] For one academic center, the annual cost of desultory enrollment was almost a million dollars.[6]

DETERMINANTS OF THE PHENOMENA

Several factors are at play. Some are of special relevance for systemic lupus erythematous (SLE) trials.[7] The general factors include the growth of the contract research organization industry,[8] increasing oversight, and distrust of the research enterprise from high-profile scientific misconduct and fraud.

In SLE trials, factors limiting higher enrollment rates, in addition, include overestimating the number of potentially eligible subjects (the Lasagna rule or Feinstein rule), logistical and entry criteria, participant burden, and the fear that a change in therapy may cause a lupus flare. Whatever the reason, potential subjects are voting with their feet and, after weighing the potential gains, downsides, and their personal priorities, have decided not to get involved. What's wrong? What can be done about it? This trend is a signal that the current trials in SLE may not be serving patients well nor those committed to developing new treatments.

There are many reasons to participate in a study, but it only takes one reason for a person not to participate. Most decisions are driven by emotions. Some questions going through a person's mind when approached for a clinical trial might be whether the question is really important to them, what is involved for the participating subjects, whether they would lose their doctor, what they have to lose and the risk involved, and what they can expect to get out of participation.

A "no" can be from the fear of losing their doctor for the study investigator, fear of being a guinea pig or experimental subject, fear of flare, being too sick, being too busy to be participating in a clinical trial that seems too complicated and too long, or not understanding and feeling anxious about a consent form that is inscrutable, complicated, and in legalese.

REVIEW OF LITERATURE ON MAXIMIZING ENROLLMENT/RETENTION

The literature addresses techniques or practices to maximize enrollment and retention; these are the subject of a *Cochrane Review*.[9] Three techniques have been identified, in addition, on SLE drugs trials, 2 of which are on preventing vascular disease in SLE.[10,11] This discussion builds on the third, a review of Ferland and Fortin discussing the issue in a controlled trial of methotrexate therapy for SLE.[12]

The literature indicates that subjects with good general health status are more likely to enroll because they feel less anxious about the possibility of worsening as a result of participation in clinical trials and are unlikely to have exclusions from other comorbid illnesses or laboratory abnormalities. Encouragement from their physician, desire to learn about their condition, the use of "opting out" of contact with the study recruitment effort, and financial incentives at invitation can increase enrollment. A well-established network of physicians and investigators can also be helpful. Subjects are more likely to join open-labeled trials than blinded trials with placebo as a possibility.

What has not generally been successful in increasing enrollment are implementing certain kind of changes to the consent procedures and giving more information. The opt-out method whereby the patient must contact the investigator if they chose not to participate yields more subjects than a trial that requires the subject to contact the investigator if they wanted to participate (opt-in).[13] However, local institutional review boards differ on what is acceptable. Consent procedures, such as getting