Clinical Trial Design Issues

KARL KIEBURTZ

Clinical trials designed to assess restorative therapies in Parkinson’s disease present several methodological challenges. By their nature restorative therapies are likely to be novel and therefore have poorly characterized efficacy as well as safety. Furthermore, many of these therapies are likely to be administered by surgical manipulation of the brain. Because of the invasive means of administration, there has been, and will be, a debate regarding appropriate controls and study design. In addition, advanced Parkinson’s disease, the likely target for such interventions, is associated with a highly variable disease state and prior studies have demonstrated a moderate to marked placebo effect in intervention studies. The longitudinal clinical course of the disease state likely to be studied is also quite variable and prone to respond to many types of modulation. Given the relatively labor-intensive nature of the surgical interventions, sample size for the trials will likely be small. This will require efficient, perhaps novel, trial designs to detect efficacy as well as safety. Lastly, the resource-intensive nature of the interventions and the complexity of the disease state suggest that functional or quality-of-life measures be used as primary outcomes. Further discussion of the ethical issues, research questions, primary outcome measures, issues regarding randomization, blinding and control groups, statistical analysis, and specific trial designs will be discussed below.

1. Ethical Considerations

All research involving human subjects needs to follow the basic principles of respect for person, justice, and benevolence. Respect for persons is primarily
demonstrated by informed and voluntary consent to participate, the right to withdraw from a trial without prejudice, and the respect for subject privacy and confidentiality. The principle of justice is demonstrated by free and equal access of appropriate patients to the research, but without coercion and with sensitivity to the needs of vulnerable populations. The principal of benevolence is manifested by an attempt to minimize risks in relation to potential benefits. With regard to clinical trials of restorative therapies in Parkinson's disease, there has been a great deal of discussion of ethical considerations, particularly regarding the use of sham operative controls in the two published trials of embryonic cell grafting (Chapter 6; Freed et al., 2001; Olanow et al., 2003).

In addition to the above general ethical considerations there are special concerns for randomized clinical trials. Randomized clinical trials are a rigorous research methodology designed to evaluate both the effectiveness and safety of interventions. Randomization allows (when effective) for equal distribution of known and unknown prognostic factors among treatment groups. Although randomization provides for important methodological advantages and helps to minimize selection bias, there must be a situation of genuine uncertainty among experts in the field regarding the relative merits of the treatments being studied in a randomized trial. This state of genuine uncertainty has been named clinical equipoise (Freedman, 1987). This state of clinical equipoise suggests that experts in the field do not know which treatment is superior and have legitimate differences of opinion regarding possible superiority. Even though a single individual may have a strongly held opinion regarding the superiority of a specific treatment, the situation of clinical equipoise still exists if uncertainty prevails among the broader community of informed investigators. It is then ethically justified to assign research subjects to the treatment arms by chance and the methodologic benefits of the randomized study are achieved. With the current status of restorative therapies for Parkinson's disease there is little debate that randomized trials are ethically justified especially in advanced Parkinson's disease. Furthermore, there is little debate that restorative therapies should be compared to best available or standard therapy as a comparator arm. The major questions arise as to whether some type of “placebo” intervention should also be provided along with the standard medical therapy and what the nature of that placebo intervention should be.

In the two published studies of fetal cell transplantation in Parkinson's disease sham-operative procedures were employed as a placebo intervention (Olanow et al., 2003; Freed et al., 2001). The specifics of the sham-operative procedures differ between the two studies. In the Freed study burr holes were placed under local anesthesia, but no instrumentation was passed through the dura mater. In the Olanow study burr holes were placed under laryngeal mask general anesthesia, but the inner table of the skull was not penetrated. In addition, placebo-surgery subjects received antibiotics and cyclosporine. The debate has been intense regarding these research designs. Most of the critiques of the experimental designs (occasionally with mistaken notions about