ISSUES IN CLINICAL NURSING RESEARCH

Random Assignment and Patient Choice in a Study of Alternative Pain Relief for Sickle Cell Disease[1]

Leslie Nield-Anderson
Jane Karpe Dixon
Kimberly Lee

This article presents two case examples in which women with sickle cell disease, when invited to participate in a nursing experiment, requested assignment to the experimental group. This experience stimulated the authors to explore the ethics of random assignment relative to equipoise, informed consent, patient choices, study validity, the clinician-patient relationship, patient support networks, and other issues. There is a need for in-depth discussion about random assignment and its implications within the nursing research and advanced practice communities.

> Randomized controlled trials are an anathema to the human spirit.
> —K. Schulz (1995)

Random assignment of research participants is the cornerstone of the true experiment. It is a key element of the randomized clinical trial through which the clinical effectiveness of new interventions and medications are established. Random assignment is generally considered to be ethically acceptable provided that certain conditions are met (Office of Protection from Research Risks [OPRR], 1993). However, several biomedical researchers challenge

Leslie Nield-Anderson, A.P.R.N., Ph.D., Yale University School of Nursing; *Jane Karpe Dixon*, Ph.D., Yale University School of Nursing; *Kimberly Lee*, R.N., M.S.N.

the ethics of random assignment under any conditions (Gifford, 1986; Kodish, Lantos, & Siegler, 1991; Lantos, 1994).

The debate over the ethics of random assignment is illustrated in a pair of articles published in 1991. Hellman and Hellman (1991) question the ethics of random assignment, and in a companion article, Passamani (1991) supports the ethics of random assignment. The debate is further illustrated in companion articles by Minogue, Palmer-Fernandez, Udell, and Waller (1995), and Logue and Wear in 1995. Minogue et al. (1995) attempt to illustrate how random assignment may be experienced by participants by depicting the situation of two hypothetical patients, John and Beth, with life expectancies of less than 1 year. John is desperate for a cure, and Beth is characterized as resigned to her condition. The authors propose that John and Beth's desperate and resigned states of mind affect their informed consent process. John, they assert, ethically cannot be randomly assigned because his desperation forces him to participate in the research. Beth, on the other hand, ethically can be randomly assigned because her consent can be truly voluntary. In the companion article, Logue and Wear (1995) counter Minogue et al.'s (1995) analysis, asserting that the analysis does not reflect appropriate understanding of John's need for counseling to come to grips with his terminal status, and that, as for Beth, "We simply doubt that such a patient as Beth exists" (Logue & Wear, l995, p. 61).

The issues raised in these articles are as applicable to clinical nursing research as they are to biomedical research. However, we have not found an in-depth discussion of the ethics of random assignment for evaluation of nursing interventions in the recent nursing research literature. This article is designed to initiate such discussions by presenting examples of this dilemma that were experienced by the authors while conducting a randomized clinical investigation.

BACKGROUND

The issues addressed in this article were identified during a pilot study (Lee, 1995) investigating the efficacy of a relaxation videotape as an adjuvant pain management strategy for patients with sickle cell anemia—a painful, debilitating condition. The population of interest has been identified as low users of complementary therapies in pain control (Eisenberg et al., l993).

The study was a two-group experimental design. Both groups received standard care; in addition, the experimental group experienced the study

intervention—the relaxation video. The participants were alternately assigned to an experimental group or control group, with the first participant assigned to the experimental group. Although not technically a random assignment, participants would experience this assignment method in a similar way. In retrospect, it is clear that there were problems with the design of the study. The research initially might have been structured as a cross-over study or as a quasi experiment in which intervention assignment would be determined by naturally occurring groups. Alternatively, a placebo videotape could have been used with patients in the control group. In fact, several alternatives were considered during the research development process. Although alternative approaches might have circumvented the issues that did occur, we felt these alternatives would have presented other, equally perplexing, methodological difficulties and ethical dilemmas. Random assignment is a highly respected and commonly used research strategy; thus, the decision was made to assign participants to groups as described above. The issues raised by participants' requests and preferences, which have implications beyond the specific study, are described in the following case examples.

Case Description

Mrs. D. was a 42-year-old African American single parent, diagnosed with sickle cell anemia at approximately 1 year of age. She was experiencing an average of 24 crises per year with consequent hospitalizations. Mrs. D. was started on hydroxyurea during her participation in the study, but the medication was discontinued because of adverse side effects. From September to March during the study, she was admitted to the hospital 10 times. While hospitalized, she received morphine.

It was our policy to invite all patients who were admitted in crisis to participate in the study. Mrs. D. was approached, and following procurement and signing the consent form, she was informed that she was assigned to the group not receiving the relaxation tape. Mrs. D. requested to be assigned to the alternative group, and she asked why she was assigned to the group not viewing the tape. She wanted to know why she was denied the opportunity to try a therapy that might assist in pain relief. She stated she was desperate to try anything that might help. It was agreed that for the first hospitalization she would adhere to her group assignment; however, if and when she was readmitted, she would receive the relaxation tape protocol.

Mrs. B. was a 40-year-old schoolteacher. She was diagnosed with sickle cell anemia in childhood. She had become aware of the study through Mrs. D.

During the informed consent process, Mrs. B informed the researcher that she was interested in experiencing firsthand whether the complementary method would help her manage pain without heavy doses of narcotics, and she requested to be in the relaxation tape group. She also stated that she was interested in the possibility of using the tape as a focus for support-group participation in the community. She described the isolation she experienced as well as the loneliness she observed in the sickle cell community as a consequence to pain. Immobility, fatigue, and oftentimes feelings of hopelessness eroded her motivation and consistent participation in the sickle cell community. Like Mrs. D., Mrs. B. was initially assigned to the group that did not view the relaxation tape, and on readmission, she would cross-over to the relaxation tape protocol.

Equipoise, Informed Consent, and Random Assignment

The primary ethical basis for the practice of random assignment in clinical research is the "we really don't know" premise, which Levine (1988) called equipoise—the assertion that we cannot say whether a newly proposed intervention is better than a standard treatment. Although equipoise is an inviting theoretical concept, it is difficult to achieve true equipoise in most clinical research for at least three reasons. First, like clinical research in other disciplines, the nurse investigator and patient participants usually consider the experimental nursing interventions to at least be potentially effective. This mindset is in conflict with the "we really don't know" premise of equipoise. Second, augmenting patient's autonomy, which is characterized by the patient's self-regulation and decision-making, is a significant clinical goal in nursing (American Nurses Association, l991). While patient autonomy is supported by an informed consent process, it is not supported by random assignment to treatment groups as discussed in the following section. Thus, the gestalt in which nursing research occurs seems to present an inherent conflict with the equipoise concept that, as previously noted, is the cornerstone of the ethics of random assignment. Third, to achieve true equipoise, the control group participants must receive appropriate care and must not be denied effective treatment. Nurse researchers and ethics review committees must grapple with concerns about how this principle is operationalized and how it affects the research design in each clinical nursing experiment.

In addition to equipoise, the other main ethical requirement for clinical experiments is informed consent, which was the second issue identified in the examples cited. The International Review Board (IRB) Guidebook

(OPRR, 1993) asserts that participants must "be informed when their assignment will be random, and that one of the consequences of participation is that the group to which they are assigned will turn out to have received the less effective intervention" (pp. 4-17). Participants must be told that the therapy they will receive will be determined by chance. This may be experienced by patients as discomforting. Writing about the process of negotiating informed consent, Levine (1988) stated that "the effects (of random assignment) on the expectations and wishes of many patients may be devastating" (p. 186).

When clinicians acknowledge the state of equipoise, one might argue that treatment decisions should then be determined by patient's choice, reflecting the patient's personal preference or assessment of differences between the treatments. The clinician's view of equipoise is not necessarily the patient's view of equipoise. Most often, the patient is allowed no such choice. Minogue and associates (1995) have pointed out that if participation in a randomized study is the only way to have a chance to receive an experimental treatment that is not otherwise available—an experimental treatment that the patient desires—this may be regarded as coercive, such that participation in the study may be more resigned than voluntary (Minogue et al., 1995).

Nurse researchers and human participant review committees should consider what happens when research participants are not given treatment choices and participants feel that they have been assigned to inferior treatment groups. This ethical problem can lead to methodological problems as well. For example, if randomization deprives people of choices they want, this may stimulate reactions among participants, causing them to behave in atypical ways (Cook & Campbell, 1979). In studies that are not blinded, those who feel that they are receiving less desirable treatments may experience resentful demoralization (a giving up) leading to outcomes that are uncharacteristically negative, or they may exhibit compensatory rivalry (the "John Henry effect") leading them to extraordinary efforts and, perhaps, to achievement of outcomes that are uncharacteristically positive. Because it is difficult, if not impossible, to blind participants to the experimental or control assignment in most nursing experiments, it makes them especially susceptible to these threats. Even when incorporated into biomedical research protocols, blinding may not work or be appropriate (Schulz, 1995).

Another problem is that participants who are not satisfied with their random assignment may simply withdraw from a study. For example, in a randomized study designed to assess the consequences related to duration of insertion of heparin locks, many participants withdrew after learning of their

random assignment. The authors reported that "patients disliked having their heparin locks changed" (Smith et al., 1990).

Furthermore, when combined with a full informed consent process, randomization (and its associated mystique) may stimulate reactive factors such as Hawthorne effects, placebo effects, and experimenter bias more than do other components of the study. Thus, the findings of a study using randomization may not be generalizable to other situations outside of the research context in which individuals would exercise a greater degree of choice and control.

Equipoise in a Clinical Context

Clinical trials occur in a clinical context. Our research subjects are often our patients. Our concern about these individuals goes beyond moralistic and legalistic formulations of participants' rights. As good clinicians, we also care for and about our patients/participants with all of the implications in which this term implies. A central concern about the randomized clinical study is the risk that it may obstruct the covenant between clinician and patient—the commitment to regard "the interests of the individual patient as primary and compelling" (Hellman & Hellman, 1991). Random assignment may compromise the relationship between clinician and patient by introducing a conflicting interest, such that commitment to the patient and commitment to the research process must now be held in balance. This may affect the relationship between patient and clinician.

Furthermore, within any specific clinical context, equipoise may be unachievable. The assertion of not knowing if one intervention is better than another tends to refer to not having statistical evidence to the $p < .05$ level, from prior randomized experiments. Other approaches to knowing, including the clinical hunch or statistical findings that look suggestive but fall short of statistical significance, are not included in this standard. Moreover, clinical observations made during the trial itself, as the researcher has experience with one patient after another, are also considered to be of no or little consequence for this knowing—until, perhaps, a specific statistical criterion is achieved, at which time the trial may be ended. Even in those uncommon situations in which the state of equipoise does truly apply across clinicians and patients, there is still the real possibility that for a given patient and a given clinician, one intervention might seem a better fit than the other. Yet, the need for participants for a randomized study may override the clinical wisdom on which such judgements can be based.

Finally, it must be noted that randomization may directly interfere with achievement of some clinical goals, such as encouraging patient responsibility for health care decisions and augmenting patient efforts to attempt active self-regulation relative to their health problems. These points are illustrated by the clinical examples described above. In the sickle cell patient population, for example, introduction of the relaxation study stimulated expression of patient initiative, which the researchers as clinicians (Nield-Anderson and Lee) could not appropriately ignore. Thus, flexible adaptation of the research methodology was necessary so that the study could help to meet patients' goals.

DISCUSSION

It is not uncommon for the sickle cell patients to know each other and be involved as a social network outside the hospital. In spite of this, however, sickle cell–crisis sufferers often verbalize feeling alone and helpless due to their pain and frequent hospitalizations. Participation in the study encouraged further socialization and communication because participants had an added common experience, which decreased isolation and furthered relationships. This illustrates the dilemma of conducting experimental research within a community whose members have an established interdependence through previous clinical or research efforts.

The overall impact of this study with its modified cross-over design was to empower participants while simultaneously supporting the research goals. It was not common for these patients to experience interaction with health care providers that supported their desire for self-regulation and assertiveness. Years of dependency on medical protocols and reliance on medical expertise have not encouraged this population to speak up and voice their wishes. Patients' requests to be assigned to the experimental group were viewed as appropriate assertions of rights as patients. Mrs. B and Mrs. D used the opportunity of the study to gain expertise in alternative pain management skills with a desire to rely less on narcotics.

CONCLUSION

There is need for in-depth discussion about random assignment within the nursing research and advanced practice communities. This discussion

should focus on how researchers respond to research participants' requests and preferences. Furthermore, this should include dialogue about methodological difficulties inherent in research investigations whose participants will be in closed environments such as tertiary hospital settings and nursing homes as well as in communities in which participants form strong social networks such as the sickle cell populations.

As nurses succeed in empowering health care recipients to become increasingly knowledgeable and active in their treatment decisions, research strategies congruent with patient autonomy need to be developed and examined. Research designs that incorporate the potential for participant choice and that assume a willful participant rather than a participant-as-object are essential. The modified cross-over design adopted for the sickle cell study was a step in this direction.

Another methodological approach for responding to patient preferences, while maintaining research integrity, is the addition of a nonrandom component into an experimental model. For example, in a study of a nursing special care unit for patients who were "chronically critically ill," Rudy and associates (1993) reported that although most participants were randomly assigned, a portion (16%) were assigned nonrandomly—sometimes based on preference of patient, family member, or physician for a particular unit assignment. In addition, strategies derived from action research, evaluation research, and research on unconventional therapies (Gaus & Hogel, 1995) will undoubtedly be useful in shaping new research models.

In summary, the demand for scientifically sound clinical nursing research is increasing. As nurse researchers, methodologists, and ethicists collaborate to meet the challenge to develop research methods that address the choices of research participants, research strategies that empower individuals' participation in research projects will expand.

NOTE

1. An earlier version of this manuscript was presented at the 8th Scientific Session of the Eastern Nursing Research Society in Pittsburgh, PA, April 1996, and at the 10th Annual Convention of the International Society of Psychiatric Consultation Liaison Nursing in Chicago, IL, April 1996. The case examples are taken from a study funded through an Intramural Grant, Yale University School of Nursing. The authors appreciate the advice provided by Donna Diers, M.S.N., F.A.A.N., in the preparation of this manuscript. Correspondence concerning this manuscript should be addressed to Leslie Nield Anderson, Yale University School of Nursing, 100 Church Street South, New Haven, CT 06536; (203) 737-2364; fax: (203) 785-6455; e-mail: Leslie.Nield-Anderson@yale.edu.

REFERENCES

American Nurses Association. (1991). *Nursing's agenda for health care reform*. Washington, DC: Author.

Cook, T. D., & Campbell, D. T. (1979). *Quasi-experimentation: Design and analysis issues for field settings*. Boston: Houghton Mifflin.

Eisenberg, D., Kessler, R., Foster, C., Norlock, F., Calkins, D., & Delbanco, T. (1993). Unconventional medicine in the United States: Prevalence, costs, and pattern of use. *New England Journal of Medicine*, *328*(4), 246-252.

Gaus, W., & Hogel, J. (1995). Studies on the efficacy of unconventional therapies. Problems and designs. *Arzneimittel-Forschung*, *45*(1), 88-92.

Gifford, F. (1986). The conflict between randomized clinical trials and the therapeutic obligation. *Journal of Medicine and Philosophy*, *11*, 347-365.

Hellman, S., & Hellman, D. S. (1991). Of mice but not men. *New England Journal of Medicine*, *324*(22), 1585-1589.

Kodish, E., Lantos, J. D., & Siegler, M. (1991). Opinion: The ethics of randomization. *CA-A Cancer Journal for Clinicians*, *41*(3), 180-186.

Lantos, J. (1994). Ethics, randomization, and technology assessment. *Cancer* (Suppl. 9), *74*, 2653-2656.

Lee, K. (1995). The efficacy of relaxation as an adjuvant therapy in the management of sickle cell crisis pain. Unpublished master's thesis, Yale University, New Haven, CT.

Levine, R. J. (1988). *Ethics and regulation of clinical research* (2nd ed.). New Haven, CT: Yale University Press.

Logue, G., & Wear, S. (1995). A desperate solution: Individual autonomy and the double-blind controlled experiment. *Journal of Medicine and Philosophy*, *20*, 57-64.

Minogue, B. P., Palmer-Fernandez, G., Udell, L., & Waller, B. N. (1995). Individual autonomy and the double-blind controlled experiment: The case of desperate volunteers. *Journal of Medicine and Philosophy*, *20*, 43-55.

Office of Protection from Research Risks (OPRR). (1993). *Protecting human research subjects: Institutional review guidebook*. Washington, DC: National Institutes of Health, U.S. Department of Health and Human Services.

Passamani, E. (1991). Clinical trials—Are they ethical? *New England Journal of Medicine*, *324*, 1589-1591.

Rudy, E. B., Vaska, P. L., Daly, B. J., Happ, M. B., & Shiao, P. (1993). Permuted block design for randomization in a nursing clinical trial. *Nursing Research*, *42*(5), 287-289.

Schulz, K. F. (1995). Subverting randomization in controlled trials. *Journal of the American Medical Association*, *274*(18), 1456-1458.

Smith, I., Hathaway, M., Goldman, C., Ng, J., Brunton, J., Simor, A. E., & Low, D. E. (1990). A randomized study to determine complications associated with duration of insertion of heparin locks. *Research in Nursing & Health*, *13*, 367-373.