Communication of Randomization in Childhood Leukemia Trials

Eric Kodish, MD
Michelle Eder, MA
Robert B. Noll, PhD
Kathleen Ruecione, MPH, RN
Beverly Lange, MD
Anne Angiolillo, MD
Rebecca Pentz, PhD
Stephen Zyzanski, PhD
Laura A. Siminoff, PhD
Dennis Drotar, PhD

Clinical trials provide the foundation of evidence-based medicine, and randomization is the paramount principle of trial design. Despite theoretical concerns about the ethics of randomized trials, empirical knowledge is lacking. Thousands of children with cancer have been enrolled in randomized clinical trials (RCTs) during the past 40 years. The cure of childhood leukemia, one of the great success stories of modern medicine, has been a direct result of these trials. For children with newly diagnosed leukemia and their families, randomization is the key feature that distinguishes research participation from treatment outside an RCT. Placebos are not used in childhood leukemia RCTs.

Federal regulations require that parents of a child recently diagnosed as having leukemia provide informed consent for research participation before that child’s treatment is randomly allocated to one of multiple treatment groups of the RCT. Parental understanding of the process of randomization is therefore necessary but not sufficient for truly informed consent.

One key question is whether the informed consent process results in understanding of randomization. Some studies have shown that understanding randomization is limited among research participants. Other studies have analyzed the explanation of randomization during the informed consent process without attempting to measure participants’ understanding of the concept.

To investigate physicians’ explanation and parental understanding of randomization during childhood leukemia RCTs.

**Context**

Most children diagnosed as having leukemia become research subjects in randomized clinical trials (RCTs), but little is known about how randomization is explained to or understood by parents.

**Objective**

To investigate physicians’ explanation and parental understanding of randomization in childhood leukemia RCTs.

**Design and Setting**

A multisite study of the informed consent communication process for RCTs of childhood leukemia. Consecutive cases were recruited from pediatric oncology inpatient wards at 6 US children’s hospitals associated with major academic medical centers from July 1, 1999, until December 31, 2001. The informed consent conferences were observed and audiotaped, and the information obtained was coded and analyzed. Parents were interviewed shortly after the conference to ascertain their understanding.

**Participants**

Parents and members of the health care team who participated in 137 informed consent conferences for children with newly diagnosed acute leukemia.

**Main Outcome Measures**

Observed explanations of randomization and parental understanding of randomization after the consent conference.

**Results**

Randomization was explained by physicians in 83% of cases and a consent document was presented during the conference in 95% of cases. Interviews after the conference demonstrated that 68 (50%) of 137 parents did not understand randomization. Parents of racial minority and lower socioeconomic status were less likely to understand randomization (P < .001 for each). Discussion of specific clinical trial details and the presence of a nurse during the conference were associated with understanding. Eighty-four percent of children were enrolled in a leukemia trial.

**Conclusions**

Despite oral and written explanation, half of the parents in this study did not understand randomization for childhood leukemia trials. To make informed consent more effective, future research must seek to improve communication during this critical interchange.

JAMA. 2004;291:470-475 www.jama.com
domination in this context, we conducted the Project on Informed Consent (PIC). We hoped to answer the question, “Do parents understand that their child’s treatment will be randomly allocated?” Unlike previous studies, this research included both audiotaping of the informed consent conference (ICC) and interviews with parents after the conference. Accordingly, it provides a unique contribution to knowledge in communication and research ethics by examining what physicians said in relationship to what parents understood.

**METHODS**

**Recruitment and Study Procedures**

Before starting the PIC study, research associates were trained to ensure uniformity in methods across sites. We then recruited consecutive cases at 6 institutions from July 1, 1999, until December 31, 2001. We obtained the informed consent of the parents, physicians, and patients (when appropriate) shortly after each patient’s diagnosis of either acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML).

The research was performed at the Children’s Hospital of Philadelphia, Philadelphia, Pa; Children’s Hospital Los Angeles, Los Angeles, Calif; Rainbow Babies and Children’s Hospital, Cleveland, Ohio; Children’s Hospital National Medical Center, Washington, DC; Children’s Hospital Medical Center, Cincinnati, Ohio; and MD Anderson Cancer Center, Houston, Tex. The appropriate institutional review board approved the study at each site.

Research associates were present to observe and audiotape the ICCs that physicians convened to discuss RCT participation. Research associates only observed and did not participate in the conference. Each taped ICC was then coded by using the Observer Checklist, an instrument developed to examine behaviors specific to clinical discussions related to cancer, and subsequently transcribed for qualitative analysis. For quantitative analyses, we used SPSS statistical software version 11.0 (SPSS Inc, Chicago, Ill) and the level of statistical significance was set at P<.05.

Parents were interviewed within 48 hours of the conference. To avoid conflicting responses from multiple family members, we limited interviews to the parent or surrogate who was the most active participant during the conference whenever possible.

**Outcome Measures**

**Observer Checklist.** All Observer Checklist items were coded independently by the site research associate, one of the authors (M.E.), and the project director, and reconciled according to a rule book designed to limit misinterpretation of each coded item. Explanation and understanding of randomization were defined as the main outcome measures for this analysis. To be coded as “explains the concept of randomization,” our coding rules required that “the clinician explains what randomization means.” Any explanation of how treatment is selected for participants in the RCT qualified for this code. For items reported in this article, the mean κ score for intercoder reliability was 0.70 (range, 0.54-0.95), which is considered to be good agreement among coders.

**Parent Interview.** The parent interview was designed, based on preliminary research, to ascertain parental understanding. The interview was pilot tested in an iterative sequence to confirm its accuracy in measuring parental comprehension. All parent interview instruments were professionally translated and back-translated to Spanish and were available for use at the discretion of the parent participants. Interpreters were used for parent interviews when necessary.

Understanding of randomization was determined by an author (M.E.) by using the following protocol. A combination of 2 interview questions that assess understanding of randomization directly was evaluated first. These questions were as follows: “In this clinical research study, how will it be decided which treatment your child will receive?” and “If your child enrolled in this clinical research study, will you be able to choose the treatment option you want?” If responses to these 2 items did not indicate parental understanding, we proceeded to a global search of the parent’s answers to all interview items for evidence of understanding. We considered parents to understand randomization if at any point during the interview they were able to articulate that their child would be assigned by chance to 1 of multiple treatment groups if they chose to enroll in the clinical trial. The Observer Checklist and parent interview instruments are available at http://www.rainbowbabies.org/professionals/ethics.asp.

**Demographics.** We collected demographic information that included patient age and sex and parent age, sex, education, occupation, and race. We used data on occupation and education level to calculate the Hollingshead Index of Social Position (ISP), which assigns socioeconomic status (SES), for each case. On this scale of 1 to 5, a lower ISP score represents a higher SES.

**RESULTS**

The results are organized to provide information on demographic and conference characteristics, general communication about the clinical trial, and communication specific to randomization.

**Demographic Characteristics**

We approached 164 parents to request consent for the PIC study and 140 parents (85%) agreed to participate. Because clinical factors precluded eligibility for randomization in 3 cases, the analyses reported herein were performed on a sample of 137 parent participants.

The diagnoses of the children included 122 with ALL and 15 with AML. These children, 78 boys and 59 girls, had a mean age of 7 years (range, 1-18 years). The parents, 83 women and 54 men, had a mean age of 35 years (range, 18-51 years). A total of 44% of the parents were of racial minority, primarily of Latino origin. The conferences were conducted in English in 111 cases. Twenty-four non-English cases included interpreters and 2 were conducted completely in Spanish. We tracked the 24 cases in which parents
declined the PIC study and found no difference in the rate of participation in the leukemia RCT between those 24 cases compared with the 137 cases reported herein.

**Conference Characteristics**
The mean length of conferences was 79 minutes (range, 25-183 minutes), with 7 participants per conference (range, 2-15). The Children’s Cancer Group (CCG) clinical trials presented included CCG-2961 (AML, n=15), CCG-1952 (standard-risk ALL, n=24), CCG-1991 (standard-risk ALL, n=33), and CCG-1961 (high-risk ALL, n=65). We observed presentation of the consent document during the conference in 95% of cases. This occurred at the end of the conference in 51% of these cases. An attending physician led the conference in 68% of cases and a fellow led the conference in 32%. A nurse was present in 47% of cases but nurses never led the conference or explained randomization during the observed ICC. One hundred fifteen (84%) of 137 parents ultimately provided consent for the leukemia RCT.

**General Communication About the Clinical Trial**
Discussion of direct benefit to the child from the clinical trial was observed in 53% of cases and reference to altruism occurred in 73% of cases. Treatment options outside the trial were discussed in 89% of conferences and an explanation of how the trial differs from standard therapy was observed in 91% of cases. Physicians explained the consent document content in 73% of cases, drew a diagram to explain the trial in 25%, and offered to answer questions about the study in 59% of ICCs. Physicians described the trial as voluntary in 97% of cases but 18% of parents did not understand that they were free to refuse study enrollment. Nineteen percent of parents reported feeling pressure to enroll in the RCT. The right to withdraw was discussed in 72% of cases but 20% of parents did not know that their child could withdraw from the trial at any time.

**Explanation and Parental Understanding of Randomization**
We observed an explanation of randomization in 83% of cases. Sixty-eight (50%) of 137 parents we interviewed did not understand randomization. Conferences with an observed explanation of randomization were not associated with an increased proportion of parents who understood (P=.47). Parents who did not understand randomization were more likely to consent to the RCT than parents who did understand randomization, although this finding did not reach statistical significance (P=.07). Factors associated with parental understanding of randomization are shown in Table 1.

| Table 1. Factors Associated With Understanding of Randomization (N = 137)* |
|-----------------|-----------------|-----------------|
| Factor                          | Understood Randomization, No. (%) | Did Not Understand Randomization, No. (%) | P Value† |
| Clinician explained randomization | Yes 59 (52) 48 (57) | No 10 (43) 13 (57) | .47 |
| Race                          | Majority | Minority | .001 |
| ISP score                      | 1 or 2 | 3 or 4, 5 | <.001 |
| Parents read consent document | Yes 66 (67) 33 (92) | No 2 (8) | .001 |
| Discussion of treatment groups | Yes | No | .03 |
| Discussion of how trial differs from standard treatment | Yes | No | .04 |
| Clinician explained right to withdraw | Yes | No | .004 |
| Discussion of 1 group of trial being standard treatment | Yes | No | .02 |
| Presence of nurse | Yes | No | .005 |

Abbreviation: ISP, Hollingshead Index of Social Position.
*Race includes white majority and minority race.
†Comparison of understood vs did not understand randomization and comparison of factors are by χ² test.

©2004 American Medical Association. All rights reserved.
racial differences. By contrast, we found no significant parental sex differences in understanding of randomization.

Factors Associated With Better Understanding

Conference characteristics that were associated with parental understanding of randomization included explanation of the different groups of the trial, how the trial differed from standard treatment, the right to withdraw from the RCT, and the fact that 1 group of the RCT is standard treatment (Table 1). Additionally, parents who reported reading the consent document for the RCT were more likely to understand randomization.

Physician factors, including years of experience, training status (fellow vs attending physician), and sex, were not associated with differences in parental understanding, but the presence of a nurse at the ICC was associated with understanding of randomization. The mean conference duration in cases demonstrating parental understanding was 83 minutes compared with 74 minutes in cases without parental understanding.

Explanation of Randomization

We conducted a qualitative examination of the specific ways in which physicians explained randomization to parents. A total of 17% of the ICCs did not include any explanation of randomization. In some of these ICCs, there was no discussion of randomization at all; in others, the physician gave an explanation of randomization that did not meet our coding requirements. For example, one physician’s explanation was limited to “We’re not in control of selecting.”

The various descriptions of randomization that were used by physicians in our sample of 137 cases were grouped into 3 categories. Many physicians (31% of ICCs) included descriptions from more than 1 category in their explanation of randomization. Fifty-eight percent of ICCs included reference to a computer, 45% included the use of 1 or more metaphors, and 16% included reference to a “center” or “office” where the randomization would take place. Seven examples that typify the various explanations of randomization are given in Box 1. The 2 metaphors most commonly used to explain randomization were “coin toss” (48 ICCs [35%]) and “chance” (15 ICCs [11%]).

We examined each of the description categories to determine which were associated with parental understanding of randomization. There were no significant differences in parental understanding when the various description categories were compared.

COMMENT

A fundamental principle of communication science is that there are frequently discrepancies between what is said and what is heard.21 Our findings demonstrate that common strategies to explain randomization are not effective. Although physicians explained randomization in 83% of cases, we found that 50% of parents did not comprehend this key aspect of their decision. Most children (84%) were enrolled in the RCT despite this lack of understanding and parents who did not understand randomization were slightly more likely to consent to a leukemia trial.

The fact that optimal informed consent was not obtained does not make these studies unethical.22-24 Therapeutic misconception has been shown to be prevalent in clinical research,22-24 and our results suggest that it may be important in the context of childhood can-

| Table 2. Explanation and Understanding of Randomization* |
|-----------------|-----------------|-----------------|
| **Race**        | **ISP Score**   | **Value**       |
| **Minority**    | **Majority**    | **Minority**    |
| **Randomization explained** | **Randomization understood** | **Randomization explained** |
| Majority (n = 77) | Minority (n = 60) | P Value | 1 or 2 (n = 34) | 3, 4, or 5 (n = 102) | P Value |
| 65 (84) | 49 (82) | .67 | 26 (77) | 87 (85) | .24 |
| 53 (69) | 16 (27) | < .001 | 29 (85) | 40 (39) | < .001 |

Abbreviation: ISP, Hollingshead Index of Social Position.

*Data are No. (%) of patients. Socioeconomic status was measured by the ISP, which assigns socioeconomic status using education and occupation. On this scale of 1 to 5, a lower ISP score represents a higher socioeconomic status.

†One missing value.

©2004 American Medical Association. All rights reserved.
Box 2. Suggestions to Improve Understanding of Randomization

Encourage parental participation in ICC, including question asking.
Describe different groups of the RCT, including the standard group.
Explain differences between treatment in RCT and off-study therapy.
Discuss the right to withdraw from the RCT.
Stress importance of reading consent document and give parents time to do so.
Seek formal communication training, including cultural sensitivity training.
Promote nurse attendance at ICCs.
Give parents and patient as much time as possible to make decision about RCT.
Provide parents with improved emotional support.
Assess parental understanding of randomization.
Provide further explanation of randomization until understanding is achieved.

*ICC indicates informed consent conference; RCT, randomized clinical trial.

Concern about consent problems specific to racial minority and lower SES subgroups prompted us to conduct analyses of cases involving these families. We found that barriers to understanding were especially pronounced among these parents. Although explanation of randomization observed during the conference was consistent regardless of race and SES, a higher proportion of parents of racial minority and lower SES did not understand randomization. These findings suggest the need for tailored interventions to improve communication for these families. Such interventions may be directed toward physicians, parents, or both sets of participants in the ICC. Because question asking is an effective way for parents to elicit information about the trial during the consent conference,31 strategies to encourage a more interactive consent process may be helpful. Many of the parents in our study who did not understand randomization were of Latino ethnicity. In this population, sensitivity to cultural issues will be critical in developing improved communication. For example, the concept of respeto (respect for authority) may be so powerful in some Latino cultures as to discourage question asking.32 Culturally sensitive interventions designed to promote interaction during informed consent might empower parents and facilitate higher levels of understanding. Training in communication skills could assist physicians with this important and challenging task.

Our results suggest several ways to improve communication of randomization (Box 2). Cases in which the physician went beyond a basic explanation to discuss details of the RCT were associated with a higher proportion of parental understanding. These details included a description of the different groups of the RCT, the differences between standard treatment and treatment in the RCT, and an explanation that standard treatment is one of the groups of the RCT. Additionally, discussion of the right to withdraw from the RCT at any time was associated with a higher proportion of parental understanding. These findings indicate that presentation of this cluster of explanations can enhance parental understanding.

The presence of a nurse at the conference was strongly associated with parental understanding. This may reflect the benefits of better emotional support for parents at this difficult time, creating an environment in which parents feel empowered to speak up, ask questions, and seek clarification.33 Although we did not observe nurses engaging in the explanation of randomization, it is possible that their presence at the ICC forged a relationship that allowed for later, effective explanation of randomization before the parent interview. Future efforts to improve communication should investigate the role of the nurse and seek to capitalize on this finding.

Parents who read the consent document were more likely to understand randomization. There are many reasons why reading the document could affect understanding. Many parents may read or reread the document after they have had time to absorb the shock and trauma of their child’s diagnosis and are thus in a better state to comprehend the information about randomization. In addition, parents may understand information better when they see it in writing or after receiving information a second time.34 Encouraging parents to read the consent document carefully or reviewing it with them during the ICC may be effective ways to enhance parental understanding.

Our quantitative and qualitative analyses showed no relationship between the explanation of randomization and parental understanding. This finding may be partially explained by the fact that parents can come to understand randomization in ways other than explanation by the physician. Some parents may come into the ICC with prior understanding of randomization through past experience with RCTs. Others may learn the meaning of randomization by reading the consent document or talking with other health care providers such as nurses.

Effective communication depends on interaction between the provider of information and the recipient. Physicians must always determine whether their efforts at informed consent achieve the desired outcome of parental understanding. After discussing an RCT, physicians should assess understanding of randomization and clarify its meaning for those who do not yet understand.35

Several limitations of this study must be recognized. First, some consent discussions with parents may not have been observed and taped. Once a new case was identified, the trained researchers were diligent in their effort to observe and record all discussions, with 23% of cases involving more than 1 meeting. Second, the fact that we observed in-
formed consent may have affected the consent process. Observation did not, however, affect leukemia RCT participation rates and if physician performance was improved by the presence of an observer, the resulting lack of parental understanding is of even more concern. Third, the study was conducted at major academic children’s hospitals in urban settings that may not reflect practice at all hospitals. Finally, the emotional shock that parents experience at the time of their child’s leukemia diagnosis may limit the generalizability of our findings. Studies that examine the consent process in other contexts can address this question.

Clinical research is the key to medical progress but it must be conducted in accordance with the highest ethical standards. Although clinical research fulfills the duty to experiment, there is an equally compelling ethical obligation to continually improve the quality of informed consent. Future research must identify the source of the gap between explanation and understanding, with special attention to barriers noted in parents of racial minority and lower SES. With the current lack of training and increasing attention to research ethics, the time is right for intervention studies aimed at improving communication. Lessons learned from such efforts may apply to communication research in a wide variety of clinical settings. Although formidable challenges remain, we hope that the results of this study will stimulate work toward improving informed consent.

Author Contributions: Dr Kodish had full access to all the data in the study and takes responsibility for the integrity of the data analysis. Study concept and design: Kodish, Noll, Ruccione, Lange, Pentz, Siminoff, Drotar. Acquisition of data: Kodish, Eder, Noll, Ruccione, Lange, Angiolillo, Pentz, Siminoff.}

REFERENCES