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Abstract

Comprehension of randomization is a vital, but understudied, component of informed consent to participate in cancer randomized clinical trials (RCTs). This study examines patient comprehension of the randomization process as well as sources of ongoing uncertainty that may inhibit a patient's ability to provide informed consent to participate in RCTs. Cancer patients living in rural Appalachia who were offered an opportunity to participate in a cancer treatment RCT completed in-depth interviews and a brief survey. No systematic differences in randomization comprehension between patients who consented and those who declined participation in a cancer RCT were detected. Comprehension is conceptually distinct from uncertainty, with patients who had both high and low comprehension experiencing randomization-related uncertainty. Uncertainty about randomization was found to have cognitive and affective dimensions. Not all patients enrolling in RCTs have a sufficient understanding of the randomization process to provide informed consent. Healthcare providers need to be aware of the different types of randomization-related uncertainty. Efforts to improve informed consent to participate in RCTs should focus on having patients teach back their understanding of randomization. This practice

could yield valuable information about the patient's cognitive and affective understanding of randomization as well as opportunities to correct misperceptions. Education about RCTs should reflect patient expectations of individualized care by explaining how all treatments being compared are appropriate to the specifics of a patient's disease.

Keywords: Cancer clinical trials, Oncology research, Health disparities, Randomization, Uncertainty, Decision making

Background

Randomized clinical trials (RCTs) are the gold standard for evaluating emerging discoveries in cancer treatments and, as such, the approval of new cancer treatments depends on enrolling a sufficient number of participants in a timely manner [1]. Unfortunately, advances in cancer treatment are often delayed due to slow rates of RCT accrual, particularly among vulnerable populations such as rural residents [2].

While enrollment in cancer RCTs is an important indicator of the extent to which vulnerable populations have the ability to access state-of-science treatment, another factor that should be considered is a patient's ability to

give informed consent to treatment [3]. Informed consent in the context of RCTs is particularly challenging because patients must understand both the nature of their disease and associated therapies as well as the role of probability in experimental research design in order to make an informed decision about their healthcare. Although strategies for promoting patient understanding of a cancer diagnosis, prognosis, and conventional treatment options are well documented [4–6], more research is needed on patient comprehension of scientific research design and randomization-related uncertainty in the context of cancer RCTs.

Randomization Comprehension

Given the importance of randomization in the informed consent process, there is a growing body of research focused on how people understand randomization and their attitudes about using randomization procedures to determine medical treatment in RCTs [7–10]. Kerr and colleagues showed that college students accurately identified methods of random allocation (e.g., flip of a coin), but had negative attitudes toward using these methods to determine medical treatment [7]. Similarly, Appalachian cancer patients and their caregivers understood randomization conceptually, with different forms of gambling (e.g., lottery) being the most readily accessible example of random selection [8]. Unfortunately, comprehension of randomization may not be better among patients enrolled in cancer RCTs than the general public.

Randomization-Related Uncertainty

The challenge of explaining randomization to patients lies in the high degree of uncertainty inherent in the concept. In most medical contexts, healthcare providers engage in educational efforts to *reduce* a patient's uncertainty about their illness. Illness uncertainty exists when the elements of a health situation are perceived as complicated, ambiguous, variable, or probabilistic [11–13]. In many healthcare situations, education should decrease some forms of uncertainty [14]. However, increased knowledge about randomization cannot be expected to decrease uncertainty because the relationship between uncertainty and probability is curvilinear [13]. Uncertainty is lowest when individuals perceive the probability of a certain event as 0 or 100 % and highest when it is 50 %. Thus, a patient with high comprehension of randomization enrolled in a two-arm RCT should have a very high degree of uncertainty regarding the treatment she or he will receive. The unique relationship between comprehension and uncertainty in the cancer RCT context is important to explore because of the potentially significant implications for patient well-being as well as willingness to participate in medical research. As such, the purpose of the current study is to explore the

relationship between comprehension and uncertainty, particularly as related to cancer RCT participation among an underserved and highest risk population.

Methods

Participants

Participants included 49 patients who were offered a cancer treatment RCT within the last 2 years and lived in or were treated for cancer in 1 of 32 Appalachian Ohio counties. Patients were recruited from a large, urban comprehensive cancer center ($n = 17$, 35 %) and four rural community cancer centers ($n = 32$, 65 %). The sample ranged in age from 33 to 79 years ($M = 59.67$, $SD = 11.46$) and was predominately female ($n = 29$; 59 %). Eleven participants did not enroll in a RCT; among these, ten were female (see Table 1). Interview data from three participants were eliminated from further analysis because they were offered non-RCT studies.

Procedure

The protocol approved by the university Institutional Review Board entailed clinic staff identifying patients who had been offered an RCT in the past 2 years and lived in (or were treated) in an Appalachian county. Researchers mailed patients a recruitment letter signed by their treating physician. For three clinics, a researcher conducted follow-up phone calls to provide additional study information and schedule interviews for those who agreed to participate. Semi-structured interviews were conducted by a trained research team member, were audio-recorded, and ranged from 30 min to 3 h in length. Interviews were conducted face-to-face at a location of the participant's choice (e.g., home, hospital treatment room). After the interview, participants completed a brief, self-administered survey and were remunerated US\$30.00 for their time. The survey included five true/false items measuring randomization comprehension [15]. Participants received 1 point for each item answered correctly (range 0–5). Responses were summed to create a Randomization Comprehension Index (RCI; Table 2).

Data Analysis

The interview audio files were uploaded to a password-protected computer, transcribed verbatim, and imported into NVivo 10. Transcripts were read multiple times by the principle investigator (J. L. K.) and three additional members of the data analysis team to familiarize themselves with the content. Four authors conducted data analysis through an iterative combination of independent and

Table 1. Participant characteristics (*n* = 49)

Characteristic	Number (%)
Sex	
Female	29 (59)
Male	20 (41)
Race	
White	47 (96)
Asian/Pacific islander	1 (2)
Unreported	1 (2)
Participated in a RCT*	
Yes	35 (71)
No	11 (22)
Ineligible (offered a non-RCT study)	3 (6)
Cancer type*	
Breast	19 (39)
Multiple myeloma	9 (18)
Prostate	7 (14)
Colon	6 (12)
Lung	5 (10)
Other	3 (6)
Annual income below US\$49,000	
Yes	23 (50)
No	23 (50)
Health insurance	
None	3 (6)
Medicaid/Medicare	19 (39)
Insured through employer	24 (49)
Other	3 (6)
Education	
8th grade through some high school	4 (8)
High school diploma or equivalent	19 (39)
Vocational training/associates	17 (35)
College graduate or more	9 (18)

*Values do not equal 100 % due to rounding

collaborative coding over a period of 16 weeks [16]. First, thought units pertaining to uncertainty were identified and open-coded as a team. Second, transcripts were open-coded independently followed by weekly meetings to compare the textual composition and conceptual labeling of thought units in each transcript, discuss discrepancies, and negotiate agreement [17, 18]. Third, axial coding was used to compare codes within and across transcripts, resulting in the creation of categories. A codebook was created and continually refined throughout the process that included conceptual labels, definitions, examples, and negative cases for each category. The resulting categories are discussed in detail in the following section.

There were a number of measures taken throughout the data collection and analysis process to ensure the trustworthiness of the findings [19]. Credibility was enhanced through triangulation, in that the textual composition and labeling of codes were agreed upon by at least two (and

Table 2. Randomization Comprehension Index (RCI) items (*n* = 46)

Question	Number (% correct)
RCI 1: In a clinical trial, randomization means that a patient is just as likely to get one treatment as another	34 (74 %)
RCI 2: Randomization means that patients in a clinical trial are allowed to choose a treatment out of a list of options.	33 (72 %)
RCI 3: Doctors who place their patients in clinical trials often choose the treatment that their patients should receive.	29 (63 %)
RCI 4: In a clinical trial, one way to decide a patient's treatment would be to toss a coin.	8 (17 %)
RCI 5: The goal of a clinical trial is to match people to the best treatment for them	22 (48 %)

up to four) investigators. Dependability and confirmability were ensured through extensive theoretical and process memoing. Our audit trail includes memos for each interview (created during data collection) and each transcript (created during data analysis). Furthermore, the team kept a memo describing key decisions and developments in the data analysis process.

Results and Interpretations

Randomization Comprehension and RCT Participation

Participants were divided into high and low randomization comprehension groups based on their RCI score (see Table 2). High comprehension patients had an overall RCI score of 4 or 5 (*n* = 18; 39 %). Low comprehension patients had an overall RCI score of 3 or lower (*n* = 28; 61 %). A goodness-of-fit (chi-square) analysis found no statistically significant differences between the RCI scores of patients who participated in a RCT as compared to those who declined (see Table 3).

Randomization Comprehension and Uncertainty

Overall, comprehension of randomization (as measured by the RCI) was conceptually distinct from uncertainty,

Table 3. Randomization Comprehension Index scores of RCT participants versus nonparticipants

RCI Score	Clinical trial		Total
	Yes	No	
0–3 items correct	21	7	28
4–5 items correct	14	4	18

$\chi^2(1, n = 46) = .05, p = .83$

with patients at all levels of comprehension experiencing randomization-related uncertainty. However, patients described two different types of uncertainty associated with the randomization process: (1) cognitive dimensions and (2) affective dimensions.

Cognitive Dimensions of Uncertainty about Randomization

Cognitive dimensions of uncertainty were thought units pertaining to perceived ambiguity about procedural aspects of randomization, such as assignment to treatment groups and probability of receiving effective treatment. Patients reported that their oncologists used a variety of descriptions for explaining randomization to treatment arms, including flipping a coin, lottery process, and a computer (described below). Many patients struggled with these explanations because they could not visualize the procedures being used to assign patients to treatment. For example, Jeanine, a patient with low comprehension of randomization (RCI = 2), agreed to participate in an RCT. When randomization was explained to her, she laughed and said, "You're gonna put my name in a hat and draw us out and see which one I'm gonna get?" As illustrated by this quote, patients recognized these explanations of randomization as metaphorical in that researchers would not be literally flipping coins or drawing slips of paper out of a hat in order to assign them to their treatment. However, using metaphors to describe the process did little to reduce patient uncertainty about who would be determining which treatment they would receive or how that decision would be made.

Some healthcare providers tried to convey the idea that a patient's treatment is chosen randomly by a computer. However, this explanation was also associated with uncertainty. Patients are accustomed to computers being used to deliver highly individualized medical care, such as recording their medical history through electronic medical records. Given that computers are typically used to provide individualized patient care, such as identify whether a patient is at risk for potential drug interactions, patients had difficulty understanding why the computer would not use the information in their medical record to match them to the best possible treatment. To illustrate, Alice agreed to participate in a RCT. Despite having a high level of randomization comprehension (RCI = 5), she expressed confusion about the role of probability in determining how her treatment was chosen. She stated, "He (health care provider) told me the computer would pick what group I was in, whether I would be in the control group or the test group (...) it's just random (...) It was pretty confusing." Although Alice understood randomization at a conceptual level, she did not understand why the computer would make a determination "at random" when information was available in her electronic medical records that could be used to match her to the most appropriate treatment. The relationship between

computers and the randomization process in an RCT demonstrates the tension between patient expectations of individualized care and the seemingly impersonal nature of how randomization was conducted.

The second procedural concern was the probability of receiving effective treatment in the RCT. Many patients misinterpreted the role of probability as the chance of receiving treatment for their cancer, not the chance of receiving one of two (or more) possible treatments. Samantha had high comprehension of randomization (RCI = 4) but declined participation in a RCT because, "There's a possibility you don't get the proper treatment. And I think later on, when I talked to different people, that's really not the case. I think you get—I don't know. I'm still a bit confused on that." She went on to explain that she was more comfortable with a more personalized treatment plan: "I just wanted the best—you know, I wanted to make the best decision. I just felt like the best decision was the known plan or the plan laid out by the doctor not an experimental (study)." Similarly, Kristy (RCI = 3) participated in an RCT, but was concerned that randomization meant that she might not receive treatment for her cancer:

When I signed up for (the RCT), I just worried about whether I was getting the drug or not getting the drug. You know, I'd say, 'Well, what arm am I gonna be in?' And I think I'd have probably been disappointed if I would have gotten the placebo. That thinking all along that maybe I'm taking a drug, and it's gonna be helping me. And then to find out that, 'Oh, I didn't really get it.'

Affective Dimensions of Uncertainty about Randomization

Affective dimensions of uncertainty refer to the emotional valence of patient descriptions of randomization. Given that randomization entails uncertainty, we examined the extent to which patients used emotionally valenced terms to describe how patients would be allocated to treatment condition. As would be expected, the affective tone of randomization narratives ranged from neutral to negative. Neutral narratives were those that utilized impersonal or scientific explanations of equal chance in allocation to treatment arm. For example, Gloria, who agreed to participate in an RCT, had a relative strong understanding of randomization (RCI = 4). She was matter-of-fact in describing how randomization was explained to her by a health care provider (HCP) during her treatment decision-making process:

Some people will get the additional drug, and some won't. And if you decide to sign up for the study, we (HCP) won't know if you're one of them that will get it or not until we get all the information entered into the computer. Then, it will tell us (HCPs).

Narratives reflecting a negative affective valence contained implicit disapproval (e.g., sarcasm) or explicit use of

negative terminology to describe the randomization process. Samantha, like Gloria, had a strong understanding of randomization (RCI = 4). Unlike Gloria, Samantha chose not to enroll in the RCT. In the following excerpt, Samantha verbalizes a negative affective response to the role of probability in determining her treatment. Specifically, she uses sarcasm (“my luck”) and dehumanizing language (“you’re a number”) to refer to the potential of being assigned to the treatment arm utilizing a placebo. Finally, she contrasts the “placebo” treatment to arms that are “over-aggressive” and “middle of the road” indicating she perceived the RCT as offering an ineffective treatment arm despite her acknowledgement that patients receive treatments in addition to the placebo:

One group would get this, this, and this, which is kind of like over aggressive and one group would get this, this, and this, which is kind of like your middle-of-the-road, and one group would get some placebos and this and this. So I’m thinking, ‘Well, my luck, I’ll be in the group three.’ And you don’t know and they don’t know (...) You’re a number and you get in a bin and we can’t say we want you to get this treatment or we want you to get that treatment.

In other cases, patients produced negatively valenced narratives as indicated by the use of specific terminology with a negative connotation. Cathy had a strong understanding of randomization (RCI = 4) but chose not to enroll in an RCT. She articulated her concern in the following way, “Had there been one thing that might have helped, I would have probably (enrolled in the RCT). But, they didn’t know that. You know, that’s why it’s a trial.” In this example, Cathy equates a *clinical trial* with the colloquialism *trial and error*, which has overtly negative connotations in the context of cancer treatment.

Guinea pig was another term used to express negative feelings toward randomization by patients at various levels of randomization comprehension. For example, Tracy (RCI = 4) and Taylor (RCI = 1) both refused RCT participation. Tracy stated that the most influential factor in her decision not to participate was “the scariness of it really not being approved by the FDA. You know, using something kind of like a guinea pig type thing.” Similarly, Taylor said, “You get the cutting edge treatment or drugs or whatever they had but then on the other hand, were you going to be used as a guinea pig for new stuff?” Tracy and Taylor illustrate that cognitive comprehension of randomization may be unrelated to their affective response to the process.

Discussion

RCTs are an important pathway for investigating successful cancer treatments. While RCTs help reduce scientific uncertainty about treatment efficacy, the role of randomization in determining treatment increases the medical

uncertainty of patients. The purpose of the current study was to explore the relationship between patient comprehension of randomization, treatment uncertainty, and willingness to participate in cancer RCTs. We found no evidence of a statistically significant association between randomization comprehension and participation in cancer RCTs. We posit that randomization comprehension is conceptually distinct from uncertainty, as patients with all levels of comprehension experienced uncertainty. Finally, we showed that randomization uncertainty has both cognitive and affective dimensions.

Cognitive dimensions of uncertainty involved statements expressing concern about how randomization would be accomplished and the role of probability in determining treatment. These statements revealed that being assigned to treatment by chance was conceptually at odds with mental models of medicine grounded in an expectation of personalized care as well as the belief that medicine is a science and operates according to a system of rules and proven practices. Thus, the notion that an oncologist cannot choose the treatment that best matches the patient’s cancer in a RCT was unsettling to patients.

Affective dimensions of uncertainty were statements revealing emotional reactions to the role of randomization in determining treatment. In some cases, patients revealed their emotional responses through the use of irony or sarcasm in their descriptions of randomization while others used overtly negative words, such as “trial and error” and “guinea pig.” Addressing patient concerns and emotions about the safety of randomization are vital in the RCT accrual process, a finding that complements and extends results from previous studies [8, 9].

An unexpected finding was that patients expressing both cognitive and affective dimensions of uncertainty had participated in a RCT. The fact that patients consented to participate in research despite significant uncertainty about treatment efficacy indicates a dire need to develop translational communication strategies to promote patient comprehension of scientific design in the medical context. A major source of misinformation was the belief that one treatment arm was superior to the others or that one arm was vastly inferior to the others. Given that RCTs are conducted only in cases of clinical equipoise, it is noteworthy that patients did not view the arms as equivalent. Instead, patients over- or underestimated the known efficacy and safety of the experimental arm.

The current study benefits from a number of strengths. Noteworthy methodological strengths include recruiting an underrepresented population of Appalachian cancer patients who had been offered an opportunity to participate in a cancer RCT, a substantial sample, and a rigorous analytical approach. The specific focus on Appalachian cancer patients illuminates the potentially unique concerns of rural cancer patient populations and contributes

an understanding of RCT recruitment among rural, Appalachian cancer patients, a population that experiences significant cancer incidence and mortality disparities [20]. There are study limitations that should be noted. First, the generalizability of our findings beyond rural, Appalachian populations is limited. Furthermore, the selection criteria included all types of cancers and treatments; therefore, the results could not be generalized to studies focusing on a specific diagnosis(es) or particular RCTs. Future research should investigate how cancer type, stage, and type of treatment offered is associated with the likelihood of participating in an RCT.

The results of the current research have important practical implications. Efforts to improve informed consent to participate in RCTs should focus on having patients teach back their understanding of randomization. This practice affords providers the opportunity to assess a patient's cognitive and affective understanding of randomization as well as opportunities to correct misperceptions. Also, education about RCTs should reflect patient expectations of individualized care by explaining how all treatments being compared are appropriate to the specifics of a patient's disease.

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