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Barriers to Clinical Research Participation in a Diabetes Randomized Clinical Trial

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Abstract

Little is known about how barriers to research participation are perceived, affected by or interact with patient characteristics, or how they vary over the course of a clinical trial. Participants (285) in the Renin-Angiotensin System Study (RASS), a randomized clinical primary prevention study of diabetic nephropathy and retinopathy at 2 Canadian and 1 US university, rated potential barriers to research participation yearly for 5 years. Baseline barriers rated as most adversely affecting participation were: missing work; frequency of appointments and procedures; study length; number of appointments and procedures; access to study location; and physical discomfort associated with procedures. Inadequate social support, unstable job, and use of alcohol and drugs were cited relatively infrequently, suggesting that although they may be important, candidates for whom these might be issues likely self-selected out of the study. Gender and gender by age interactions were found for specific perceived barriers, such as work and child care, and baseline barriers correlated with adherence. Elucidating the natural history of barriers to research participation is a step toward identifying strategies for helping participants overcome them, and ultimately may enhance the conduct of research.

Keywords

barriers; adherence; research participation; clinical trial

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Main text

Biomedical innovation is predicated, in part, on the willingness of human participants to participate in research investigations of promising compounds and technologies. Without controlled studies of how well new pharmaceutical agents, medical devices, and medical procedures actually affect the research participants who use them, it would not be possible to develop scientific bases for advancing medical care. Clinical investigation is fundamental to delineating the safety, effectiveness, and efficacy of new clinical approaches. However, clinical research does not proceed in a vacuum: It is subject to all manner of human vagaries that may affect participants' capacity to participate. Just as a range of factors can hinder patients' seeking and receiving healthcare services (Reif, Golin, & Smith, 2005), barriers presumably have an impact on participants' ability to participate in research, including their ability to adhere faithfully to research regimens. Ultimately, barriers, or even individuals' perceptions or predictions of barriers, may affect the conduct and fidelity of clinical investigations.

The concept of "barriers" has played an important role in various theories about health behavior. It was originally introduced in Rosenstock's (1966) Health Belief Model in which barriers were construed as costs inherent in health action. In essence, the greater the perceived costs and the lower the perceived benefits to adhering to a protocol, the lower the likelihood a patient will adhere to it. In the Health Belief Model barriers were conceptualized as participative phenomena. A review of the model determined that barriers (e.g., inconvenience) were the most powerful determinant across various study designs and behaviors (Janz & Becker, 1984). In contrast, Andersen's (1968) model of Health Service Utilization equated barriers with a lack of or reduced access to care. It broadened the Health Belief Model view of barriers to include those external to the individual and that were objectively identifiable (McCulloch-Melnyk, 1988). Despite the potential value of theory to undergird our understanding of barriers, much of the research that addresses the concept of barriers is not grounded on the Health Belief Model, the Health Service Utilization model, or any other theories. Instead, barriers research has been relatively atheoretical in nature, typically seeking simply to identify factors that predict specific behaviors (McCulloch-Melnyk, 1988).

A number of barriers that are related to seeking and receiving medical care have been identified. For example, researchers have grouped barriers to adherence to clinical regimens and self-care into categories related to: (a) the sequela of the particular disease state; (b) systems factors (e.g., access to clinics; length of appointments or procedures; gap between seeking and receiving care), and (c) patient factors (e.g., problems with medication, mental illness, incomplete understanding, and distrust of health care professionals (Spilker, 1991; Robiner & Keel, 1997). With regard to these factors, Cramer (1991a) posits that forgetfulness is the most common personal factor undermining adherence to health regimens. The roles barriers play in the treatment of psychiatric disorders have also been studied (e.g., Bourgeois, 2005). For example, financial barriers to the purchase of psychotherapy, psychotropic medication, or copayments for appointments, lack of transportation, and lack of child care have been identified as challenges to adherence in mental health care.

Methodologies for measuring adherence to health regimens in the literature have been heterogeneous. For example, some studies employ direct methods (e.g., observation of medication use, monitoring the level of medication use or metabolite in biological fluids, tracking clinical attendance). Others have used indirect methods such as patient report, pill counts, and electronic medication monitors (Rosen, Rigsby, Salahi, Ryan, & Cramer, 2004). Generally, a combination of direct and indirect methods may be most effective in measuring adherence (Spilker, 1991), though consensus on methodology remains elusive.

Quantification of adherence is central to evaluating adherence-enhancing strategies. Various approaches have been used to improve clinical adherence. These include increasing the flexibility of clinic scheduling; minimizing wait time for services; promoting frequent and positive contact between patients and health professionals; involving others (e.g., spouses) in patients' care; providing information and education about disease management; simplifying regimens (e.g., streamlining dosing, reducing frequency of medication administration); and integrating contingencies to reinforce adherence (Cramer, 1991a; Cramer 1991b; Spilker, 1991; Zinman, 1997). Addressing patients' personal circumstances and motivation also can be helpful (Cramer 1991a). At times, mental health consultation can be beneficial, or even critical (e.g., when poor adherence becomes life-threatening [Kramer, Jacobson, Ryan, Murphy and the DCCT Research Group, 1994]). In general, effective compliance-enhancing efforts are usually multifaceted (Bourgeois, 2005). Identification of barriers may be a useful step toward developing and implementing strategies for overcoming them so as to facilitate consistency in how patients execute health behaviors.

Despite a robust literature addressing barriers to seeking and receiving healthcare for a broad range of conditions (e.g., Eggleston, Coker, Das, Cordray, & Luchok, 2007; Krueger, Berger, & Felkey, 2005; Rozanski, 2005; Ward-Begnoche & Speaker, 2006), relatively little attention has focused on barriers that affect participation in research trials and adherence to research regimens (Ross, Grant, Counsell, Gillespie, Russell, & Prescott, 1999; Lowton, 2005). Beyond those barriers inherent in clinical care that presumably are likely to generalize to the research context, barriers to participants' enactment of research protocols may include variables associated with the conduct of research such as: the study demands including the experimental treatment regimens; understanding and accepting the necessity of randomization; perspectives of the research enterprise and funding agencies; and psychosocial factors. For example, barriers may be associated with experimental regimens (e.g., discomfort associated with procedures; frequency of appointments and procedures) as well as factors peripherally related to the study (e.g., financial, social support, child care, transportation, emotional functioning) or participants' personal resources (e.g., time, expenses). There is assumedly considerable variability in how any specific potential barrier may affect any individual participant. For example, whereas the primary hurdle for some participants may be transportation and parking at research sites, for others, the salient hurdles may be time (e.g., away from work, school, or family responsibilities), while for yet others the larger obstacles may be internal (e.g., motivational, organizational, mental health problems).

A fundamental challenge in conducting research is to enroll participants who are willing to volunteer and who can be counted on to comply faithfully with assigned experimental protocols. This process includes assuring that prospective participants understand the rationale for the study and the procedures that they would be expected to follow. In addition to the *quantitative* challenges of study recruitment (i.e., enrollment of sufficient participants to satisfy sample size derived by power analyses) there are *qualitative* challenges. The latter include selecting those participants who will be motivated and capable of consistently adhering to the research protocol. These have implications for all phases of a study, including recruitment, data collection, and data analysis. After participants' randomization to treatment arms, the challenge is to promote consistent adherence to the protocol and monitor adherence so as to provide assurance that participants indeed did what they intended. Ethical prohibitions against coercing participants to comply with experimental regimens, even if they had earlier agreed to do so, necessitate that researchers develop positive approaches to facilitate regimen adherence (i.e., consistently fulfilling the experimental regimen) and follow-up adherence (fulfilling the research protocol's planned assessments; See Kramer et al., 1994; Robiner, 2005).

Unfortunately, researchers have long observed that some study participants have difficulty fulfilling their intention of following regimens through endpoint (Collins, Williford, Weiss,

Bingham, Klett, 1984; Lasagna & Hutt, 1991; Probstfield, Russell, Insull, & Yusuf, 1990). Studies of diverse treatments and patient populations have revealed inconsistency in how well participants follow protocols. For example, participants may fail to take medications on schedule or may miss scheduled meetings with research staff. This is neither trivial nor inexpensive. A review of IRB records of 25,855 participants who consented to participate in U.S. industry-sponsored studies revealed that only 74% completed their trials (Gamache, 2002). The potential role of barriers in contributing to such trends and costs by undermining adherence to clinical research is not known.

One way of conceptualizing research participation is that participants forego non-study related activities and navigate around potentially interfering circumstances to successfully follow investigational regimens. That is, participants may perceive, encounter, and need to surmount barriers so as to participate in accordance with study designs. Greater understanding of the role and magnitude of perceived barriers to research could yield clues to help participants, or research-eligible candidates, negotiate barriers so as to maximize participation in research and exposure to investigational regimens.

Despite the potentially important roles that barriers may play in research adherence, little is known about them or about how barriers may be affected by or interact with patient characteristics (e.g., age, gender). Similarly, it is not clear how transient or stable barriers may be over time (e.g., the course of a research trial) or how they may affect concurrent or serial trial participation. We are not aware of previous efforts to delineate how the salience of perceived barriers may change during the course of a study. Given that the long duration of some studies can affect adherence (e.g., Spilker, 1991), it stands to reason that individuals' perceptions of barriers, as well as the circumstances and challenges that they contend with, may change over time. The aim of the present study was to examine the role and course of barriers to participating in a clinical trial. We explored patterns of barriers over the first four years of a 5-year study, as well as the effect of demographic factors (i.e., gender, age) on participants' perceptions of barriers.

Methods

Participants

This investigation was an ancillary study of the Renin-Angiotensin System Study (RASS) (Mauer, Zinman, Gardiner, Drummond, Suissa & Donnelly, 2002; Mauer, Zinman, Gardiner, Suissa, Sinaiko & Strand, 2008). The RASS was a double-blind, placebo-controlled, random-allocation primary prevention study of diabetic nephropathy and retinopathy conducted between 1997 and 2005. The objective of the RASS was to determine whether a regimen of angiotensin converting enzyme inhibitors (ACE-1) or angiotensin II receptor blockers (ARB) in Type I Diabetes Mellitus (DM) participants, who had no clinical nephropathy findings, could delay or prevent the emergence of renal structural changes or dysfunction and retinopathy, potentially devastating diabetic complications, by blocking the RAS. More specifically, the RASS endeavored to inhibit the RAS, so as to prevent an increase in glomerular mesangial fractional volume as measured through repeat renal biopsies 5 years apart. Sixty-eight participants (24%) had participated in an earlier natural history study of diabetic nephropathy (Mauer, Drummond, for the International Diabetic Nephropathy Study Group, 2002).

RASS participants were surveyed annually throughout their participation. A total of 1,065 potential participants were screened for the RASS; 73 did not meet eligibility requirements and 707 refused, yielding a 28.7% accrual rate. Ninety-six were randomized from the University of Minnesota; 95 from McGill University in Montreal; and 94 from the University of Toronto, yielding a cohort of 285 across the three sites. Regrettably, we did not survey potential participants who did not enroll about their reasons for declining.

At baseline, mean age was 30.5 years (S.D. = 9.8) and duration of Type I diabetes was 11.3 years (S.D. = 4.7). Mean age at diagnosis was 18.8 years (S.D. = 10). The sample was 53% female. Despite efforts to recruit a diverse participant pool, the sample was mostly White (97.9%). Nearly all (92%) randomized participants completed the study and reached the 5-year biopsy endpoint. Three participants died; 23 declined final evaluation or were lost to follow-up. Participants' consent to undergo multiple quarterly and annual tests and procedures, as well as renal biopsies at baseline and 5 years (90%), reflects the high motivation of the cohort. The protocol for the RASS, including for this ancillary study, was approved by the IRB of each participating institution. An external safety and monitoring committee reviewed the study progress annually and a drug monitoring committee convened regular reviews of adverse events.

Relationship status of participants at study entry was: 33% married; 54% single; 11% "partnered"; and 2% divorced/separated. Overall, it was a well-educated cohort with 80% having some college, including 19% with graduate education. At entry, 28% were students and 65% were employed (half in professional or technical positions).

Design

At entry, participants were administered a series of psychological instruments, including ratings of their perceptions of a range of potential barriers to research participation. Items were screened for readability. Participants were retested annually to assess the stability of the perceived barriers over time. Participants' responses to the survey were not considered until after RASS recruitment had been completed. French language versions of the instruments were developed for the French-speaking Montreal participants. These alternate versions were interpreted bidirectionally by study staff to ensure comparable forms. A small number of RASS participants did not complete all of the measures due to minor delays in the initiation of the barriers study in the RASS and some participants' circumstances (e.g., developmental problems). All psychological data were submitted confidentially in sealed envelopes and forwarded to the Coordinating Center so that staff at trial sites could not access it, and only personnel working on this ancillary study could see it. This was to promote participants' comfort with submitting psychological data, which presumably encouraged fuller candor in participants' responses.

Materials

The present study focused on a survey of potential research barriers created expressly for this study. The list of barriers was based on the literature (e.g., Glasgow, 1991; Cramer, 1991a; Spilker, 1991) and the clinical experiences of members of the research group in earlier studies (e.g., the Diabetes Control and Complications Trial [DCCT Research Group, 1993]). Items were included that were judged as having the potential to interfere with a participant's participation in a research trial (e.g., access to location; length of study, emotional functioning; see Table 1). While the composition of the survey was not based on the work of Ross et al. (1999), which was published after this study started, there is considerable overlap of items with the list of patient barriers they reported. Items were anchored by how much each item was estimated to be a barrier to being in the study (1 = low; 2 = moderate, 3 = high). The reliability at baseline among items for the barriers was high ($\alpha = .92$). A correlational analysis was conducted with all of the items. As expected, the majority of the intercorrelations were significant.

Procedure

Participants were surveyed at five time points: at entry and at the end of years 1–4. Adherence to medication regimen was measured by covert pill counts conducted by RASS staff (i.e., participants returned medication vials and unused medications at quarterly visits to the research

centers and were given new vials. Differences between expected and actual remaining medications were tabulated as an index of adherence). Records of keeping clinic visits were also used as an index of adherence. Pill count data were treated as a continuous variable and analyzed by Pearson correlations. Two variables were related to clinic visits: clinic visits were treated as both a continuous variable (i.e., the percentage of visits kept) and as a dichotomous variable (i.e., whether or not participants kept 100% of scheduled visits). ANOVA were conducted on demographic variables and the barrier items over time.

Results

Perceived Barriers

At the outset of the study approximately half of the participants believed that barriers would not affect their participation, whereas about 45% believed that their participation would be “mildly” affected. At baseline (i.e., entry to the study), the barriers that were perceived as relatively most problematic were: missing work; length of study; frequency of appointments/procedures; number of appointments/procedures; access to study location; and physical discomfort associated with the procedures. In general, these barriers continued to be perceived as the most problematic throughout the study (see Table 1). Interestingly, barriers such as inadequate social support, unstable job, and the use of alcohol and drugs were rated relatively low as potential barriers to their involvement.

Results also revealed that the mean number of barriers coded as a moderate or high across participants at baseline was 4.7. One participant identified 20 items as high. At baseline, more than a quarter of the participants did not find any of the items to pose more than a low barrier to participation. Some participants (17.5%) identified 1 or 2 items as moderate or high barriers, 24.1% identified three to six items as moderate-high barriers, and 23.6% identified 7 or more items as posing significant barriers.

Demographic Effects

Demographic factors were also assessed via a series of 2 (gender) $\times$ 4 (age at baseline) ANOVAs conducted on baseline barriers. Age was categorized as ≤ 21 , 22–31, 32–41, and ≥ 42 . Men ($M = .77$) rated unstable job as being a potentially greater barrier to participation than women ($M = .59$), $F(1, 261) = 4.97$, $p = .03$. Men ($M = .63$) also judged their own use of alcohol and/or drugs as a potentially more problematic barrier to participation than did women ($M = .43$), $F(1, 262) = 6.39$, $p = .01$.

For some ages, certain barriers were perceived as potentially more problematic than for other ages. For example, as might be expected, missing school was perceived as affecting younger individuals' participation in research more than other age groups, $F(3, 261) = 16.45$, $p < .01$. Conversely, younger individuals were less likely to consider other family commitments as potentially problematic for their participation, $F(3, 26) = 2.65$, $p = .05$. For relatively older individuals, the health problems of other family members, $F(3, 262) = 2.71$, $p < .05$, and child care, $F(3, 261) = 6.70$, $p < .01$, were viewed as potentially greater barriers to participation. For child care there was an Age $\times$ Gender interaction in which women in the 32–41 age group rated child care ($M = 1.17$) as more problematic than any other age or gender group, $F(3, 261) = 4.60$, $p < .01$.

Effects of Time on Perceived Barriers

A composite index was derived for all 32 barrier items to assess overall patterns of perceived barriers to research participation. A repeated measures ANOVA on the composite score with time as the independent variable (i.e., baseline and at the end of years 1–4) and collapsed across gender was conducted. It yielded a main effect of time, $F(4, 128) = 4.38$, $p < .01$ (see Figure

1). Follow-up analyses revealed that the composite score at baseline was greater than at the end of year 1, $F(1,32) = 9.73, p < .01$, the end of year 2, $F(1,32) = 6.62, p < .02$, and the end of year 3, $F(1, 32) = 9.42, p < .01$. The difference between the composite score at baseline at the end of year 4 did not reach statistical significance, $F(1, 32) = 3.48, p = .07$. Likewise, the remaining pairwise comparisons were not significant (all probability values were between .17 – .70). The pattern that emerged was for the composite score to be greater at the outset of the participants' involvement in the study, to diminish significantly during the middle portion of the study, and then increase toward the end of their participation.

The aforementioned effect of time was further evaluated with separate repeated measures ANOVA's for each gender with time as the independent variable. The ANOVA for men produced a main effect of time. Follow-up analyses indicated that the composite score for men was higher at baseline compared to year 1, $F(1, 17) = 7.17, p < .02$, and year 3, $F(1, 17) = 5.01, p < .04$. The remaining pairwise comparisons were not significant (all p values were between .08 – .68). The results of the ANOVA for women were not significant. Comparable repeated measures ANOVA with age as the independent variable produced neither significant main effects nor interactions.

Barriers and Adherence

The number of perceived barriers at baseline was correlated with two indices of adherence. Participants with more frequent ratings of barriers as medium or high at baseline had less compliance during the first year in terms of total pills taken ($r = -.203; p < .001$) and in terms of keeping appointments ($r = -.182; p < .001$) with the research staff. The negative correlation with kept appointments was also seen during the 4th year ($r = -.180; p < .001$), but not years two and three. This presumably reflected the greater perception of barriers during the first and fourth year. Baseline perceptions of barriers were not consistently associated with medication adherence beyond the first year.

Discussion

This study explored the barriers to research participation in the first four years of a primary prevention trial of diabetic nephropathy and retinopathy. Baseline data revealed that nearly half of this randomized sample perceived several barriers as having the potential to interfere with their participation in research. The temporal fluctuations in perceived barriers to research participation (i.e., higher at entry, lower during the middle, and then increasing toward the end) observed in RASS participants are intriguing. The tendency of participants to perceive barriers as higher at baseline might be due to early concerns being somewhat vague and abstract. It is possible that once participants actually began the study, they perceived actual barriers as more surmountable than originally anticipated. Also, it is possible that as trial coordinators developed better understanding of individual participants' situations during their first year in the study, they may have been informally helping them address barriers or structurally modifying logistics of participation (e.g., better accommodating participants' schedules), resulting in fewer perceived barriers. The variation in barriers over time has implications for designing mechanisms for tracking barriers during studies, such as periodically addressing perceptions of barriers from the beginning of participants' recruitment until reaching end point.

The increase in perceived barriers toward the end of the study suggests that the temporally shifting appraisal of barriers may be a factor in "study fatigue." It is unclear from our study whether the increase in perceived barriers at year 4 was due to a change that may occur naturally after a few years of participation, or whether it was due to participants' approaching their final year in the research protocol, which may somehow have affected their appraisal or tolerance of barriers.

Perceived barriers also appear to play a role in participants' regimen and follow-up adherence in clinical research. In this study, the number and severity of perceived barriers at baseline were significantly associated with medication taking adherence during the first year of the study. In addition, the number of perceived barriers at baseline was associated with fulfillment of the scheduled sequence of assessments in follow-up visits. To our knowledge, this linkage between participants' early perceptions of barriers and their actual adherence during a randomized clinical trial is the first empirical demonstration of the role of barriers in adherence to research.

Participants' acknowledgement of barriers to research underscores the need to identify and address barriers in future clinical research. Targeted interventions to address those barriers and increase adherence starting at the outset, and repeated periodically during the research, and even toward the end of studies, may be fruitful in facilitating research adherence. For example, it may be useful to evaluate barriers during recruitment and randomization to initiate problem-solving, provide support, and to marshal resources to counter them so as to help participants cope optimally with potential barriers, thereby minimizing their impact.

It may be useful to address perceptions of barriers periodically as a means of reinforcing efforts to deal with previously identified barriers. At various stages of long-term studies, it may be useful to renew efforts to help participants deal with barriers as they may emerge or increase in salience during the study. In the event of a decrement in adherence, reassessment of individuals' perceived and actual barriers to participation might be warranted.

Greater elucidation of the role of personal circumstances in affecting perceptions of barriers is indicated. Future research should explore how and why specific barriers may affect participants' research participation and adherence, including the role of side effects, which are critical factors in individual patients' regimens. Interestingly, in our study, inadequate social support, unstable job, and use of alcohol and drugs were cited relatively infrequently as potential barriers to research involvement. Given the potential centrality of such circumstances in people's lives and functioning, it would seem intuitive that these factors would play pivotal roles in influencing a person's ability to meet the demands of a research protocol. Although the minimal ratings these barriers received suggests that in this specific sample they were not salient, it would be imprudent to assume that they are not significant deterrents to research participation in other individuals. Presumably research candidates for whom these were significant issues, are likely to have been excluded or to have self-selected out of the study. Future investigations of barriers to research could address this by following up with individuals who opt out of participating to determine their reasons for not participating and the incidence of such factors. Replication of our results is needed to assess the role of all barriers, including even the relatively low-rated barriers in this sample, in affecting potential participants' roles as research participants.

This study is limited in focusing on a single patient population (i.e., Type 1 diabetes participants without overt diabetic complications). It is unclear if the findings would be replicated with other specific populations or with a broader sample, as well as with less motivated individuals and individuals who had not participated in previous studies. It is possible that because all participants had a chronic disease that requires ongoing medical contacts, they may have been less disconcerted by some barriers than people with fewer interactions with health professionals. It was also limited in terms of not exploring why potentially eligible participants who were contacted for the RASS did not participate, though it is presumed that the dual renal biopsies in the study design were a factor. It would be useful to solicit perceptions of barriers from all screened participants to develop a more comprehensive understanding of these factors. It may also be fruitful to analyze the impact on perceptions of barriers of treatment allocation, and to explore the relationships between barriers and how well participants adhere with

protocols and persevere in studies (i.e., whether they withdraw or are lost to follow-up; Moher, Schulz, & Altman for the Consort Group, 2001). The homogeneity of the sample precluded evaluation of the role of ethnicity as a potential barrier. Because severely ill (e.g., with life-threatening or terminal conditions) participants were excluded, it is not known how perceived barriers might affect their participation in research or whether disease-specific factors may play potential roles.

As with clinical adherence enhancement efforts, multifaceted approaches to surmounting barriers and improving adherence in clinical research seem likely to be most effective (Robiner, 2005). Because adherence in research is affected by many of the psychological factors affecting clinical practice (Bourgeois, 2005), research personnel (e.g., PIs, trial coordinators) need to address them directly. For some research endeavors, enlisting the expertise of mental health professionals (e.g., health psychologists) as core members of the research team (e.g., Kramer et al., 1994) or as consultants, may be advantageous in helping participants contend with and overcome barriers as part of their broader efforts to maximize participants' adherence.

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Figure 1. Scores on the Barriers Scale Over Time

Note: A higher score indicates more barriers endorsed. The impact of barriers to participation was measured at the outset of the study and after years 1–4 (5 time points). Range: 0–3.

Table 1

Baseline Percentage of Participants' Rating of Barriers to Research Participation.

Barrier^I	Not Applicable	Low	Medium	High
1. Missing work	14.0	51.1	29.2	5.7
2. Length of study	9.2	58.8	29.4	2.7
3. Frequency of appointments, procedures	13.7	55.1	27.4	3.8
4. Number of appointments, procedures	13.7	56.7	27.4	2.3
5. Access to study location	12.1	63.3	20.1	4.5
6. Physical discomfort associated with procedures	11.7	64.0	20.1	4.2
7. Length of appointments, procedures	13.0	62.2	22.9	1.9
8. Scheduling conflicts with appointments, procedures	12.5	62.0	24.3	1.1
9. Transportation (for example, time or costs involved)	15.7	64.0	18.4	1.9
10. Concern about being in a demanding treatment	15.8	66.8	14.3	3.4
11. Location of study	16.7	64.3	16.4	2.7
12. Complying with treatment	13.6	72.7	11.0	2.7
13. Concern about being in a less effective treatment group	17.8	66.3	11.7	4.2
14. Emotional discomfort associated with procedures	17.0	70.9	9.8	2.3
15. Other family commitments	18.6	68.1	11.8	1.5
16. Uncertainty of results of study	19.0	70.7	8.7	1.5
17. Financial concerns (not directly related to study)	23.9	64.4	8.7	3.0
18. Family concerns or problems	23.6	64.6	9.9	1.9
19. Interference with vacation time	23.5	65.1	9.1	2.3
20. Availability of parking	22.3	67.2	8.7	1.9
21. Emotional concerns or problems	21.6	69.7	6.1	2.7
12. Health problems of other family members	24.9	64.9	6.4	3.8
23. Expenses related to study	25.0	64.8	7.2	3.0
24. Distrust of health professionals	26.8	67.5	2.6	3.0
25. Inadequate social support	26.9	67.8	4.2	1.1
26. Missing school	42.4	44.3	10.6	2.7
27. Unstable housing	37.4	58.1	3.4	1.1
28. Unstable job	38.6	56.4	3.8	1.1
29. Unstable significant relationship	38.8	58.2	2.3	0.8
30. Child care	55.7	35.2	5.7	3.4
31. Use of alcohol or drugs (family member)	50.8	46.6	1.9	0.8
32. Use of alcohol or drugs (own)	49.8	48.3	1.5	0.4
Mean Across Barriers	23.9	61.3	12.3	2.5

Not applicable; 1 = Low; 2 = Medium; 3 = High.