Noninvitation of Eligible Individuals to Participate in Pediatric Studies

A Qualitative Study

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Objective: To identify subjective factors that lead investigators not to invite eligible individuals to participate in pediatric studies.

Design: Qualitative study with semistructured interviews.

Setting: Four pediatric teaching hospitals in Paris.

Participants: Pediatric investigators (n=24).

Main Outcome Measure: Report by investigator that eligible patients were not invited by him or her to participate in a clinical research study.

Results: Sixty-three percent of investigators (15 of 24) reported not inviting eligible patients. The noninvitation patterns were global (ie, investigators did not invite anyone) (37.5% [9/24]) or targeted specific patient subgroups (37.5% [9/24]). Noninvitation was often described as driven by ethical concerns related to the study design or patients or by anticipated patient refusal (58.3% [14/24]). None of the investigators kept records of noninvitation rates or refusal rates. Investigators estimated refusal rates of 1% to 10%, and none remembered a study that had failed because of potential subjects' refusals (including healthy participants).

Conclusions: Noninvitation to participate in studies is not an absence of action but rather is an organized practice that reflects investigators' perceptions. Consequences are practical (eg, recruitment bias and study failure) and ethical (eg, unequal access to trials and failure to respect the autonomy of eligible patients). Our data suggest an urgent need for quantitative studies aimed at documenting and understanding noninvitation of eligible patients to participate in research studies in pediatrics and in other medical specialties.

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REGULATORY AGENCIES INCREASINGLY REQUIRE EFFICACY AND SAFETY STUDIES CONDUCTED SPECIFICALLY AMONG PEDIATRIC POPULATIONS BEFORE APPROVING DRUGS FOR USE IN CHILDREN.1-3 AS A RESULT, A GROWING NUMBER OF CLINICAL TRIALS ARE BEING CONDUCTED AMONG PEDIATRIC PATIENTS. RECRUITMENT OF PEDIATRIC PATIENTS INTO CLINICAL TRIALS IS DIFFICULT, AND FAILURE TO MEET RECRUITMENT GOALS OCCURS. THIS, ALONG WITH INCLUSION RATE REQUIREMENTS, IS A MAJOR CAUSE OF RESEARCH FAILURE THAT RESULTS FROM LACK OF EVIDENCE DUE TO INSUFFICIENT NUMBERS OF SUBJECTS AND FROM FINANCIAL CONSEQUENCES OF DELAYS THAT LEAD TO ABANDONING THE RESEARCH.

Two categories of obstacles have been identified, objective and subjective obstacles. Objective obstacles are typically related to the number of potential subjects or the conditions of access to them (eg, geographic dispersion).4 Subjective obstacles (ie, obstacles pertaining to individuals and not to external conditions) are rooted in poor comprehension or limited motivation among those who could be involved in a study. Investigations into subjective obstacles have focused mainly on patients and their parents.5,6 Little is known about subjective obstacles related to investigators.

We designed a qualitative study among investigators to identify subjective obstacles to patient recruitment for pediatric research. The results suggest that subjective factors leading investigators not to invite potential participants may constitute a major cause of failure to meet inclusion schedules in pediatric trials. We are unaware of previous studies documenting noninvitation to participate in research studies.

METHODS

The sociology of organizations was used as the theoretical framework for this study.7 This

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branch of sociology focuses on the coordination of actors in a social situation that they organize (eg, collective actions or corporations). We used qualitative research that is appropriate for identifying and understanding behaviors and reasons that drive actions, as well as for building typologies of actions and actors that can serve in subsequent quantitative investigations. In this preliminary qualitative phase, numbers of responses cannot be construed as generalizable measurement values.

To collect data from investigators, we derived a semi-structured interview from the interview guide developed by Amiel et al8 for obtaining experiential information from health care professionals and adult patients participating in biomedical research. The responses were recorded on an audiotape and were transcribed word for word. We used conventional methods for conducting the interviews and for analyzing the qualitative data.10 The first investigators enrolled in the study were identified by the study staff with the help of the Centre d’Investigation Clinique 9202, which coordinates research efforts within the Hôpital Robert Debré. Physicians to interview were chosen based on (1) their experience, as estimated by the study staff, in biomedical research and (2) their reputation among the study staff for having experienced success or failure in meeting recruitment goals as investigators. Quantitative criteria defining investigators to interview (eg, the number of publications or research grants in assessment of biomedical research experience or the number of successes or failures in recruitment) were not made explicit. These investigators suggested additional investigators for interview. Investigators were contacted by telephone to arrange an appointment and were interviewed face to face.

According to French law and international recommendations, written consent is not required for this type of study. The investigators who were interviewed received oral information about the study objectives and were told that the study was being conducted on a volunteer basis. They gave their oral consent to having the interview recorded. Approval by a formal ethics committee is not required for this type of study and was not sought. However, the research project as part of the Clinical Research Hospital Project was reviewed by independent experts and was approved by the appropriate authorities.

### RESULTS

We interviewed 24 investigators in 2 waves: first, 15 investigators working at the Hôpital Robert Debré; and then 9 investigators at other pediatric teaching hospitals in and near Paris (Hôpital Armand-Trousseau [n=1], Hôpital Necker–Enfants Malades [n=7], and Hôpital Louis-Mourier [n=1]). The specialties and number of investigators in each are given in Table 1. Among these investigators, 8 were professors of pediatrics, 15 were pediatricians without academic positions, and 1 was a clinical fellow in pediatrics. One interviewed pediatrician who was active in clinical research was a general pediatrician (ie, without subspecialty).

#### NONINVITATION OF ELIGIBLE PATIENTS AND FAILURE TO MEET INCLUSION SCHEDULES

None of 24 investigators remembered having been involved in a research project that failed because of a high refusal rate among potential participants, even among healthy volunteers invited to participate in a control group. Fourteen investigators (58.3%) reported very low refusal rates, and none reported a high refusal rate among patients or parents invited to participate in research projects. Seven investigators (29.2%) gave estimated refusal rates, which ranged from 1% to 10%. However, the investigators did not have records of refusals to participate. Refusal should be differentiated from premature withdrawal, for which exact numbers are obtained during clinical trials.

Specific situations or research protocols were identified by 15 investigators (62.5%) as being associated with decisions not to invite potential participants. Two types of noninvitation were reported, selective and global. Selective limitation of invitations consisted of targeting specific families for study inclusion or exclusion among the total pool of eligible families; selective noninvitation was reported by 9 investigators (37.5%). Global limitation (ie, complete absence of invitations by an investigator working in a center that had agreed to participate in the study) was reported by 9 investigators (37.5%).

Decisions by investigators not to invite potential participants were reported as a cause of failure to meet inclusion rate requirements. For instance, failure of a phase 1 trial owing to slow recruitment was ascribed to limited invitations by investigators, not to a high refusal rate among participants. One investigator (a part-time hospital physician in general pediatrics) said: “When it’s part of a treatment, the investigators are more likely to accept... It didn’t work because it was not clear [to the physician] how the patients would benefit.”

Noninvitation was often described in positive terms as a behavior driven by ethical concerns (58.3% [14/24]) and as an integral part of recruitment activities (although the end result was absence of recruitment). None of the investigators kept records of their noninvitation rates.

### REASONS FOR NONINVITATION

The investigators reported 3 primary reasons for noninvitation. These included (1) concern about the characteristics of the research project, (2) perceptions of the patient or family, and (3) anticipated refusal to participate.

#### Concern About the Characteristics of the Research Project

Subjective concerns about the research project were reported by investigators as leading to noninvitation (Table 2). Half (50.0%) of the investigators (12 of 24)
thought that inviting potential participants was easy when they had a favorable perception of medical benefits from the research project and was difficult when their perception was negative. Regarding methods, 25.0% of investigators (6 of 24) reported a reluctance to include patients in projects requiring invasive procedures (including blood sample collection) in healthy control subjects. Typical comments included the following: “Control groups are sometimes just barely ethical. . . . For a child who is ill, OK, maybe. . . . But for the controls, you can challenge that. Besides, they have their blood collected specifically for the project. Patients get blood collected anyway. . . .” The interviewed pediatricians reported concerns about placebo therapy and about randomization that were similar to those voiced by physicians in other specialties.11 These indicated that the investigators did not necessarily view clinical research as a specific scientific activity warranted by the need to gain knowledge, as opposed to the need to treat patients adequately.12

Perceptions of the Patient or Family

Forty-two percent of the investigators (10 of 24) thought that patients with severe disease were easier to invite than those with mild disease. The subjective assessment of the balance between risks (or burdens) and benefits was dependent on disease severity. One investigator said: “Getting parents to accept a research project is fairly easy when the disease is serious and the constraints imposed by the study are limited; getting them to accept a project with similar constraints when their child has next to nothing is hard.” Among 20.8% of the investigators (5 of 24), concerns included a perception that difficulties would arise regarding compliance with the research project or regarding comprehension of the research project.

Anticipated Refusal to Participate

Anticipated refusal was described in different ways as a major reason for noninvitation. Selective recruitment among families who were expected to agree to participate was reported by 16.7% of the investigators (4 of 24). Comments included “I think the reason we don’t have many refusals is that we know who to ask” and “I only ask if I’ve known the family for a long time and we trust each other.” Anticipated refusal with noninvitation to avoid the embarrassment of being turned down was implicit in various attitudes reported by the investigators. Thirty-eight percent (9 of 24) thought that recruiting one’s own patients was easier, as reflected in the following statement: “I feel more comfortable with patients that I know.” On the other hand, 16.7% (4 of 24) preferred to refrain from recruiting their own patients, in particular because they thought that the freedom of choice of their patients was restricted by a desire to please or by a fear of the consequences of displeasing their physician. The investigators reported the following perceived reasons that their patients would agree to participate in research projects: desire to help research (54.2% [13 of 24]), hope for a medical benefit for the child (33.3% [8 of 24]), and trust (41.7% [10 of 24]). These findings are consistent with earlier reports.13

Our results are based on a qualitative study. The following 3 types of limitations are associated with the study methods.

The first limitation is that recruitment of investigators for the study was initially nonrandomized, and the risk exists that a certain type of behavior or attitude toward clinical research could be overrepresented, as well as certain categories of physicians (ie, endocrinologists in our sample). On the other hand, our findings represent a typology of concrete behaviors that is useful for a future quantitative study. Typology is not sensitive to recruitment bias in the same way as measurement processes. Recruitment can be oriented to maximize the heterogeneity of the sample when results cannot be obtained by randomization among a small population (eg, experienced investigators at a hospital).14,15 Investigator types identified in our study include the following types: type 1, investigators who invite eligible patients exhaustively vs type 2, investigators who do not invite exhaustively. Type 2 can be subdivided into type 3, investigators who limit invitation selectively (selective noninvitation) vs type 4, investigators who do not invite at all (global noninvitation), although both types agreed to participate in the research as investigators. Translated in terms of resulting cohorts of patients, our findings suggest the following breakdown into types: (type a) ineligible patients vs type b, eligible patients. Type b is further subdivided into type c, eligible patients invited to participate vs type d, eligible patients not invited to participate. The assessment of the weight of type d in the cohorts of potential subjects for clinical research, as well as of the ratio of investigators or behaviors of types c and d, is beyond the scope of our study. Such assessments should be performed in a future quantitative study.

A second limitation is related to characteristics of the French research climate. According to a 2004 survey on the ranking of France in international clinical research,16 France is behind the top international competitors in terms of research productivity, including recruit-

| Table 2. Subjective Concerns Reported by the 24 Investigators as Limiting Their Invitation Efforts |
|---------------------------------|-----------------|
| Subjective Concern               | No. (%)         |
| Related to the research project  |                 |
| Medical risks and adverse effects| 9 (37.5)        |
| Scientific value of the project  | 8 (33.3)        |
| Medical benefit for the participants| 6 (25.0)       |
| Practical burdens associated with participation (eg, having the patient and parents come to the hospital for a full day of testing) | 5 (20.8) |
| Related to the patients and families |                 |
| Uncertainty about the treatment and its adverse effects | 12 (50.0) |
| Invasive procedures required by the research project | 11 (45.8) |
| Practical constraints            | 7 (29.2)        |
| Desire to protect the child from medical intrusion | 6 (25.0) |
| Absence of benefits counterbalancing the constraints | 3 (12.5) |


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ment speed and number of patients by trial and broad participation of inactive centers (ie, centers that agreed to participate in the research but recruited no subjects). Therefore, our findings may be relevant to the French experience and may not be generalizable to other parts of the world.

A third limitation is that our findings do not address psychological reasons why investigators interviewed acted as they reported. The lack of a psychological perspective derives from our methodological choice not to investigate psychological motives. We focused on the what (noninvitation of eligible patients) and the how (selective and global noninvitation), not the why. Our study did not address the kinds of explanations that psychologists or anthropologists like to use (eg, emotional or cultural background of behaviors). In fact, focusing on concrete actions and forgoing the traditional interpretative angle is what identified the phenomenon of noninvitation of eligible patients. Characteristics and consequences of the phenomenon are discussed in the following subsections.

NONINVITATION AS AN ORGANIZED ACTION

Noninvitation could be considered mere absence of action.17,18 However, our findings suggest that failure to recruit stems from a set of reasons that investigators describe in rational terms. Therefore, the difference between selective and global noninvitation patterns argues in favor of considering noninvitation as an organized behavior, along with the knowledge that noninvitation stems from choices, thoughtful consideration of various factors, and perceived justifications. Noninvitation falls in the “seen but unnoticed” category of practices described by ethnomethodologists19; this practice is such an integral part of conducting clinical trials that it is taken for granted. Noninvitation crystallizes the subjectivity of investigators, which encompasses the perceptions of each investigator and the existence of the investigator as a subject striving for autonomy, freedom, and accountability, regardless of the rules that must be followed to conduct valid clinical research.

PRACTICAL AND ETHICAL IMPLICATIONS FOR CONDUCTING CLINICAL TRIALS

Noninvitation of eligible participants affects the conduct of clinical trials in many ways and should be investigated in specific studies. In addition to selection bias, noninvitation has several organizational consequences, about which little has been published. Therefore, global noninvitation should be differentiated from complete refusal to participate in a given protocol or type of protocol (typically protocols with a placebo arm), although the reported reasons may be the same, with both resulting in failure to conduct the study. When organizing multicenter trials, explicit refusal from 1 or more centers or investigators to participate is probably less harmful than if they do not invite patients after having agreed to participate. Explicit refusal gives the option of enrolling other centers that will actively participate. Inactive centers have a negative effect on the achievement of the recruitment schedule and are difficult to predict, which can be lethal for research because of an unexpected lack of subjects and the financial consequences of delay.

Noninvitation raises the following 2 ethical problems: (1) Patients (or families) who are not offered participation in the trial are deprived of equal access to trials (assuming that participation is viewed as beneficial) or of the opportunity to carry their fair share of the clinical research burden (assuming that participation is viewed as potentially harmful). (2) Failure to offer the trial infringes on the right of patient autonomy, as patients cannot consent to something that they do not know exists. In other words, noninvitation compromises the 2 major principles of research ethics, justice and autonomy, as delineated by ethics codes (initially published in the Belmont Report20). Despite protocol dilemmas, physicians who agree to participate in research should invite eligible patients without selection.

AVENUES FOR RESEARCH

The number of patients who are not invited to participate in a trial can be computed by subtracting from the number of eligible patients the number of included patients plus the number of patients who refused to participate. Noninvitation should be quantified and explained for each study protocol, whether or not inclusion objectives are met, as recommended in the Consolidated Standards of Reporting Trials (CONSORT) statement.21 The CONSORT requirements are not followed routinely, even by high-quality journals.22 The CONSORT criteria should be used for reporting all types of biomedical studies in humans. For many studies, the number of eligible patients can be estimated. Because the number of included patients is recorded for a study, recording the number of refusals allows computation of the number of patients who were not invited to participate. Therefore, the effect of noninvitation on inclusion rates and failure to meet inclusion objectives can be determined from the data obtained by calculating the number of refusals. This information could be used to develop means of improving recruitment practices and of achieving equal access among patients to trials.23 Because approval of a study by an institutional review board may be insufficient to convince potential investigators that a trial is ethical, increased communication with investigators is needed regarding the scientific value and ethical aspects of studies. Recruitment enhancement systems might also be set up (eg, routine invitations to participate by specially trained personnel working independently of the investigator).

The results of this study suggest an urgent need for investigations in this area. Quantitative studies are needed to document and explain noninvitation of eligible patients to participate in biomedical research studies in pediatrics and in other medical specialties.

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