

Participant and Parent Experiences in the Parenteral Insulin Arm of the Diabetes Prevention Trial for Type 1 Diabetes

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OBJECTIVE — To assess participant and parent experiences in the parenteral insulin arm of the Diabetes Prevention Trial for Type 1 Diabetes (DPT-1).

RESEARCH DESIGN AND METHODS — Before trial results were publicized, surveys were completed by 82 intervention participants (the intervention group) (who received annual 4-day insulin infusions and daily insulin injections), 81 closely monitored control subjects (the closely monitored group), and 135 parents of children in the trial.

RESULTS — Survey results suggest that participant perspective (adult, child, parent, and sex), study procedures, and group assignment have important implications when planning clinical trials. Parents rated the trial more favorably but worried about hypoglycemia and diabetes onset. Children had the least favorable reaction to the study. Parents preferred assignment to the intervention group; child/adult participants preferred assignment to the closely monitored group. The intervention group rated the annual 4-day insulin infusions more negatively than all other study procedures. Intervention group participants/parents reported poorer insulin injection adherence over the course of the study. Intervention group participants, parents, and female subjects expressed an interest in additional psychosocial support during the trial. Random assignment was viewed negatively by both study groups. Close observation for diabetes onset was viewed as the most favorable aspect of the study. Behaviors outside of the study protocol to prevent or delay diabetes onset were common and should be monitored in future prevention studies.

CONCLUSIONS — Overall, most participants were positive about the trial, and many expressed optimism about the intervention's potential for success. These results have implications for study design, recruitment, and retention procedures in future prevention trials.

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The Diabetes Prevention Trial for Type 1 Diabetes (DPT-1) tested whether insulin could prevent or delay type 1 diabetes onset in relatives of type 1 diabetic patients. There were two separate arms in the trial. Relatives with >50% risk of developing diabetes within 5 years were offered randomization to a closely monitored control condition (the

closely monitored group) or a parenteral insulin intervention (the intervention group) requiring annual hospitalizations for 4-day intravenous insulin infusions as well as twice-a-day low-dose insulin injections administered at home. Relatives with a 5-year risk of 26–50% were offered randomization to oral insulin therapy or a placebo (1).

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Abbreviations: DPT-1, Diabetes Prevention Trial for Type 1 Diabetes; OGTT, oral glucose tolerance test. A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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The design of prevention trials like the DPT-1 often involve tension between scientific considerations as to what interventions should be tested and practical and ethical concerns about the demands placed on trial participants. This tension is usually resolved based on investigators' experiences conducting similar studies, since there are very little data from trial participants per se. Documenting participant experiences in prevention trials is particularly important when the trial involves children and the trial procedures are difficult or painful. Although parenteral insulin failed to prevent or delay type 1 diabetes in the DPT-1 (1), study participant reports of their trial experiences could help inform investigators designing future trials and provide important information to future potential subjects who are asked to join a trial. To collect this type of information, DPT-1 participants were asked to complete a survey about their study experiences at the end of the trial, before the results were known. We report here the survey responses of participants in the parenteral arm of the DPT-1.

RESEARCH DESIGN AND METHODS

Survey development

A survey (fifth-grade reading level) was developed to address the following: 1) distress at the beginning of the trial, 2) decision-making around trial participation, 3) reactions to group (intervention or closely monitored) assignment, 4) reactions to study procedures, 5) adherence with study demands, 6) efforts to prevent diabetes, 7) need for psychological support, and 8) beliefs about the use of parenteral insulin to prevent or delay type 1 diabetes.

Each of the nine U.S. DPT-1 centers obtained institutional review board approval to administer the surveys to participants ≥10 years of age and to parents of participants <18 years old at the start of the study. Survey completion was voluntary and confidential. For participants aged 10–17 years, the child's parent decided whether the survey should be given

to the child. Every effort was made to administer surveys at the end of the trial before study results were publicized.

Because knowledge of the trial results could bias response, only surveys of participants and parents who reported no knowledge of trial results were analyzed (82 intervention and 81 closely monitored participants, representing 54% of all participants aged ≥ 10 years at trial's end and 107 parents [67 mothers, 40 fathers] of 67 intervention group children and 128 parents [71 mothers, 57 fathers] of 86 closely monitored group children, representing 72% of participants who began the trial as children). As expected, survey participants were older (intervention group $M = 22.7 \pm 12.0$; closely monitored group $M = 20.5 \pm 11.4$) than the full-trial participants (intervention group $M = 18.8 \pm 10.7$; closely monitored group $M = 18.6 \pm 10.2$), since surveys were given only to those aged ≥ 10 years. Fifty-one percent of the survey respondents were female, comparable with the 48% female participation rate in the full trial.

Data analysis

Survey item frequency distributions were reviewed, and, where appropriate, item responses were recoded to normalize the data. Highly correlated items were grouped into multiple item scales. *t* tests, repeated-measures ANOVA, and multiple/logistic regression techniques were used to test study protocol (study group and study procedure) and respondent (participant age, participant versus parent, and sex) effects.

RESULTS

Distress at the beginning of the trial

Most participants (78% intervention group and 80% closely monitored group) and parents (95%) reported being upset with the news of their own or their child's increased diabetes risk. On a 0- to 3-point scale (0 = not upset at all, 3 = very upset), parents ($M = 2.15 \pm 0.88$) were more upset than participants ($M = 1.41 \pm 0.97$; t [380] = 7.72; $P < 0.001$), and mothers ($M = 2.30 \pm 0.85$) were more upset than fathers ($M = 1.95 \pm 0.89$; t [232] = 3.04; $P < 0.01$). Similarly, most participants (59%) and parents (55%) acknowledged being scared when they started the study. On the 5-point scale (1 = very happy, 5 = very scared), fathers ($M = 3.32 \pm 0.88$) were less scared than mothers ($M = 3.67 \pm 0.89$; t

[230] = 2.94; $P < 0.01$) or participants ($M = 3.54 \pm 0.81$; t [243] = 2.02; $P < 0.05$).

Decision to participate in the trial

On a scale from 1 (very easy) to 5 (very hard), respondents described the decision to participate in the trial as relatively easy ($M = 2.40 \pm 1.06$). Although the decision to participate was made before random assignment to study groups, those assigned to the intervention group ($M = 2.54 \pm 1.13$) recalled the decision to participate as more difficult than the closely monitored group respondents ($M = 2.27 \pm 0.98$; F [1,379] = 6.28; $P < 0.05$). Only 10% of participants and 13% of parents reported that there was a family member who opposed trial participation.

Reactions to group (intervention or closely monitored) assignment

The survey asked two questions about study group assignment (how glad/sad they were with their assignment and whether they wished they had been assigned to the other study group), which were highly correlated ($r = 0.68$, $P < 0.001$) and combined into a single 3-point scale (0 = positive, 1 = negative, and 2 = very negative). Closely monitored group participants had more positive reactions ($M = 0.44 \pm 0.63$) to their assignment than intervention group participants ($M = 0.80 \pm 0.66$; t [158] = 3.61; $P < 0.001$). Among closely monitored group participants, 70% were "glad" or "very glad" about their study assignment; only 35% sometimes wished they had been assigned to the intervention group. In contrast, only 21% of intervention participants were glad or very glad about their assignment; 47% sometimes wished they were assigned to the closely monitored condition. The opposite finding emerged for parents. Intervention group parents ($M = 0.46 \pm 0.57$) had more positive reactions than the closely monitored group parents ($M = 1.10 \pm 0.73$) to study group assignment (t [233] = 7.30; $P < 0.001$). Among intervention group parents, 53% were glad or very glad about their child's assignment; only 25% sometimes wished their child had been assigned to the closely monitored condition. In contrast, few closely monitored group parents reported being glad (27%) about their child's assignment; the majority (74%) sometimes wished the child had been placed in the intervention group.

Reactions to study procedures

Each respondent answered three questions about each study procedure (how much it hurt, how difficult it was, and how much they disliked it). Answers to the three questions were highly correlated for a given procedure (α ranged from 0.59 for the oral glucose tolerance test [OGTT] to 0.71 for the 4-day insulin infusion) and were combined into a single measure of procedure distress (0 = no distress, 1 = some distress, and 2 = great distress). Each participant or parent was also asked whether he or she would be willing to participate in a future study with the same procedure (0 = no, 1 = maybe, and 2 = yes).

Study procedure distress. All participants experienced two study procedures: OGTT every 6 months and finger sticks for blood glucose tests every 3 months. Both participants and parents rated the OGTT ($M = 0.96 \pm 0.47$) as more distressing than finger sticks ($M = 0.75 \pm 0.41$; F [1,392] = 67.7; $P < 0.001$). The intervention group also experienced an annual 4-day insulin infusion and daily insulin injections. Respondents rated the OGTT ($M = 0.94 \pm 0.43$) and the 4-day insulin infusion ($M = 0.96 \pm 0.56$) as more distressing than insulin injections ($M = 0.62 \pm 0.46$) or finger sticks ($M = 0.77 \pm 0.39$; F [3,552] = 30.47; $P < 0.001$). However, parents rated insulin injections as less distressing ($M = 0.50 \pm 0.41$) than participants ($M = 0.78 \pm 0.48$; t [185] = 4.43; $P < 0.001$). Further, adult participants ($M = 1.19 \pm 0.51$) rated the 4-day insulin infusion as more distressing than child participants ($M = 0.86 \pm 0.54$; t [80] = 2.84; $P < 0.01$).

Willingness to be in another study with similar procedures. Willingness to participate in another study with the same procedure provides a good overall indicator of respondent reaction to each study procedure, including random assignment. Fig. 1 depicts the percentage of respondents answering "yes" by study procedure for parents, all participants, and for participants who were children (aged < 18 years) versus those who were adults (aged ≥ 18 years).

All study participants experienced three study procedures: random assignment, OGTT, and finger sticks. Respondents were most willing to be in another study involving finger sticks and least willing to participate in another study involving random assignment (F [2,682] = 29.65; $P < 0.001$). However, parents were more willing to participate in an-

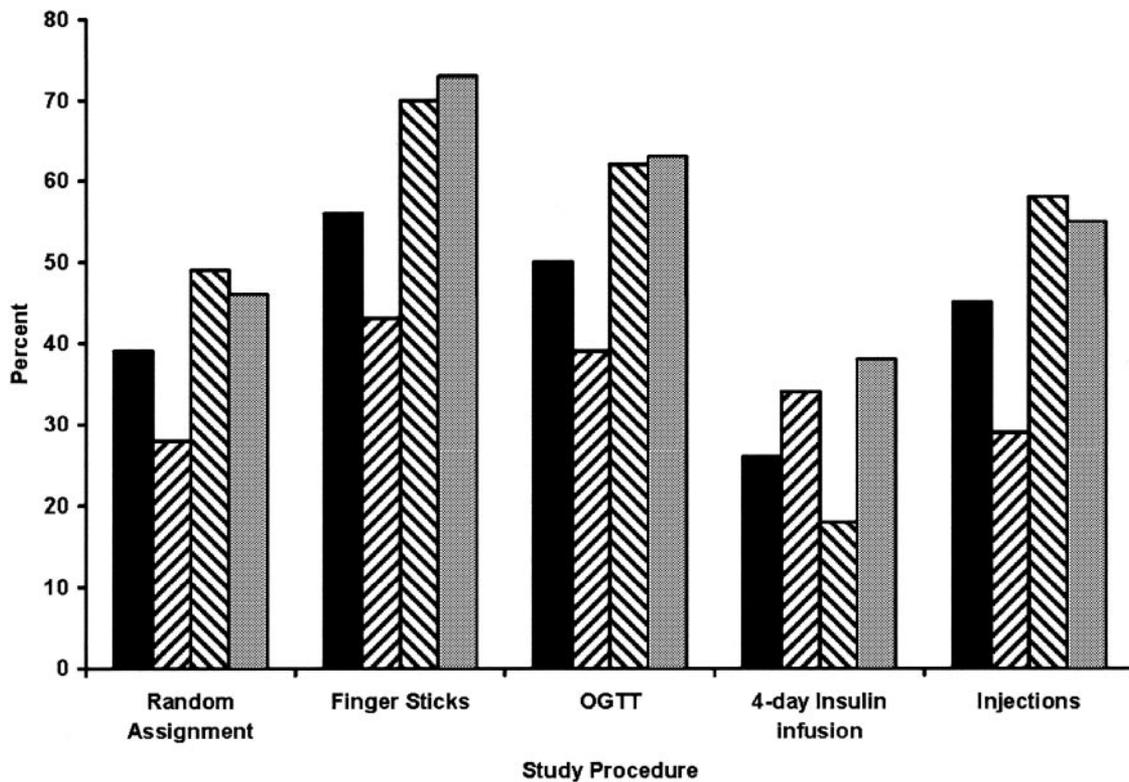


Figure 1—Percent of participants and parents willing to be in another study by study procedure. ■, all participants; ▨, child participants; ▩, adult participants; ▪, parents.

other study with any of these three procedures compared with participants ($F [1,341] = 11.75$; $P < 0.001$).

The intervention group participants experienced two additional study procedures: annual 4-day insulin infusions and daily insulin injections. Respondents were most willing to be in another study involving finger sticks and were least willing to be in another study involving 4-day insulin infusions and random assignment ($F [4,568] = 20.39$; $P < 0.001$). Again, intervention group parents were more willing to be in another study involving any of the study procedures compared with intervention group participants ($F [1,142] = 11.60$; $P < 0.001$). However, adult participants were more willing to be in another study than child participants ($P < 0.05$). In fact, adult participants were comparable with parents for all study procedures except the 4-day insulin infusion, which they rated less favorably. In contrast, child participants differed from adult participants and parents on all procedures except the 4-day insulin infusion, which they rated more favorably than adult participants (see Fig. 1).

The worst and best parts of the study

Asking respondents to select the single worst and best part of the study was another method used to identify procedures that were perceived to be particularly difficult or beneficial. For intervention group participants, the 4-day insulin infusion was selected most often as the study's worst aspect (37%), followed by worrying about getting diabetes (18%), finger sticks (12%), and insulin injections (10%). For the closely monitored group participants, the OGTT (38%) or worrying about getting diabetes (31%) was selected most often. Among parents, worrying about the child getting diabetes was most often selected as the worst aspect of the study (58%), a choice made significantly more frequently among parents than participants (Wald = 39.6; $P < 0.001$). Parents also selected the 4-day insulin infusion (24% of intervention group parents), the OGTT (17%), and study group assignment (15% of closely monitored group parents) as the worst part of the study. Most participants (58%) and parents (78%) stated that the best part of the study was being observed for the possible development of type 1 diabetes.

Adherence with study procedures

Blood glucose testing. All study participants were asked to do finger sticks every 3 months. Intervention group participants were also asked to test if they suspected hypoglycemia. Blood glucose testing frequency reports were converted to a 4-point scale (0 = testing every 6 months or less, 1 = testing every 3 months, 2 = testing monthly or weekly, and 3 = testing every day). At the beginning of the study, intervention group respondents ($M = 1.50 \pm 0.96$) reported doing more tests than closely monitored group respondents ($M = 1.10 \pm 0.71$; $t [317] = 4.24$; $P < 0.001$). Most (70%) closely monitored group respondents reported testing once every 3 months, consistent with the study protocol. In contrast, 43% of intervention group participants and 52% of intervention group parents reported testing every 3 months, but another 43% of participants and 38% of parents reported testing more often.

By the end of the study, blood glucose testing declined for the intervention group participants ($M = 1.27 \pm 1.14$) and increased for the closely monitored group participants ($M = 1.42 \pm 1.20$; $F [1,309] = 9.85$; $P < 0.01$). Parents, re-

ardless of study group, reported an increase in testing ($F [1,309] = 4.42; P < 0.05$). Child participants also reported an increase in testing over time, while adult participants reported a decline ($F [1,130] = 20.52; P < 0.001$).

Twice-daily insulin injections (intervention group only). Intervention group participants were instructed to administer a low dose of long-acting ultralente insulin each day before breakfast and before bed. Respondents were asked how often injections were missed in a normal week at the beginning and end of the study. The mean number of injections missed per week by participant report was 1.03 ± 2.42 at the study's beginning and 3.52 ± 5.15 at study end, a significant increase ($t [71] = 4.33; P < 0.001$). The number of injections missed per week by parent report also increased over the course of the study (1.04 ± 2.29 injections missed at study beginning and 2.34 ± 4.10 at study end; $t [81] = 3.46; P < 0.001$). At study end, 15% of participants and 7% of parents reported that the participant was not taking any injections at all. There were no significant differences in reported number of missed injections between parents and participants or between child and adult participants. In fact, in the 33 cases where both a mother and her child completed the survey, the correlation between mother and child report ($r = 0.82$ at study beginning and 0.96 at study end) was excellent.

Concerns about hypoglycemia (intervention group only)

Many (44%) intervention group participants and most (82%) intervention group parents worried about hypoglycemia, a statistically significant difference ($t [184] = 5.44; P < 0.001$). Worry was not associated with poorer insulin injection adherence. However, parental fear of hypoglycemia was associated with increased blood glucose testing at study beginning ($r = 0.29, P < 0.01$) and end ($r = 0.20, P < 0.07$).

Efforts to prevent diabetes onset

Approximately half of participants (57%) and parents (48%) reported doing something to delay or prevent diabetes onset. Participants were more likely to report diet (47%), exercise (28%), and stress reduction (10%) changes compared with parents (36% diet, 14% exercise, and 3% stress reduction; all Wald tests $>3.72; P < 0.05$). More closely monitored group respondents (17%) reported using vita-

mins and other alternative medicines than intervention group respondents (10%; Wald = 4.07; $P < 0.05$).

Need for psychological support

Two survey items examined whether respondents would have liked the opportunity to see a counselor or share their experiences with other study participants. More parents (16% yes, 27% maybe) than participants (7% yes, 20% maybe) expressed interest in speaking to a counselor (Wald = 9.94; $P < 0.01$). More participants/parents in the intervention (15% yes, 27% maybe) compared with the closely monitored (10% yes, 22% maybe) group also expressed interest in speaking to a counselor (Wald = 4.45; $P < 0.05$). Female participants/parents (16% yes, 26% maybe) were more interested in speaking to a counselor than male participants/parents (8% yes, 22% maybe) (Wald = 5.13; $P < 0.05$). Female participants/parents (37% yes, 34% maybe) were also more likely to express an interest in meeting with other study participants than male participants (21% yes, 38% maybe) (Wald = 8.40; $P < 0.01$).

Overall reaction to study participation

Three survey items examined overall reactions to study participation: "Overall, how do you feel about being in the DPT-1?" (0 = liked it a lot, 1 = neutral, and 2 = disliked it a lot), "Do you think being in the DPT-1 was a good decision?" (0 = a great decision, 1 = neutral, and 2 = a bad decision), and "Would you recommend it to a friend?" (0 = yes, 1 = maybe, and 2 = no). The items were highly correlated ($\alpha = 0.75$) and were combined into a single score. Participants expressed generally positive views toward the trial. Only 14% of participants and 3% of parents stated they disliked the trial, 3% of participants and 1% of parents thought it was a bad decision to participate, and 13% of participants and 3% of parents would not recommend the trial to a friend. Parents ($M = 0.28 \pm 0.38$) were more favorable than participants ($M = 0.55 \pm 0.58; t [395] = 5.56; P < 0.001$), and adult participants ($M = 0.39 \pm 0.49$) were more favorable than child participants ($M = 0.69 \pm 0.63; t [161] = 3.37; P < 0.001$).

Beliefs about the use of insulin injections to stop or delay diabetes onset

Two items assessed views about insulin injections as a method to stop or delay diabetes onset. Both were rated on a 3-point scale (0 = no, 1 = don't know or maybe, and 2 = yes). Intervention group respondents ($M = 1.12 \pm 0.47$) were more confident that insulin could stop diabetes onset compared with closely monitored group respondents ($M = 0.84 \pm 0.59; t [369] = 5.05; P < 0.001$). Parents were more likely to believe that insulin could stop ($M = 1.03 \pm 0.52$) or delay ($M = 1.14 \pm 0.48$) diabetes onset compared with participants ($M = 0.84 \pm 0.60$ for stop; $t [369] = 3.30; P < 0.001$; and $M = 1.02 \pm 0.56; t [369] = 2.23; P < 0.05$ for delay). Child participants (aged <18 years) ($M = 1.15 \pm 0.61$) were more confident that insulin could delay diabetes onset than adult participants ($M = 0.90 \pm 0.49; t [134] = 2.65; P < 0.01$).

CONCLUSIONS— Our data suggest that study group assignment, study procedures, and whether the respondent is an adult, child, parent, male, or female all have important implications for trial design and subject recruitment. Parents generally viewed the trial more positively; they rated the trial overall more favorably and were more likely to agree to another study with similar procedures. They were also more optimistic that the study intervention could prevent or delay diabetes onset. However, parents were also more distressed at the news of the child's increased risk, were more likely to worry about hypoglycemia, were more likely to express a desire to speak to a counselor during the trial, and were more worried about the child getting diabetes. Mothers, in particular, acknowledged considerable distress and fear at the beginning of the trial and were more likely to express a desire to speak to a counselor or meet with other study participants. These findings suggest that future trials targeting parents of young children may find a favorable response even when the trial procedures are demanding, although parental fears and need for psychosocial support may need specific attention.

Children were less favorable about their experiences than adult participants and parents and were less likely to agree to be in another similar study. The Office of Human Research Protection requires that children assent to research when "they are capable of providing it," al-

though this requirement can be waived in some instances (2). Age of assent is often as young as 7 years (3). While parents may agree to trials like the DPT-1, children may be less willing, raising practical questions about how to provide children the right of assent or refusal when their parents are strongly in favor of trial participation.

Certain study procedures generated more distress than others. The annual 4-day insulin infusion was selected as the worst aspect of the study by 37% of intervention group participants and 24% of intervention group parents. Interestingly, adult participants were particularly negative; only 18% would agree to be in another trial with this as part of the study protocol. Although parents and children were more favorable, only one-third would agree to another study involving insulin infusions. Participants also rated insulin injections as more distressing than parents. Children were particularly negative; only 29% stated they would be in another study involving daily injections. In contrast, a majority of adult participants and parents would agree to such a procedure.

Random assignment was also viewed negatively, with less than one-half of those surveyed indicating they would be in a future study using this methodology. Other studies have reported that random assignment is poorly understood by study participants (4,5), suggesting that this is a potential barrier to future study recruitment. Improved educational methods to clarify the purpose and benefits of random assignment need to be developed not only for trial participants but for the public at large.

While study participants preferred assignment to the closely monitored group, parents strongly preferred the insulin intervention group, highlighting the very different perspectives and expectations parents and participants have to study group assignment. Compared with participants, parents were more likely to believe that insulin could stop or delay diabetes onset, which may explain their preference for the intervention group. It is clear that both parents and participants have strong opinions about study group assignment and the method used to make that assignment. Both need to be given careful consideration in the design of future prevention trials.

Although parents preferred the intervention group, this did not mean that they found the intervention group protocol

easy. Compared with the closely monitored group, more intervention group respondents expressed a desire to speak to a counselor during the trial and recalled the decision to participate in the trial as more difficult. This latter finding is interesting because it suggests that intervention arm participation biases recall of the difficulty respondents had in making the decision to join the trial, a decision that was made before group assignment. Future trials with demanding protocols should give serious consideration to the provision of psychosocial support.

Most intervention group respondents acknowledged difficulty maintaining the study's twice-daily insulin injection requirement. At study's end, participants reported an average of 3.5 missed injections per week and 15% stated they were not taking any insulin. This may be an underestimation of the number of missed injections since survey participants probably represent the most dedicated DPT-1 subjects. The impact of intervention group participants' failure to receive the amount of insulin prescribed in the study protocol on the trial's power to assess insulin injections as a diabetes prevention strategy remains unknown. However, it seems clear that adherence with daily study demands is likely to decline over time, and future trials need to put procedures in place to monitor and address this problem.

Blood glucose testing also declined among adult participants and among those in the intervention group. In contrast, both children and parents reported an increase in testing. Intervention group participants may have tested more often at the study's beginning due to hypoglycemia concerns, concerns that likely dissipated over time, particularly for adults. Parents may test children more often in an effort to detect possible hypoglycemia in the intervention group or diabetes onset in the closely monitored group. In fact, parental fear of hypoglycemia was associated with increased blood glucose testing throughout the study. Previous reports (6,7) document parental blood glucose monitoring of unaffected siblings in families with a diabetic child, a finding similar to the increased blood glucose testing reported in the closely monitored group. Finger stick was the study procedure rated as least distressing and most acceptable as part of a future trial, suggesting that it may be easily accepted as part of future diabetes prevention studies.

Interestingly, most participants in

both study groups initiated behaviors outside of the study protocol to try to prevent diabetes. Disease prevention efforts have been previously reported in high-risk individuals (6,8). Since unknown environmental triggers are thought to play a role in type 1 diabetes onset in genetically at-risk individuals (9), such behavior may undermine the integrity of any trial.

Despite the rigors and length of the DPT-1 (median 3.7 years), >80% of participants and >95% of parents stated that they liked participating, felt it was a good decision, and would recommend the study to a friend. The majority felt the best part of the trial was knowing that someone was observing the participant for possible development of type 1 diabetes. Many respondents also had favorable views of the potential impact of the study intervention (twice-daily insulin injections) on the delay or prevention of the disease. Other investigators have reported similar results (10).

It is important to recognize this study's limitations. Only participants aged ≥ 10 years were surveyed; we are unable to comment on the experiences of younger children except from their parents' point of view. Since not all eligible participants and parents completed the survey, survey responses may not be representative of the full trial nor do they represent the opinions of individuals who were offered trial participation but refused. Further, since the DPT-1 recruited participants from relatives of patients with type 1 diabetes, the survey findings may not be applicable to studies recruiting from the general population. However, the survey results are clearly relevant to planning and recruitment for prevention and new-onset studies to be conducted by Type 1 Diabetes TrialNet, the successor study group to DPT-1.

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References

1. Diabetes Prevention Trial Type 1 Diabetes Study Group: Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med* 346:1685–1691, 2002
2. National Institutes of Health, Office of Extramural Research: OER human subjects Web site: research involving children HHS regulatory requirements for research

- involving children described in subpart D [article online], 2007. Available from <http://grants2.nih.gov/grants/policy/hs/children1.htm>. Accessed 26 March 2007
3. National Cancer Institute: Children's assent to clinical trial participation [article online], 2007. Available from <http://www.cancer.gov/clinicaltrials/understanding/childrensassent0101>. Accessed 26 March 2007
 4. Eiser C, Davies H, Jenney M, Glaser A: Mothers' attitudes to the randomized controlled trial (RCT): the case of acute lymphoblastic leukaemia (ALL) in children. *Child Care Health Dev* 31:517–523, 2005
 5. Greenley RN, Drotar D, Zyzanski SJ, Kordish E: Stability of parental understanding of random assignment in childhood leukemia trials: an empirical examination of informed consent. *J Clin Oncol* 24:891–897, 2006
 6. Baughcum A, Johnson SB, Carmichael S, Lewin A, She J-X, Schatz D: Maternal efforts to prevent type 1 diabetes in at-risk children. *Diabetes Care* 28:916–921, 2005
 7. Lucidarme N, Domingues-Muriel E, Castro D, Czernichow P, Levy-Marshall C: Appraisal and implications of predictive testing for insulin-dependent diabetes mellitus. *Diabetes Metab* 23:550–553, 1998
 8. Johnson SB, Tercyak K: Psychological impact of islet cell antibody screening for IDDM on children, adults, and their family members. *Diabetes Care* 18:1370–1372, 1995.
 9. Knip M, Veijola R, Virtanen SM, Hyoty H, Vaarala O, Akerblom HK: Environmental triggers and determinants of type 1 diabetes. *Diabetes* 54 (Suppl. 2):S125–S136, 2005
 10. Tercyak K, Johnson SB, Schatz D: Patient and family reflections on the use of subcutaneous insulin to prevent diabetes: a retrospective evaluation from a pilot prevention trial. *J Diabetes Complications* 12: 279–286, 1998