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Recruiting young pre-symptomatic children for a clinical trial in type 1 diabetes: Insights from the Fr1da insulin intervention study

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ABSTRACT

Background: Although detection of children at high risk of developing type 1 diabetes and diagnosis of early stages is possible, up to now there exists no approved therapy to delay or prevent type 1 diabetes. Thus it is vital to develop evidence-based interventions. For this a sufficient number of trial participants is crucial but difficult to obtain especially in asymptomatic children.

Aim: Identifying family characteristics that lead to or impede trial participation and analyze reasons stated by families for non-participation.

Methods: Participants for the Fr1da Insulin Intervention study are recruited from the Fr1da study, a population based screening for early stage type 1 diabetes in Bavaria. Families with eligible children were invited to enroll. We analyzed sex and age of the child, distance of the family to the study center in Munich and the existence of a first degree family member with type 1 as possible influential factors for study participation. We also analyzed reasons stated by families who declined study participation in a phone interview.

Results: Of 146 eligible children 77 (53%) were enrolled into the trial. None of the tested family characteristics differed significantly between the enrolling and the families not participating, but in general enrolling families lived closer to the study site than families not participating. This is also reflected in the reasons given by non-participating families. The most frequent reason stated were time restrictions. The second most frequent reason

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was the venous blood draw.
Conclusion: The factors for non-participation identified in this project need be taken into account for the design of future trials in young children to ensure proper recruitment and thus to generate valid results for medical treatment of children. More research on the reason of participation and non-participation in clinical trials is needed.

1. Introduction

Recruitment of research participants into pediatric clinical trials is a major issue that investigators and sponsors have to tackle. The pool of eligible children is often small, and the threshold for gaining consent is often higher and more complex because parents have to make decisions about trial participation on behalf of their child.

Nevertheless, recruitment of patients into clinical trials is crucial for reaching target sample size and being able to test the trial hypotheses with adequate power. Only with a sufficient number of participants it is possible to provide evidence-based results for the development of therapies and medical strategies for several diseases like type 1 diabetes in children.

While there is quite some insight into recruitment practices and problems in adults [1–4], especially for severe diseases like cancer [5–7], evidence on successful techniques of increasing recruitment numbers is still sparse [8,9].

This is even more true for pediatric trials recruiting infants. Recruitment strategies [10] and participant characteristics that predict recruitment are rarely reported [11]. For preventive trials in asymptomatic children the problem of slow recruitment seems to be even more evident [12] but not much information is available on this topic.

In the Fr1da Insulin Intervention study children with early type 1 diabetes receive oral insulin or placebo for 12 months as a secondary prevention in order to test immune efficacy of oral insulin up to a dose of 67.5 mg. Early type 1 diabetes is characterized by multiple islet autoantibodies. The dose of oral insulin was defined in a preceding pilot study (Pre-Point) that demonstrated that this dose resulted in an immune response with signs of T cell regulation [13].

Almost all children eligible for the trial will develop symptomatic T1D in the near future [14]. While T1D is well treatable, it still comes with significant restrictions due to disease-specific problems for children [15] and their parents [16]. Despite that recruitment into the trial was slower than expected. Here we cover the difficulties in recruitment of children and their parents for participation in the study.

2. Methods

The first step of the project is a population based screening for early stage type 1 diabetes - the Fr1da study (ethics no.: 70/14) [17]. Inclusion criteria were:

1. The child is between 2 and 5 years old
2. The child is living in Bavaria, Germany.

The screening is offered by primary care and has been established in January 2015. It is still ongoing and aiming to include 100,000 children. The concept of the Fr1da study was published by Raab et al. [18].

In a second step all children participating in the screening and diagnosed with antibodies to glutamic acid decarboxylase (GAD65), to insulin (IAA), autoantibodies to IA-2 (IA2A), or autoantibodies to zink transporter 8 (ZnT8A) are asked to participate in the Fr1da Insulin Intervention trial. Parents were contacted to schedule an appointment for an initial visit.

The Fr1da Insulin Intervention study is a randomized, placebo-controlled, double-blind, mono-center secondary intervention study of high-dose oral insulin to delay or prevent clinical symptomatic type 1 diabetes (clinicaltrials.gov NCT02620072).

A child is eligible for the Fr1da Insulin Intervention trial if it:

1. is two to 12 years old
2. has at least two confirmed positive islet autoantibodies out of GADA, IAA, IA2A, or ZnT8A and time between screening sample collection and randomization did not exceed 90 days.
3. has a normal glucose tolerance after an oral glucose tolerance test. Normal glucose tolerance is defined as fasting glucose < 110 mg/dl, and a glucose level 2 h after ingestion of oral glucose < 140 mg/dl, and intermediate glucose levels at 30 min and 60 min and 90 min after ingestion of oral glucose < 200 mg/dl.

Included children are randomized to the insulin or placebo group in a 1:1 ratio. The allocated study capsules are administered for 12 months as powder spotted on food. Children who completed the intervention period and who have not developed type 1 diabetes will be continued to be monitored for at least one year and a maximum of 7 years. Study related burdens are daily administration of insulin powder in food over 12 months and five study visits during the one-year intervention period at the study site in Munich, taking approximately 2.5 h including a physical examination, a saliva sample and a venous blood draw with five sampling times. Additionally, an OGTT is performed and stool is collected every six months. After the intervention period families are asked to visit the study site every six months. During each visit an OGTT will be performed. During the whole observation period families are asked to document adverse events and additional medications.

This manuscript consists of two main analyses:

1. Parents of eligible children who did not agree to participate in the trial were called and asked for reasons for their non-participation. The reasons given by the parents were categorized. Percentages, medians and ranges were calculated according to the data type.
2. We analyzed sex and age of the child, distance of the family to the study center in Munich and the existence of a first degree family member with type 1 diabetes of all eligible children. To identify if those factors were influencing the participation in the trial we calculated a logistic regression model. From this model we calculated Odds Ratios and the respective 95% confidence limits and the p

Table 1
Baseline characteristics of eligible patients and Odds Ratios and p values from the logistic regression model.

	All	Participating	Not participating	Odds ratio (95% CI)	P value
N	146	77	69	–	–
Median Age in years (Min-Max)	4 (2–10)	4 (2–10)	4 (2–10)	1.09 (0.88–1.35)	0.4511
Male sex, n (%)	84 (58)	43 (56)	41 (59)	0.78 (0.39–1.53)	0.4633
First degree relative with type 1 diabetes, n (%)	21 (14)	12 (16)	9 (13)	0.98 (0.36–2.66)	0.9685
Median distance to study center in km (Min-Max)	88 (0–270)	68 (0–270)	88 (0–270)	1.00 (0.99–1)	0.0699

values of the Wald test.

3. Results

Overall, by January 2018 72,192 children were screened in the context of the Fr1da-study and 146 Fr1da children who were eligible according to the inclusion criteria were invited to participate in the Fr1da Insulin Intervention trial. Of those 77 (53%) were eventually enrolled in the study. Baseline characteristics are described in Table 1. Neither the age of the child nor sex, distance to the study center or a first degree relative with type 1 diabetes had a significant influence on the decision to participate in the study.

The parents who declined trial participation for their children were asked for the main reason on the phone. Of 69 families who did not participate in the study 61 responded to the call (Fig. 1). Table 2 summarizes the reasons given by the parents for not participating in the study.

Most parents stated time issues as their main reason for refusal (36%). Regarding this, families state long travelling distance especially if they have more children. Consequentially, only 19% of the families from Munich state time as the main reason for non-participation while 42% of families do so who need to travel longer. The second most frequent reason for refusal was the venous blood draw (30%). 11% of parents did not specify their decision. 8% of the parents were still undecided whether they should agree to participate in the study. These parents will be contacted again. 7% of the parents were not convinced of the concept of the study and stated no need to participate in an intervention trial to prevent type 1 diabetes. The same number defined the possibility to receive placebo as main reason for refusal. Just one family did not want to be contacted by the study team.

4. Discussion

Participants of randomized clinical trials (RCTs), including those assigned to placebo, have outcomes similar to or better than those of eligible non-participants. In the case of type 1 diabetes, participants may have lower complication rates at disease onset with a significant reduction in the frequency of diabetic ketoacidosis, a better long term metabolic control, and a reduction in hospitalization rates compared to children outside of RCTs [19].

Continuous monitoring of the blood glucose as part of the Fr1da Insulin Intervention study prevents undiscovered changes in glucose metabolism. Medical attendance and training by the study team provides the families with information about the disease and facilitates coping with type 1 diabetes, especially for families with no experience concerning the disease. Taken together participation in the Fr1da Insulin Intervention study might result in an improved medical care [20–22]. Also, the intervention with high-dose oral insulin was shown to be safe in the Pre-POINT study [12], in the Pre-POINT Early study (clinicaltrials.gov NCT02547519) and in the TrialNet TN20 trial (clinicaltrials.gov NCT02580877) using an even higher dose (ADA oral presentation 2017). Thus it seems surprising that almost half of the parents of eligible children who were informed of the study did not enroll their children.

Neither age nor sex of the child nor a relative with type 1 diabetes influenced parental decision on trial participation. Also the use of placebo in the control group was not a major reason for non-participation as it was reported in other research [23]. The two main reasons for non-participation were time restrictions and the venous blood draw. Time restriction is also mirrored in the distance to study center. Families enrolling in the trial lived closer to the study site than families refusing to enroll. Especially families with more than one child were reluctant to enroll if they needed to travel longer and study participation would use up a lot of time, also because older children miss school and have to catch up missed material.

Non-enrolling families stating as their main reason the venous blood-draw often reported either negative experiences with previous venous blood draws or a general reluctance regarding such interventions. As soon as the induction of immune efficacy and immune regulation using oral insulin at a dose of 67.5 mg has been demonstrated in this secondary prevention study, future studies may be able to replace venous blood draws by a capillary blood test thereby facilitating easier recruitment to this type of studies.

A limitation of our work is that we unfortunately do not have more information on families to explore reasons for non-participation in more detail such as socioeconomic status, parental education or length of the initial information visit that were shown to be relevant for participation in other studies [11,24].

A French review on the topic of recruitment in pediatric clinical trials reports much lower rates of non-participation (median refusal rate 12.5%) [24] than we saw in the Fr1da insulin intervention trial (47%). This might in part be due to the structure of the study but could also reflect some pre-selection occurring in other trials. Usually there are two barriers to trial participation: which eligible families are approached by the doctor and do these families agree to enroll. In our scenario with a population based screening without any preselection as a prerequisite to trial inclusion we see that efforts to inform families better about the benefits and lower the burden of clinical trials could result in much higher rates of study participation.

5. Conclusions

This project shows the lack of information on the reasons why families decline or agree to enroll their children into clinical trials and points out why it is important to identify factors that impede trial participation in children. The factors identified in this study were mainly time restrictions and the venous blood draw. These factors may be taken into account for future designs of trials in pediatric population, or be taken up in awareness and education programs to better inform

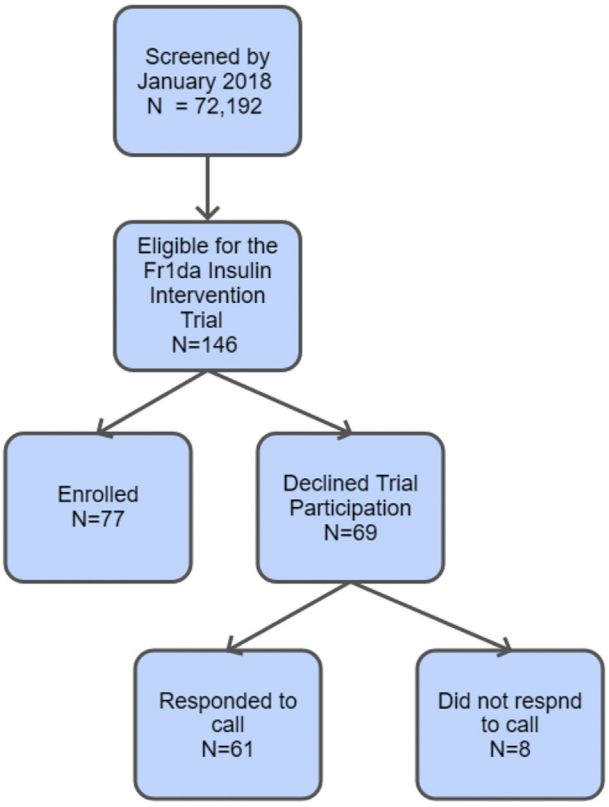

Fig. 1. Flowchart of the transfer of children from the Fr1da screening to the Fr1da Insulin Intervention Trial.

Table 2
Recruitment of participants for the Fr1da Insulin Intervention study.

reason for non-participation	total number of families (N = 61)	percentage (%)
time restriction	22	36
venous blood draw	18	30
without specification	7	11
still undecided	5	8
placebo	4	7
no need to participate	4	7
contact undesirable	1	2

families of the necessity and impact of certain trial elements. To maximize the benefit for participating children and the scientific community the benefits for parents and their children have to be highlighted: currently there is no known treatment to prevent or delay type 1 diabetes in children or adults but study participants will have the opportunity to access a promising treatment to delay or even avoid clinical symptomatic diabetes [25].

Declarations of conflicts of interest

The authors declare that they do not have any conflicts of interest.

Trial registration number and trial register

Fr1da study (approval by a local ethics committee in Germany (Ethikkommission der Fakultät für Medizin der Technischen Universität München, reference number: 70/14).

Fr1da-Insulin-Intervention Study (EudraCT-no.: 2015-003028-30; Clinicaltrials. gov Identifier: NCT02620072; approval by a local ethics committee in Germany (Ethikkommission der Fakultät für Medizin der Technischen Universität München, reference number: 420/15Af)).

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.conctc.2018.08.004.

References

[1] N.S. Abraham, J.M. Young, M.J. Solomon, A systematic review of reasons for nonentry of eligible patients into surgical randomized controlled trials, Surgery 139 (4) (2006) 469–483.
[2] J.M. Watson, D.J. Torgerson, Increasing recruitment to randomised trials: a review of randomised controlled trials, BMC Med. Res. Meth. 6 (2006) 34.
[3] P.H. Caldwell, S. Hamilton, A. Tan, J.C. Craig, Strategies for increasing recruitment to randomised controlled trials: systematic review, PLoS Medicine 7 (11) (2010) e1000368.
[4] B. Carlisle, J. Kimmelman, T. Ramsay, N. MacKinnon, Unsuccessful trial accrual and human subjects protections: an empirical analysis of recently closed trials, Clin. Trials 12 (1) (2015) 77–83.
[5] E.J. Mills, D. Seely, B. Rachlis, L. Griffith, P. Wu, K. Wilson, et al., Barriers to participation in clinical trials of cancer: a meta-analysis and systematic review of patient-reported factors, Lancet Oncol. 7 (2) (2006) 141–148.
[6] A.L. Dias, J.H. Chao, D. Lee, Y. Wu, G.H. Kloecker, Patient perceptions concerning clinical trials in oncology patients, Contemporary Clinical Trials Communications 4 (2016) 179–185.
[7] Y. Brandberg, H. Johansson, M. Bergenmar, Patients' knowledge and perceived understanding – associations with consenting to participate in cancer clinical trials, Contemporary Clinical Trials Communications 2 (2016) 6–11.
[8] C. Mc Daid, Z. Hodges, D. Fayter, L. Stirk, A. Eastwood, Increasing participation of cancer patients in randomised controlled trials: a systematic review, Trials 7 (2006) 16.
[9] C.L. Tishler, N.S. Reiss, Pediatric drug-trial recruitment: enticement without coercion, Pediatrics 127 (5) (2011) 949–954.
[10] B.F. Hudson, L.J. Oostendorp, B. Candy, V. Vickerstaff, L. Jones, M. Lakhanpaul, et al., The under reporting of recruitment strategies in research with children with life-threatening illnesses: a systematic review, Palliat. Med. 31 (5) (2017) 419–436.
[11] L. Robinson, P. Adair, M. Coffey, R. Harris, G. Burnside, Identifying the participant characteristics that predict recruitment and retention of participants to randomised controlled trials involving children: a systematic review, Trials 17 (1) (2016) 294.
[12] M. Franciscus, A. Nucci, B. Bradley, H. Suomalainen, E. Greenberg, D. Laforte, et al., Recruitment and retention of participants for an international type 1 diabetes prevention trial: a coordinators' perspective, Clin. Trials 11 (2) (2014) 150–158.
[13] E. Bonifacio, A.G. Ziegler, G. Klingensmith, E. Schober, P.J. Bingley, M. Rottenkolber, et al., Effects of high-dose oral insulin on immune responses in children at high risk for type 1 diabetes: the Pre-POINT randomized clinical trial, Jama 313 (15) (2015) 1541–1549.
[14] A.G. Ziegler, M. Rewers, O. Simell, T. Simell, J. Lempainen, A. Steck, et al., Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children, Jama 309 (23) (2013) 2473–2479.
[15] A. Nieuwesteeg, F. Pouwer, R. van der Kamp, H. van Bakel, H.J. Aanstoot, E. Hartman, Quality of life of children with type 1 diabetes: a systematic review, Curr. Diabetes Rev. 8 (6) (2012) 434–443.
[16] S.M. Moore, N.J. Hackworth, V.E. Hamilton, E.P. Northam, F.J. Cameron, Adolescents with type 1 diabetes: parental perceptions of child health and family functioning and their relationship to adolescent metabolic control, Health Qual. Life Outcome 11 (2013) 50.
[17] R.A. Insel, J.L. Dunne, A.G. Ziegler, General population screening for type 1 diabetes: has its time come? Curr. Opin. Endocrinol. Diabetes Obes. 22 (4) (2015) 270–276.
[18] J. Raab, F. Haupt, M. Scholz, C. Matzke, K. Warncke, K. Lange, et al., Capillary blood islet autoantibody screening for identifying pre-type 1 diabetes in the general population: design and initial results of the Fr1da study, BMJ open 6 (5) (2016) e011144.
[19] P.H. Caldwell, S.B. Murphy, P.N. Butow, J.C. Craig, Clinical trials in children, Lancet 364 (9436) (2004) 803–811.
[20] L.M. Duca, B. Wang, M. Rewers, A. Rewers, Diabetic ketoacidosis at diagnosis of type 1 diabetes predicts poor long-term glycemic control, Diabetes Care 40 (9) (2017) 1249–1255.
[21] C. Winkler, E. Schober, A.G. Ziegler, R.W. Holl, Markedly reduced rate of diabetic ketoacidosis at onset of type 1 diabetes in relatives screened for islet autoantibodies, Pediatr. Diabetes 13 (4) (2012) 308–313.
[22] H. Elding Larsson, K. Vehik, R. Bell, D. Dabelea, L. Dolan, C. Pihoker, et al., Reduced prevalence of diabetic ketoacidosis at diagnosis of type 1 diabetes in young children participating in longitudinal follow-up, Diabetes Care 34 (11) (2011) 2347–2352.
[23] D.L. Buscariollo, M.A. Davidson, M. Black, W.E. Russell, R.L. Rothman, D.J. Moore, Factors that influence parental attitudes toward enrollment in type 1 diabetes trials, PLoS One 7 (8) (2012) e44341.
[24] F. Kaguelidou, P. Amiel, A. Blachier, C. Iliescu, J.C. Roze, M. Tsimaratos, et al., Recruitment in pediatric clinical research was influenced by study characteristics and pediatricians' perceptions: a multicenter survey, J. Clin. Epidemiol. 66 (10) (2013) 1151–1157.
[25] J.P. Krischer, D.A. Schatz, B. Bundy, J.S. Skyler, C.J. Greenbaum, Effect of oral insulin on prevention of diabetes in relatives of patients with type 1 diabetes: a randomized clinical trial, Jama 318 (19) (2017) 1891–1902.