CLINICAL TRIALS RECRUITMENT AND RETENTION Clinical Trials 2014; 11: 150–158

Recruitment and retention of participants for an international type 1 diabetes prevention trial: A coordinators' perspective

Margaret Franciscus[a], Anita Nucci[b], Brenda Bradley[c], Heli Suomalainen[d], Ellen Greenberg[e], Diane Laforte[f], Paivi Kleemola[d], Mila Hyytinen[d], Marja Salonen[d], Mary Jean Martin[g,h], Daniel Catte[j], Jacki Catteau[j] and The TRIGR Investigators

Background The Trial to Reduce Insulin Dependent Diabetes Mellitus in the Genetically at Risk (TRIGR) is the first multicenter international type 1 diabetes (T1D) prevention trial to be undertaken. A unique feature of TRIGR has been recruitment of eligible pregnant women and enrollment of newborns for long-term follow-up assessments.

Purpose Our purpose is to summarize the recruitment and retention strategies used to conduct TRIGR from the perspective of the study coordinators.

Methods TRIGR was designed to test whether weaning to formula containing hydrolyzed versus intact cow's milk protein would be efficacious in decreasing risk for development of T1D-associated autoantibodies and T1D among infants identified to be at increased risk for T1D based on their human leukocyte antigen (HLA) profile and family history. Multiple strategies tailored to local issues were required to enroll and follow the target number of infants.

Results This study was conducted in the United States, Canada, Australia, and 12 countries in Europe. Of the 5606 mothers registered worldwide, 5000 of their infants were randomized. Of these, 2159 were HLA eligible and enrolled in the 8-month intervention and 10-year follow-up phases of this study. The TRIGR study met the accrual goal after 4.7 years of recruitment, 2.7 years longer than projected initially. Challenges included difficulty in finding fathers with T1D, a higher than expected rate of premature delivery among T1D mothers, and implementation of new privacy regulations mid-trial. The majority of participants were recruited from primary care antenatal clinics located near the study centers and from a general hospital or pediatric center that was affiliated with a TRIGR Study center. Internet and magazine advertisements were found to be useful for recruitment of families. Alternative follow-up strategies are offered to families who wish to reduce or discontinue participation.

Limitations Our experience is limited to a single international multicenter trial.

[a]Department of Pediatric Medicine, University of Pittsburgh, Pittsburgh, PA, USA, [b]Department of Nutrition, Georgia State University, Atlanta, GA, USA, [c]Children's Hospital of Eastern Ontario Research Institute, Ottawa, ON, Canada, [d]Institute of Clinical Medicine, University of Helsinki, Helsinki, Finland, [e]Naomi Berrie Diabetes Center, Columbia University, New York, USA, [f]Montreal Children's Hospital, Montreal, QC, Canada, [g]Division of Maternal Fetal Medicine, Department of Obstetrics and Gynaecology, Mount Sinai Hospital, Toronto, ONT, Canada, [h]Department of Endocrinology, Hospital for Sick Children, Toronto, ONT, Canada, [i]University of Manitoba, Winnipeg, MB, Canada, [j]Department of Endocrinology and Diabetes, The Children's Hospital at Westmead, Sydney, NSW, Australia.

Author for correspondence: Anita Nucci, Department of Nutrition, Georgia State University, P.O. Box 3995, Atlanta, GA 30302-3995, USA.
Email: anucci@gsu.edu

10.1177/1740774513510070

Conclusions TRIGR coordinators played key roles in the recruitment and intervention periods and continue to be instrumental in retaining families and children during the 10-year follow-up period for each child. *Clinical Trials* 2014; **11:** 150–158. http://ctj.sagepub.com

The incidence of type 1 diabetes (T1D) in young children has been increasing worldwide and is predicted to continue rising [1]. The cause of T1D is believed to be a combination of genetic predisposition and β cell autoimmunity induced early in life by environmental or lifestyle risk factors. The risk of developing T1D is higher among children born to men with T1D than among those whose mother or sibling has T1D [2]. The environmental or lifestyle triggers believed to influence the expression of the disease include viruses such as Coxsackie B, mumps, and congenital rubella; growth parameters; and early introduction of foreign dietary proteins during infancy or childhood [3,4].

International research trials designed to evaluate prevention approaches for chronic diseases are essential in order to improve worldwide health. The large sample size required of prevention trials necessitates effective coordination strategies to recruit participants from different countries and healthcare settings [5]. For this reason, the role of study coordinator is especially important during recruitment. An effective study coordinator must possess the following qualities: (1) excellent interpersonal and organizational skills to maximize recruitment opportunities and ensure that the study protocol is followed precisely, (2) flexibility to provide maximum convenience to participating families, and (3) collegiality to share successful recruitment strategies with other study coordinators. Few publications discuss the challenges of coordinating a pediatric multicenter, international clinical trial. Furthermore, even less information exists in the literature regarding the ethical and logistical challenges of recruitment of unborn children into a double-blind randomized controlled trial. Incomplete sample size can result in the inability to conclude whether there is a difference in outcomes between the treatment groups; recruitment phase extension adds costs [6].

Reasons reported for nonparticipation in longitudinal studies of children have included the family moving away from the study center, the child being diagnosed with a medical problem, lack of interest or time, difficulty scheduling visits, and family problems (e.g., parents separated or divorced, loss of employment) [7]. Liese *et al*. [8] evaluated the association between demographic characteristics of children with diabetes and level of study participation and reported a decline in participation rate as the age of the child increased. However, families of children with T1D more often participated than those with type 2 diabetes or other diabetes type. Karlson and Rapoff [9] examined attrition rates reported in 40 randomized studies of cognitive behavioral interventions in children with chronic conditions, including diabetes. Of all families eligible for a study, 37% refused to participate. The most common reasons reported for dropping out included parent being too busy, loss of interest, technical complications with study procedures, travel distance, and too many appointments. Janus and Goldberg [10] compared factors that influenced participation in a prospective study in families of children under 1 year of age with and without chronic illness. During the course of the study, 35.4% of families were lost. The majority of families with children who had a chronic illness reportedly dropped out because they were too busy.

The Trial to Reduce Insulin Dependent Diabetes Mellitus in the Genetically at Risk (TRIGR) study is a randomized, double-blind trial to evaluate whether hydrolyzed infant formula compared to cow's milk-based formula decreases development of T1D in children with increased genetic susceptibility [7]. The study is being conducted successfully in 15 countries on three continents (North America, Europe, and Australia). Our purpose is to summarize the strategies used by the study coordinators to implement TRIGR, with a specific focus on communication, screening, recruitment, and retention, in order to contribute to a knowledge base for future clinical trials designed to enroll pregnant women and their unborn children.

Methods

A full description of the TRIGR study protocol has been published [7]. The trial was approved by the Ethics Institutional Review Board (IRB) or Committee of Human Experimentation in all participating institutions. Children at increased risk for developing T1D from the United States, Canada, Australia, and 12 countries in Europe enrolled in the trial between May 2002 and December 2006. As newborns, they were randomized to receive one of four color-coded, blinded formulas for use after weaning from breastfeeding or in the absence of breastfeeding. Two formulas contained the hydrolyzed-protein test formula (Nutramigen®; Mead Johnson

Nutrition, Evansville, IN, USA) and two contained the control formula (intact cow's milk protein formula with Nutramigen (20%) used to mask the taste and smell differences between the formulas). The duration of the intervention for each infant was until at least 6 months of age. Whenever the mother chose to breastfeed exclusively up to the age of 6 months, she was advised to give the formula thereafter when supplementation was needed until the age of 8 months. Follow-up visits including dietary interviews, clinical assessments, and blood sampling are conducted at 3, 6, 9, 12, 18, and 24 months and annually thereafter. Consent and dietary forms are available in 12 different languages.

Sample size calculations were based on previous family studies that analyzed the occurrence of autoantibodies in children with a first-degree relative with T1D. The sample size estimate of 2800 randomized infants was based on the following assumptions: a confidence level of 95%, a statistical power of 80%, a reduction of 40% in the hazard rate of T1D in the intervention group, a dropout rate of 20%, and a frequency of 10% exclusive breastfeeding up to the age of 6 months [9]. The children are monitored for T1D-associated autoantibodies and/or a diagnosis of clinical T1D until 2017 when all children will be at least 10 years old. An oral glucose tolerance test is performed at 6 and 10 years of age and again at the final study visit for all participating children who have not had a diagnosis of T1D by those ages.

The TRIGR study group used available birth rate and T1D incidence rate data across the world to set a recruitment target for study sites in each country [11]. At the beginning of the study, it was estimated that study personnel would need to recruit 6220 newborns eligible for genetic testing to meet the original goal of 2800 human leukocyte antigen (HLA)-eligible infants, under the assumption that 55% would be excluded based on a low risk of developing T1D. The primary investigators anticipated that 65% of families would be recruited from North America (USA and Canada) and that the remaining 35% of families would originate from 12 European countries and Australia. Recruitment began in May 2002 and was expected to continue for 2 years or until the enrollment target was met. However, delays in receiving ethical approvals, funding issues, and problems with customs clearance for shipments of study formula in some countries resulted in postponement of start-up for some centers. Enrollment at the target rate of 100 women per month was not reached until January 2003, 8 months after the start of recruitment. In June 2003, the eligibility criteria were revised to include infants born at 35 weeks gestation and older (previously 36 weeks) due to the high number of pregnant women with T1D who had delivered at 35–36 weeks. In May 2004, the screening target and randomization goal were revised to 4516 and 2032, respectively, based on a change in the planned analyses for the primary outcome measure. Eighteen additional centers were added in Canada and Europe to bring the final number of actively enrolling TRIGR centers to 77 by July 2005. Based on the revised target sample size and enrollment of about 800 participating families during the first 2 years, it was projected that revised sample size target would be met in December 2006, that is, by extending the accrual period to 4.7 years.

A Recruitment Form was completed for each family by a member of the study team (Figure 1). However, this form was not completed for all families to whom the study was introduced; therefore, it is not possible to report the total number of families contacted. When a family met the primary inclusion criteria for enrollment, that is, the biological parent and/or full sibling of the newborn infant had T1D as defined by the World Health Organization and the infant's parent or legal guardian gave signed consent to participate, a registration form was completed, and the family enrolled. Exclusion criteria included an older sibling of the newborn infant participating in TRIGR, multiple gestation, parents unwilling to feed the infant cow's milk-based products, the gestational age of the newborn <35 weeks, and inability of the family to take part in this study. Once enrolled, the family was randomized before or immediately after birth so that the assigned study formula could be provided and contamination with other infant formulas could be avoided. Eligibility of the infant for the study intervention and follow-up phases was determined after birth based on the results of HLA assays and a review of exclusion criteria: the infant received an infant formula other than breast milk or Nutramigen prior to randomization, the infant had a severe recognizable illness, randomization did not occur before the infant was 8 days old, or no sample was drawn via cord blood or heel stick before 8 days of age for HLA assays. Infants with eligible HLA-genotypes remained in the trial; all other infants were withdrawn from TRIGR. At least 864 families in each randomized group are expected to complete the trial [7].

In 2012, we administered a questionnaire to assess retrospectively study center recruitment resources and strategies. A study team member at each TRIGR center who had been present during the recruitment period was asked to respond to the following questions about the experience at their center: (1) Was there sufficient staff during the entire recruitment period? (2) Was there at least one person on the study team who was experienced in clinical trial recruitment? (3) Was someone available at the center at all times to answer recruitment telephone calls? (4) Were recruitment planning meetings held

TRIGR **Form 001**
Nutritional Prevention of Type 1 Diabetes

RECRUITMENT FORM

(To be completed on anyone who was contacted for the study)

Study Center I__I__I__I__I__I__I

Family member affected by type 1 diabetes

Mother ☐ Father ☐ Full Sibling ☐ Other ☐ None ☐

Location of recruitment (select one)

Antenatal clinic in primary care	☐	Adult diabetes clinic	☐
Antenatal clinic in hospital	☐	Pediatric diabetes clinic	☐
Study Center	☐	Doctor's office	☐
Other delivery hospital	☐	Other:	☐
Internet	☐	Please specify _____	
Diabetes or other magazines	☐		

Consent Form given to Family Yes ☐ No ☐

Enrolled in the Study Yes ☐ No ☐ Pending ☐

Local code _____ (required if family has enrolled)

The family not enrolled in study for the following reasons:
(required if family decides not to enroll – select all that apply)

Not interested	☐	No reply after initial contact	☐
Blood work	☐	Mother carrying multiples	☐
Too many follow-up visits	☐	Known medical problem to fetus – in utero	☐
Family does not want to know the HLA result	☐	Baby born prematurely	☐
Half sibling affected by diabetes	☐	Baby exposed to cow's milk before recruitment	☐
No type 1 diabetes	☐		
One child in the family already participating in the TRIGR intervention	☐	Family does not want to expose baby to cow's milk	☐
Other _____	☐		

Recruiter _____ **Interviewer code** (if available) I__I__I__I__I

Interview date I__I__I__I__I__I__I__I__I__I__I__I
d d m m m y y y y

Figure 1. Trial to Reduce Insulin Dependent Diabetes Mellitus in the Genetically at Risk (TRIGR) recruitment form.

before the start of the study? (5) Were recruitment training meetings held at the study center? (6) What were the greatest challenges of recruitment?

Organization and data management

The TRIGR study group is divided into regions with central coordination by the International Central Coordinating Center located at the University of Helsinki (Finland) and headed by the study principal investigator. There are two regional groups: (1) 12 European countries (Czech Republic, Estonia, Finland, Germany, Hungary, Italy, Luxembourg, The Netherlands, Poland, Spain, Sweden, and Switzerland) and Australia, with the regional coordinating center in Helsinki, Finland, and (2) North America with a coordinating center in Pittsburgh, Pennsylvania, for the United States, and another in London, Ontario, for Canada. Of 77 study centers participating in this study, 50 are in Europe, 3 are in Australia, 18 are in Canada, and 6 are in the United States. A Nutrition Special Investigator and Epidemiologist and a Nutrition Fellow, both in Finland, and a Nutrition Coordinator in North America monitored dietary compliance during the intervention period. TRIGR data are managed by the Data Management Unit (DMU) located at the Pediatrics Epidemiology Center at the University of South Florida, Tampa, Florida. The DMU developed a web-based data system that has provided web-based randomization and electronic data entry as well as online study operation documents and progress reports accessible by authorized study team members.

Role of the TRIGR study coordinators

Every country has at least one national coordinator. When there are several study centers in a country, there is also a local coordinator at each study center. In addition, one or more study monitors manage international coordination between the European countries and Australia. Each national coordinator works with the local coordinators to organize and maintain the day-to-day operations of the study center, to communicate information to the study team, and to motivate, encourage, and help the team to solve problems. At the beginning of this study, the national coordinators prepared a regional recruitment plan and assisted with implementation of the intervention at the study centers in their region. The national coordinators/monitor trained the center coordinators and organized regular telephone conferences or meetings to discuss recruitment and retention strategies and to determine the most effective tools for recruitment and retention at their center. The national coordinators, supported by the study monitor in Europe, remain responsible for ensuring study center adherence to the study protocol, updating ethical approval, monitoring data entry, conducting audits, developing data collection forms and letters to families, assisting with updates to the TRIGR Manual of Operations in order to address the needs of study sites in each country, and providing fiscal management. The national coordinators communicate directly with DMU personnel and the TRIGR International Coordinating Center. National coordinators work with local coordinators and laboratory technicians to ensure that blood samples are sent to the central laboratory in Helsinki every 3 months for analysis.

Each study center is staffed with nurses and physicians with experience in pediatrics, diabetes, neonatology or obstetrics, laboratory technicians and/or research assistants, and, primarily during the intervention period, dietitians. Local coordinators were responsible for recruitment of mothers and infants; this responsibility included development of a center-specific recruitment plan, training of staff at local delivery hospitals, direct communication with families to schedule and conduct interviews and examinations, and assistance with informing families of test results. Local coordinators currently are responsible for retention of participating families and children under follow-up at the local center.

Results

The TRIGR study team exceeded its revised recruitment goal of 2032 HLA eligible infants in September 2006. Of the 5606 mothers who were registered, 5000 were randomized. The remaining 606 participants were excluded prior to randomization due to ineligibility (e.g., preterm delivery, miscarriage, family withdrew consent) or randomization in error. Of the 2159 infants who were HLA eligible and remained in the study for intervention and follow-up, 43% were from North America and 57% from Europe/Australia, which differed from the initial estimates of 65% and 35%, respectively. About half the infants had only mothers with T1D (49%); for 34%, only the fathers had T1D (Table 1). As of 31 March 2013, 302 (14%) of 2159 participating families and children were classified as dropouts; 36 were considered to be lost to follow-up. Families who no longer are participating fully in scheduled follow-up procedures may agree to annual telephone contact by study coordinators to determine the primary outcome of T1D status for their children.

Based on Recruitment Forms completed, 2795 out of 6836 families (41%) recruited in Canada, Europe, and the United States were from hospital-based antenatal clinics or primary antenatal clinics. Other recruitment sources included adult diabetes clinics, obstetric clinics, delivery hospitals, and pediatric

Table 1. HLA eligible randomized participants by first-degree relative with T1D by country

Country	Parent(s) only with T1D			Parent(s) and sibling(s) parents with T1D					
	Mother only	Father only	Both	Mother only	Father only	Both	Sibling only	Total	Total percent
Australia	54	34	2	0	0	0	11	101	4.7
Canada	286	162	7	5	5	0	63	528	24.5
Czech Republic	89	59	0	0	0	0	16	164	7.6
Estonia	18	8	3	0	0	0	5	34	1.6
Finland	147	226	2	0	7	0	42	424	19.6
Germany	54	29	4	0	2	0	23	112	5.2
Hungary	18	2	0	0	0	0	3	23	1
Italy	32	11	0	0	1	0	10	54	2.5
Luxembourg	5	1	0	0	0	0	1	7	0.3
Netherlands	25	19	0	0	3	0	7	54	2.5
Poland	56	11	2	0	1	1	23	94	4.4
Spain	36	19	2	0	1	0	2	60	2.8
Sweden	42	37	1	1	2	0	14	97	4.4
Switzerland	3	5	0	0	0	0	5	13	0.6
United States	190	100	6	4	11	0	83	394	18.3
Total	*1055*	*723*	*29*	*10*	*33*	*1*	*308*	*2159*	*100*
Total Percent	*48.9*	*33.5*	*1.3*	*0.5*	*1.5*		*14.3*	*100*	

HLA: human leukocyte antigen; T1D: type 1 diabetes.

diabetes clinics or doctor's offices. Recruitment material was delivered through the Internet (TRIGR web pages, National Diabetes Association web pages, etc.), television advertisements, postings in pharmacies, and advertisements in journals, magazines, and newspapers targeted for diabetes professionals, people with T1D, and pregnant women. The countries with the greatest total recruitment were Canada, Finland, and the United States. Participants in Canada and Finland were recruited mainly from the TRIGR study center that was affiliated with a general hospital or pediatric center. In the United States, the majority of participants were recruited from an antenatal clinic in a hospital.

Challenges and strategies of recruitment

The recruitment strategies utilized by the TRIGR study group were developed after the establishment of recruitment targets and determination of study center locations but prior to the start of recruitment. Although the initial intent was to recruit participants primarily from the area surrounding the study centers, often a large city where high-volume endocrinology and high-risk pregnancy clinics existed, the target area was expanded in many countries in order to meet enrollment goals. Expansion of areas targeted for recruitment required additional ethics approvals and additional personnel training at remote locations.

Recruitment strategies used in TRIGR by the study centers to identify eligible pregnant women and men with T1D whose partners were pregnant are shown in Table 2. The Internet and magazine articles were useful for attracting potential participants in all regions. In Europe and Australia, the most effective strategy was face-to-face contact with parents. In North America, articles in magazines that target pregnant women, such as *Fit Pregnancy, Parenting, and Prevention*, generated many inquiries from potentially eligible families. An article that appeared in December 2002 in *Parade* magazine (Parade Publications, New York, NY), which has wide circulation in the United States, yielded the greatest number of eligible participants across TRIGR in the United States. In the North American centers, families received a small gift (e.g., bib, infant cap) after the baby was born as a token of appreciation regardless of whether or not the family and infant remained eligible for this study. In addition, the annual TRIGR newsletter was sent to families in North America regardless of eligibility. These items served to remind families of TRIGR should the first child not be eligible and the mother become pregnant again.

The TRIGR website for study personnel, which was launched in 2002, provided recruitment progress reports and minutes from annual Steering Committee meetings. A link to the TRIGR website for the public (www.trigr.org in Europe and www.TRIGRNorthAmerica.org in North America)

Table 2. Recruitment strategies used to recruit fathers with T1D and eligible pregnant women

- Interview pregnant women and their partners at antennal clinics in primary care centers and hospitals
- Review medical history of first-degree relatives of pregnant women
- Provide presentations to physicians, nurses, dietitians, and other healthcare staff at obstetrician offices as well as adult and pediatric endocrinologist offices and in person communication
- Communicated in person with parents of children with T1D who were visiting pediatric endocrinologist offices
- Place articles in magazines that target pregnant women (e.g., fit pregnancy, parenting, prevention) and fathers with diabetes (diabetes magazines)
- Place TRIGR posters and brochures in men's washrooms near antenatal clinics
- Place TRIGR posters and brochures in adult endocrinologist offices, gymnasiums, and pharmacies
- Include a photograph of a pregnant woman or a football player with T1D[a] in study advertisement posters

T1D: type 1 diabetes; TRIGR: Trial to Reduce Insulin Dependent Diabetes Mellitus in the Genetically at Risk.
[a]Permission was obtained to use photographs.

was available on frequently accessed diabetes websites (e.g., Children with Diabetes, Juvenile Diabetes Research Foundation, and American Diabetes Association), which enhanced study visibility and provided families with information about the study as well as center contact information. TRIGR Family Newsletters were distributed to recruitment sources and posted on the TRIGR website as a tool to increase awareness of the study. Study team members attended diabetes related functions (e.g., fundraising walks) to distribute recruitment materials. All recruitment materials included a toll-free telephone number and email addresses for all regional study centers. The study primary investigators also introduced TRIGR at international scientific meetings to increase awareness among endocrinologists outside of the immediate study center areas.

The questionnaire that we used to assess recruitment resources and strategies, retrospectively, revealed that the majority of country coordinators believed that they had adequate recruitment staff. All of the country coordinators reported that they had at least one person on the study team with experience with recruiting participants for a clinical trial, that someone from the study team was available to respond to recruitment calls at all times, and that recruitment planning/training meetings were held prior to the study start. Study coordinators were available at all times to support the maternity hospital staff and to collect cord blood samples for HLA typing.

Challenges to recruitment reported by the national coordinators included preference for a specific treatment arm by the parents, declining birth rates (a worldwide trend), premature birth of the infant, lack of a recruitment tracking tool at the start of the study, lack of local or regional diabetes registries, parental unwillingness to commit to long-term follow-up or blood draws from children in the study, participation of families in another T1D study, variable support from the medical community, and unrealistic recruitment goals. Identification of men with T1D who were soon to be fathers was reported to be much more difficult than identifying pregnant women diagnosed with T1D or who already had children with T1D. The challenge that had the greatest impact in the United States was enactment of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). All covered entities had to be compliant to the new regulation by 2003, which occurred during the recruitment phase of the TRIGR study. The law required that new methods be developed for recruitment that did not include study personnel contacting potentially eligible families directly; progress was slowed as ethics boards interpreted the new regulation. We subsequently relied on physician referrals and brochures/advertisements to inform families about the study so that those interested in participating could contact the study center.

Challenges and strategies of retention

The target sample size estimated for TRIGR was based on the assumption of a dropout rate of no more than 20%. A unique feature to the TRIGR study is that the family is reevaluated for eligibility after delivery of the infant and randomization. Study coordinators had the delicate task of informing families of increased T1D risk, based on HLA testing of the infant, without increasing anxiety and risking withdrawal or refusal to use the study formula.

Common retention strategies used in TRIGR centers worldwide are shown in Table 3. Given the length of time that participants need to be engaged in the study (minimum of 10 years) and the requirement for annual blood sampling, it has been important to gain and sustain the trust of the parents as well as the children as they get older. Our primary retention strategies involve methods to maintain regular communication and provide the family with easy access to the study team and for follow-up visits. The study coordinators arrange study visits at

Table 3. Retention strategies used in TRIGR

Communication	• Means for families to contact the TRIGR coordinator at all times, for example, 24-h mobile phone TRIGR hotline • Follow-up telephone calls after each blood sample • TRIGR websites (country specific) • Biannual newsletters (country specific and international) – families contributed content • Dietary interviews during the intervention (monthly) and ancillary nutrition study interviews from 18 months (biannually) • TRIGR family meetings • Informational and motivating letters sent to participants, including dropouts
Easing impact of blood sampling	• Pain control, that is, use of topical anesthetic creams and distraction techniques; for example, glucose solutions for infants, Buzzy® for pain relief, flash cards, massage • Home visits from a pediatric phlebotomist/study nurse or scheduling visits at the medical office/laboratory nearest to the family • Local laboratories that have a phlebotomist with pediatric experience
Engaging children	• Art and photography contests; winning artwork, and photographs used for holiday cards, calendars, and newsletters • TRIGR crossword puzzle • Assent of children obtained, usually at 7 years of age • PowerPoint presentation, 'Why are they taking my blood', to help children understand research and what happens to their samples • Small gifts; for example, books and games at annual visits • Birthday/Christmas/Easter cards
Assisting parents	• Compensation for travel costs • Availability of a dietitian and/or doctor to assist families whose children have health problems • TRIGR calendar to record illnesses, immunizations, appointment dates • TRIGR dietary advice booklets • Visit reminder calls and letters

TRIGR: Trial to Reduce Insulin Dependent Diabetes Mellitus in the Genetically at Risk.

the most convenient location for the family, for example, physician offices, school, other TRIGR centers, or at home with a nurse or pediatric phlebotomist. In the Netherlands, nearly all study procedures are performed at home. In Australia, home visits have been essential to retain families who live long distances from the study center. After the 6-year visit, parents are provided with autoantibody results for their child from 18 months to 6 years of age and receive results annually thereafter. Children are asked to provide assent to continue in this study, usually at the age of 7. An ancillary nutrition study on later consumption of milk and cereal products began in 2005. Families who consented to the ancillary nutrition study are contacted biannually by the study center dietitian or coordinator (starting when the child is 18 months old, for a short dietary interview). The ancillary study has been an effective method of maintaining contact with the participating families. Frequent blood sampling from children, difficult family situations, and lack of time are the primary reasons for dropout in TRIGR.

Discussion

The TRIGR study is the first international multicenter randomized clinical trial to address the research question of whether dietary intervention can prevent T1D. An important aspect of the TRIGR design was identification of eligible infants either prior to birth or within 7 days of birth to participate in an 8-month intervention period and a 10-year follow-up period. Not unique to TRIGR was a lower recruitment rate than projected when the trial was designed and limited funding for advertisement and travel for recruitment training. Study center locations were selected initially when the funding proposal was written. Although all of the initial group of study investigators have extensive research experience and clinical practice related to our target population, for example, endocrinology, obstetrics, it was difficult to identify additional study centers with large numbers of prospective participants, that is, women of childbearing age with T1D. The lack of national diabetes registries, a worldwide decline in birth rate, and, in the United States, enactment of HIPAA made recruitment to this international study particularly challenging. Nevertheless, TRIGR investigators and coordinators met our enrollment goal by continuing recruitment for 2.5 years beyond the original target date without additional funding.

Recruitment strategies for clinical trials typically are outlined in the original study protocol, and country- or center-specific recruitment plans may be

drafted before recruitment begins. We recommend that recruitment and retention strategies and materials be developed in detail before recruitment and enrollment begin and that regular communication among study coordinators be established early, facilitated by national coordinators when appropriate, and continued throughout this study to assess which strategies are most successful and which strategies should be abandoned and to develop new strategies based on observed needs and obstacles.

To date, the TRIGR study has experienced a lower rate of attrition (14%) than that reported by Karlson and Rapoff [9] (37%) in their review of attrition rates in randomized interventions in children with chronic conditions. Our success may be due in part to the efforts by the study coordinators to avoid complications with blood samples, that is, decrease anxiety by administering a topical anesthetic before blood draws and ensuring that laboratories have staff skilled in drawing blood from children, and ease travel requirements for study visits. Our dropout rate is also lower than that reported by Janus and Goldberg [10] (34.5%), who examined attrition and factors influencing participation in a prospective study by families with children under 1 year of age. The reason for dropout they reported, that is, families being too busy, is consistent with what has been observed in TRIGR. Innovative strategies to improve participant understanding of and commitment to the study protocol are necessary for satisfactory enrollment and retention rates and long-term compliance with the study protocol.

Study coordinators are key to effective recruitment and retention of participants in all clinical trials. The importance of their role is emphasized in a clinical trial in which children are enrolled at birth and followed up for number of years. The trial may be designed and funding secured by physicians or others responsible for the clinical aspects of the trial; however, each coordinator's personal commitment and ability to maintain the commitment and interest of parents and children are key to successful completion of such trials.

Acknowledgments

The investigators and members are listed in an online-only Appendix. Trial Register and Registration Number: ClinicalTrials.gov, NCT00179777.

Funding

This work was supported by the National Institute of Child Health and Human Development and National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health (grant numbers HD040364, HD042444 and HD051997), the Canadian Institutes of Health Research, the Juvenile Diabetes Research Foundation International, the Commission of the European Communities (specific RTD program 'Quality of Life and management of Living Resources', contract number QLK1-2002-00372 'Diabetes Prevention'. It does not reflect its views and in no way anticipates the Commission's future policy in this area), the EFSD/JDRF/Novo Nordisk Focused Research Grant, and the Academy of Finland. The study formulas were provided free of charge by Mead Johnson Nutritionals.

Conflict of interest

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors have no financial interest in the products mentioned in this article and no compensation was received for preparation of this manuscript.

References

1. **Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G; EURODIAB Study Group**. Incidence trends for childhood type 1diabetes in Europe during 1989–2003 and predicted new cases 2005–20: A multicentre prospective registration study. *Lancet* 2009; **373**: 2027–33.
2. **Warram JH, Krolewski AS, Gottlieb MS, Kahn CR**. Differences in risk of insulin-dependent diabetes in offspring of diabetic mothers and diabetic fathers. *N Engl J Med* 1984; **311**: 149–52.
3. **Virtanen SM, Knip M**. Nutritional risk predictors of beta-cell autoimmunity and type 1 diabetes at a young age. *Am J Clin Nutr* 2003; **78**: 1053–67.
4. **Knip M, Virtanen SM, Åkerblom HK**. Infant feeding and the risk of type 1 diabetes. *Am J Clin Nutr* 2010; **91**(Suppl.): 1506S–13S.
5. **Aitken LM, Pelter MM, Carlson B, *et al***. Effective strategies for implementing a multicenter international clinical trial. *J Nurs Scholarsh* 2008; **40**: 101–08.
6. **Oude Rengerink K, Opmeer BC, Logtenberg SLM, *et al***. Improving participation of patients in Clinical Trials – rationale and design of IMPACT. *BMC Med Res Methodol* 2010; **10**: 85–90.
7. The TRIGR Study Group. The Trial to Reduce IDDM in the Genetically at Risk (TRIGR) study: Recruitment, intervention and follow-up. *Diabetologia* 2011; **54**: 627–33.
8. **Liese AD, Liu L, Davis C, *et al***. Participation in pediatric epidemiologic research: The SEARCH for diabetes in Youth Study Experience. *Contemp Clin Trials* 2008; **29**: 829–36.
9. **Karlson CW, Rapoff MA**. Attrition in randomized controlled trials for pediatric chronic conditions. *J Pediatr Psychol* 2008; **34**: 782–93.
10. **Janus M, Goldberg S**. Factors influencing family participation in a longitudinal study: Comparison of pediatric and healthy samples. *J Pediatr Psychol* 1997; **22**: 245–62.
11. **Hamilton BE, Martin JA, Sutton PD**; National Center for Health Statistics. Births: Preliminary data for 2002. *Natl Vital Stat Rep* 2003; **51**(11): 1–20.