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Recruitment and Retention of Participants for an International Type 1 Diabetes Prevention Trial: A Coordinators' Perspective

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Abstract

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 vs. 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—The study was conducted in the United States, Canada, Australia and 12 countries in Europe. Of the 5,606 mothers registered world-wide, 5,000 of their infants were randomized. Of these, 2,159 were HLA eligible and enrolled in the 8-month intervention and 10-year follow-up phases of the 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 amongst 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.

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.

Keywords

Type 1 diabetes; Recruitment; Coordinator

The incidence of type 1 diabetes (T1D) in young children has been increasing worldwide and is predicted to continue rising¹. 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 T1D². 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 childhood³⁻⁴.

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 settings⁵. 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 costs⁶.

Reasons reported for non-participation 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)¹⁰. Liese et al. 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 increased⁷. However, families of children with T1D more often participated than those with type 2 diabetes or other diabetes type. Karlson and Rapoff examined attrition rates reported in 40 randomized studies of cognitive behavioral interventions in children with chronic conditions, including diabetes⁸. 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 compared factors that influenced participation in a prospective study in families of children under 1 year of age with and without chronic illness⁹. 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 IDDM 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 susceptibility¹⁰. 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 published¹⁰. 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 2,800 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 breast feeding up to the age of 6 months⁸. 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 country¹¹. At the beginning of the study, it was estimated that study personnel would need to recruit 6,220 newborns eligible for genetic testing to meet the original goal of 2,800 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 to 36 weeks. In May 2004, the screening target and randomization goal were revised to 4,516 and 2,032, 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, i.e., 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, i.e., 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 the 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 human leukocyte antigen (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 trial¹⁰.

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 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, and 2) North America with a coordinating center in Pittsburgh, Pennsylvania. for the United States (USA) and another in London, Ontario, for Canada. Of 77 study centers participating in the study, 50 are in Europe, 3 are in Australia, 18 are in Canada and 6 are in the USA. A Nutrition Special Investigator & 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 the 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 three 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 2,032 HLA eligible infants in September 2006. Of the 5,606 mothers who were registered, 5,000 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 2,159 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 March 31, 2013, 302 (14%) of 2,159 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, 2,795 out of 6,836 families (41%) recruited in Canada, Europe and the USA were from hospital-based antenatal clinics or primary antenatal clinics. Other recruitment sources included adult diabetes clinics, obstetric clinics, delivery hospitals, and pediatric diabetes clinics or doctors 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 USA. 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 USA 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 USA, yielded the greatest number of eligible participants across TRIGR USA. 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 the 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) 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 world-wide 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 USA 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 drop-out rate of no more than 20%. A unique feature to the TRIGR study is that the family is re-evaluated 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 the most convenient location for the family, e.g. physician offices, school, other TRIGR centers, or at home with a nurse or pediatric phlebotomist. In the Netherlands, nearly all study procedures are performed in the 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 the 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 drop-out 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 type 1 diabetes. 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, e.g. endocrinology, obstetrics, it was difficult to identify additional study centers with large numbers of prospective participants, i.e., women of childbearing age with T1D. The lack of national diabetes registries, a world-wide decline in birth rate, and, in the USA, 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 the 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 (37%) in their review of attrition rates in randomized interventions in children with chronic conditions⁸. Our success may be due in part to the efforts by the study coordinators to avoid complications with blood samples, i.e., 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 drop-out rate is also lower than that reported by Janus and Goldberg (34.5%), who examined attrition and factors influencing participation in a prospective study by families with children under 1 year of age⁹. The reason for drop-out they reported, i.e., 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 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.

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Appendix A

LIST OF TRIGR INVESTIGATORS FOR PUBLICATIONS / version September 2013

<u>Administration/ Country</u>	<u>Study center</u>	<u>Last name</u>	<u>First name</u>	<u>Position</u>
Data Safety Monitoring Board		Mandrup-Poulsen	Thomas	Chair
		Arjas	Elias	Member
		Läärä	Esa	Member
		Lernmark	Ake	Member
		Schmidt	Barbara	Member
International Coordinating Center (ICC), Helsinki, Finland		Krischer	Jeffrey P.	Observer
		Åkerblom	Hans K.	PI of the Study until 30.6.08, Deputy PI from 1.7.2008
		Hyttinen	Mila	European Study Monitor
		Knip	Mikael	Deputy PI until 30.6.2008, PI of the Study from 1.7.2008, National Investigator
		Koski	Katriina	European Study Monitor
		Koski	Matti	IT Specialist
		Pajakkala	Eeva	European Study Monitor
		Salonen	Marja	Study Coordinator
		Cuthbertson	David	Biostatistician
		Krischer	Jeffrey P.	PI of the DMU
Data Management Unit (DMU), Tampa, FL, USA		Shanker	Linda	Coordinator
		Bradley	Brenda	National Coordinator
		Dosch	Hans-Michael	Co-Investigator for Canada
		Dupre	John	Co-PI for North America, National Investigator, Executive Committee
		Fraser	William	Co-Investigator for Canada Executive Committee
Canadian Coordinating Center, London and Ottawa, ON		Lawson	Margaret	Co-Investigator for Canada Executive Committee

<u>Administration/ Country</u>	<u>Study center</u>	<u>Last name</u>	<u>First name</u>	<u>Position</u>
USA Coordinating Center, Pittsburgh, PA and Seattle, WA		Mahon	Jeffrey L.	Co-Investigator for Canada Executive Committee
		Sermer	Mathew	Co-Investigator for Canada Executive Committee
		Taback	Shayne P.	Co-Investigator for Canada, Executive Committee
		Becker	Dorothy	Co-PI for North America, National Investigator, Executive Committee
Nutritional Epidemiology Unit, Helsinki, Finland		Franciscus	Margaret	National Coordinator
		Nucci	Anita	Nutrition Coordinator of North America
		Palmer	Jerry	Executive Committee
		Pekkala	Minna	Research Fellow/Head of Nutritional Epidemiology Unit
Australia		Virtanen	Suvi M.	Head of Nutritional Epidemiology Unit
		Catteau	Jacki Neville	National Coordinator
		Howard	Neville	National Investigator
		Crock	Patricia	Local Investigator
Canada	AUS01 - Westmead - Children's Hospital	Craig	Maria	Local Investigator
		Clarson	Cheril	Local Investigator
		Bere	Lynda	Coordinator
	AUS02 - Newcastle - John Hunter Children's Hospital	Thompson	David	Local Investigator
		Metzger	Daniel	Local Investigator
		Marshall	Colleen	Coordinator (In Transition)
	AUS03 - Sydney - Sydney Children's Hospital	Kwan	Jennifer	Coordinator (In Transition)
		Stephure	David K.	Local Investigator
		Pacaud	Daniele	Co-Investigator
	CAN01 - London - St. Joseph's Health Care Centre			
	CAN02 - Vancouver - Children's and Women's Health Centre of British Columbia			
	CAN03 - Calgary - Alberta Children's Hospital			

<u>Administration/ Country</u>	<u>Study center</u>	<u>Last name</u>	<u>First name</u>	<u>Position</u>
	CAN04 - Edmonton - Walter MacKenzie Health Sciences	Schwarz	Wendy	Coordinator
		Girgis	Rose	Local Investigator
		Thompson	Marilyn	Coordinator
	CAN05 - Winnipeg - Health Sciences Centre	Taback	Shayne P	Local Investigator
		Catte	Daniel	Coordinator
	CAN06 - Ottawa - Children's Hospital of Eastern Ontario and The Ottawa Hospital	Lawson	Margaret L	Local Investigator
		Bradley	Brenda	Coordinator
	CAN07 - Toronto Mount Sinai Hospital/Hospital for Sick Children	Daneman	Denis	Local Investigator
		Serner	Mathew	Co-Investigator
		Martin	Mary-Jean	Coordinator
	CAN08 - Quebec - CHUQ	Morin	Valérie	Local Investigator
		Frenette	Lyne	Local Investigator
		Ferland	Suzanne	Coordinator
	CAN09 - Saint John - Regional Hospital	Sanderson	Susan	Local Investigator
		Heath	Kathy	Coordinator
	CAN10 - Montreal - L' Hospital Sainte-Justine	Huot	Celine	Local Investigator
		Gonthier	Monique	Co-Investigator
		Thibeault	Maryse	Coordinator
	CAN11 - Montreal Children's Hospital	Legault	Laurent	Local Investigator
		Laforte	Diane	Coordinator
	CAN12 - Halifax - IWK Health Centre/Dalhousie	Cummings	Elizabeth A	Local Investigator
		Scott	Karen	Coordinator
	CAN13 - St. John's - Janeway Child Health Center	Bridger	Tracey	Local Investigator
	CAN14 - Kingston - Kingston General Hospital/Queen's University	Houlden	Robyn	Local Investigator
		Breen	Adriana	Coordinator
	CAN15 - Regina - Regina Qu'Appelle	Carson	George	Local Investigator
		Kelly	Sheila	Coordinator
	CAN16 - Saskatoon - Royal University Hospital	Sankaran	Koravangattu	Local Investigator
		Penner	Marie	Coordinator

<u>Administration/ Country</u>	<u>Study center</u>	<u>Last name</u>	<u>First name</u>	<u>Position</u>
Czech Republic	CAN17 - Peterborough - Peterborough Regional Health Centre	White King	Richard A Nancy	Local Investigator Coordinator
	CAN18 - Victoria - Vancouver Island Health Research Centre	Popkin Robson	James Laurie	Local Investigator Coordinator
	CZE01 - Prague - Faculty Hospital Kralovske Vinohrady	Al Taji Aldhoon	Eva Irena	National Coordinator Co-Investigator
		Mendlova	Pavla	National Coordinator
		Vavrinec	Jan	National Investigator
		Vosahlo	Jan	Co-Investigator
	CZE02 - Brno - Hospital Milosrdnych Bratri	Brazdova	Ludmila	Local Investigator
	CZE03 - Olomouc - Faculty Hospital Olomouc	Venhacova Venhacova	Jitrenka Petra	Local Investigator Co-Investigator
	CZE04 - Usti nad Labem - Hospital of Masryk	Cipra	Adam	Local Investigator
	CZE05 - Ceske Budejovice - Hospital Ceske Budejovice	Tomiskova	Zdenka	Local Investigator
	CZE06 - Plzen - Faculty Hospital Plzen	Krekova	Petra	Local Investigator
	CZE07 - Zlin - Hospital of Bata	Gogelova	Pavla	Local Investigator
Estonia	EST01 - Tallinn - Tallinn Children's Hospital	Einberg Riikjäv	Ülle Mall-Anne	Co-Investigator Local Investigator
	EST02 - Tartu - Tartu University Children's Hospital	Ormisson	Anne	National Investigator
	FIN01 - Helsinki - Children's Hospital, University of Helsinki	Kleemola Parkkola	Päivi Anna	National Coordinator Local Investigator
	FIN02 - Helsinki - Department of Obstetrics and Gynecology, University of Helsinki	Suomalainen Järvenpää	Heli Anna-Liisa	National Coordinator Local Investigator
Finland	FIN03 - Espoo - Jorvi Hospital	Hämäläinen	Anu-Maaria	Local Investigator

<u>Administration/ Country</u>	<u>Study center</u>	<u>Last name</u>	<u>First name</u>	<u>Position</u>
Germany	FIN04 - Kotka - Kymenlaakso Central Hospital	Haavisto	Hannu	Local Investigator
		Tenhola	Sirpa	Local Investigator
	FIN05 - Lahti - Pajjat- Hame Central Hospital	Lautala	Pentti	Local Investigator
		Salonen	Pia	Local Investigator
	FIN06 - Tampere - Department of Pediatrics, Tampere University Hospital	Aspholm	Susanna	Local Investigator
		Siljander	Heli	Co-Investigator
	FIN07 - Pori - Satakunta Central Hospital	Holm	Carita	Local Investigator
		Ylitalo	Samuli	Local Investigator
	FIN08 - Jyväskylä - Central Finland Central Hospital	Lounamaa	Raisa	Co-Investigator
		Nuuja	Anja	Local Investigator
	FIN09 - Seinäjoki - South Ostrobothnia Central Hospital	Talvitie	Timo	Local Investigator
	FIN10 - Hyvinkää - Hyvinkää Hospital	Lindstrom	Kaija	Local Investigator
	FIN11 - Kuopio - Department of Pediatrics, Kuopio University Hospital	Huopio	Hanna	Local investigator
		Pesola	Jouni	Co-Investigator
	FIN12 - Oulu - Department of Pediatrics, Oulu University Hospital	Veijola	Riitta	Local Investigator
		Tapanainen	Päivi	Co-Investigator
Hungary	FIN13 - Hameenlinna - Kanta-Hame Central Hospital	Alar Korpela	Abram Paavo	Local Investigator Local Investigator
	FIN14 - Vaasa - Vaasa Central Hospital	Kaar Mustila	Marja-Liisa Taina	Local Investigator Local Investigator
	FIN15 - Lappeenranta - South Carelian Central Hospital	Virrnsalo	Ritva	Local Investigator
	FIN16 - Mikkeli - Mikkeli Central Hospital	Nykanen	Paivi	Local Investigator
	GER01 - Hannover - Kinder- und Jugendkrankenhaus - Auf der Bult	Ascheimer Dan	Berka Thomas	National Coordinator National Investigator Co-Investigator
	HUN01 - Budapest - Semmelweis Medical University	Krikovszky Mad	Dora Laszlo	Co-Investigator National Investigator

<u>Administration/ Country</u>	<u>Study center</u>	<u>Last name</u>	<u>First name</u>	<u>Position</u>
Italy	ITA01 - Rome - University Campus Bio-Medico of Rome	Khazrai Maddalena	Manon	Local Coordinator
			Ernesto Paolo	Local Coordinator
Luxembourg	SAR01 - Cagliari - St. Michele Hospital	Mannu Songini	Carla Marco	National Investigator
	LUX01 - Luxembourg - Centre Hospitalier de Luxembourg	de Beaufort Schaeffer	Ulrike	National Investigator
The Netherlands	NET01 - Rotterdam - Sophia Children's Hospital	Bruining	Jan	National Investigator
		Bisschoff	Margriet	National Coordinator
Poland	POL01 - Wrocław - Medical University of Wrocław	Basiak	Aleksander	Co-Investigator
		Wasikowa	Renata	National Investigator
	POL02 - Krakow - Polish-American Children's Hospital	Ciechanowska	Marta	Local Investigator
	POL03 - Katowice - Medical University of Silesia	Deja	Grazyna	Co-Investigator
Spain	POL04 - Lodz - Medical University of Lodz	Jarosz-Chobot	Przenyslawia	Local Investigator
		Szadkowska	Agnieszka	Local Investigator
	POL05 - Lodz - Polish Mother's Memorial Hospital (I.C.Z.M.P)	Cyryk	Katarzyna	Local Investigator
		Zawodniak-Szalapska	Malgorzata	Co-Investigator
	SPA01 - Hospital Universitario Cruces, BioCruces, UPV/EHU, CIBERDEM, CIBERER Bilbao, Spain	Castano	Luis	National Investigator
		Gonzalez Frutos	Teba	Local Coordinator
		Oyarzabal	Mirentxu	Co-Investigator
	SPA02 - Madrid - Hospital Clinico San Carlos	Serrano-Ríos	Manuel	National Investigator
		Martínez-Larrad	María Teresa	Local Coordinator
		Hawkins	Federico Gustavo	Co-Investigator
Sweden	SPA03 - Madrid - Hospital Gregorio Marañón	Rodríguez Ama	Dolores	Co-Investigator
	SWE01 - Linköping - University of Linköping	Ludvigsson	Johnny	National Investigator
		Smolinska Konecna	Malgorzata	National Coordinator
	SWE02 - Uddevalla - Uddevalla Hospital	Hanas	Ragnar	Local Investigator
	SWE03 - Göteborg -	Lindblad	Bengt	Local Investigator

<u>Administration/ Country</u>	<u>Study center</u>	<u>Last name</u>	<u>First name</u>	<u>Position</u>
Switzerland	Gothenburg The Queen Silvia Children's Hospital	Nilsson	Nils-östen	Local Investigator
	SWE05 - Halmstad - Halmstad Hospital	Fors	Hans	Local Investigator
	SWE06 - Trollhättan - Trollhattan Hospital	Nordwall	Maria	Local Investigator
	SWE07 - Norrköping - Vrinnevi Hospital	Lindh	Agne	Local Investigator
	SWE08 - Boras - Boras Hospital	Edenwall	Hans	Local Investigator
	SWE09 - Karskrona - Karlskrona Hospital	Aman	Jan	Local Investigator
	SWE10 - örebro - University Hospital	Johansson	Calle	Local Investigator
	SWE11 - Jönköping - Ryhovs Hospital	Gadient	Margrit	Local Coordinator
	SWT01 - Zurich - University Children's Hospital	Schoenle	Eugen	National Investigator
	USA01 - Pittsburgh - Children's Hospital of Pittsburgh	Becker	Dorothy	USA National Investigator / Pittsburgh Local Investigator
		Daftary	Ashi	Co-Investigator
USA		Franciscus	Margaret	USA Coordinator / Pittsburgh Coordinator
		Gilmour	Carol	Co-Investigator
		Palmer	Jerry	Local Investigator
		Taculad	Rachel	Coordinator
	USA02 - Seattle - VA Puget Sound Health Care System and University of Washington	Tanner-Blasiar	Marilyn	Coordinator
		White	Neil	Local Investigator
		Devaskar	Uday	Local Investigator
		Horowitz	Heather	Coordinator/dietitian
		Rogers	Lisa	Coordinator/dietitian
		Colon	Roxana	Coordinator
		Frazer	Teresa	Co-Investigator
		Torres	Jose	Local Investigator
	USA03 - St. Louis - Washington University			
	USA04 - Los Angeles - Mattel Children's Hospital of UCLA			
	USA05 - Ponce - Ponce School of Medicine			

<u>Administration/ Country</u>	<u>Study center</u>	<u>Last name</u>	<u>First name</u>	<u>Position</u>
Laboratories	USA06 - New York - Naomie Berrie Diabetes Center	Goland	Robin	Local Investigator
		Greenberg	Ellen	Coordinator
		Nelson	Maudene	Dietitian
	HLA-typing Laboratory - Turku - Finland	Schachner	Holly	Co-Investigator
		Sofness	Barney	Co-Investigator
		Ilonen	Jorma	Head of HLA-typing Laboratory
	HLA-typing Laboratory - Pittsburgh - PA - USA	Trucco	Massimo	Head of HLA-typing Laboratory
		Nichol	Lynn	Chief Technician
	Cow's Milk Antibody Laboratory - Helsinki - Finland	Savilahti	Erkki	Head of Cow's Milk Antibody Laboratory
		Harkonen	Taina	Co-Investigator
	Autoantibody Laboratory - Helsinki - Finland	Knip	Mikael	Head of Antibody Laboratory
		Vaarala	Outi	Head of T-cell Laboratory
	T-Cell Laboratory - Helsinki - Finland	Luopajarvi	Kristina	Co-Investigator
		Dosch	Hans-Michael	Head of T-Cell Laboratory
	T-Cell Laboratory - Toronto - ON - Canada			

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<p>TRIGR Nutritional Prevention of Type 1 Diabetes</p>	<p>Form 001</p>																
<p>RECRUITMENT FORM (To be completed on anyone who was contacted for the study)</p>																	
<p>Study Center _ _ _ _ _ _ _ _ </p> <p>Family member affected by type 1 diabetes</p> <p>Mother ☐ Father ☐ Full Sibling ☐ Other ☐ None ☐</p>																	
<p>Location of recruitment (select one)</p> <table style="width: 100%;"> <tr> <td style="width: 50%;">Antenatal clinic in primary care ☐</td> <td style="width: 50%;">Adult diabetes clinic ☐</td> </tr> <tr> <td>Antenatal clinic in hospital ☐</td> <td>Pediatric diabetes clinic ☐</td> </tr> <tr> <td>Study Center ☐</td> <td>Doctor's office ☐</td> </tr> <tr> <td>Other delivery hospital ☐</td> <td>Other: ☐</td> </tr> <tr> <td>Internet ☐</td> <td>Please specify _____</td> </tr> <tr> <td>Diabetes or other magazines ☐</td> <td></td> </tr> </table>		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 ☐					
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Other delivery hospital ☐	Other: ☐																
Internet ☐	Please specify _____																
Diabetes or other magazines ☐																	
<p>Consent Form given to Family Yes ☐ No ☐</p> <p>Enrolled in the Study Yes ☐ No ☐ Pending ☐</p> <p>Local code _____ (required if family has enrolled)</p>																	
<p>The family not enrolled in study for the following reasons: (required if family decides not to enroll – select all that apply)</p> <table style="width: 100%;"> <tr> <td style="width: 50%;">Not interested ☐</td> <td style="width: 50%;">No reply after initial contact ☐</td> </tr> <tr> <td>Blood work ☐</td> <td>Mother carrying multiples ☐</td> </tr> <tr> <td>Too many follow-up visits ☐</td> <td>Known medical problem to fetus – in utero ☐</td> </tr> <tr> <td>Family does not want to know the HLA result ☐</td> <td>Baby born prematurely ☐</td> </tr> <tr> <td>Half sibling affected by diabetes ☐</td> <td>Baby exposed to cow's milk before recruitment ☐</td> </tr> <tr> <td>No type 1 diabetes ☐</td> <td>Family does not want to expose baby to cow's milk ☐</td> </tr> <tr> <td>One child in the family already participating in the TRIGR intervention ☐</td> <td></td> </tr> <tr> <td>Other _____ ☐</td> <td></td> </tr> </table>		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 ☐	Family does not want to expose baby to cow's milk ☐	One child in the family already participating in the TRIGR intervention ☐		Other _____ ☐	
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Other _____ ☐																	
<p>Recruiter _____</p> <p>Interview date _ _ _ _ _ _ _ _ d d m m y y y y</p>																	
<p>Interviewer code (if available) _ _ _ _ _ </p>																	

TRIGR Nutritional Prevention of Type 1 Diabetes	Form 001
RECRUITMENT FORM (optional)	
Name	_____
Address	_____ _____
Phone #	(H) _____ (w) _____ (Cell) _____
Email address	_____
Expected date of delivery	_____
Date information packet sent	_____
Follow up call date	_____
Name of recruiter	_____ ID# _____

Figure 1.

Table 1

HLA Eligible Randomized Participants by First Degree Relative with T1D by Country

Country	Parent(s) Only with Type I Diabetes			Parent(s) & Sibling(s) Parents with Type 1 Diabetes					
	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
<i>Total</i>	<i>1055</i>	<i>723</i>	<i>29</i>	<i>10</i>	<i>33</i>	<i>1</i>	<i>308</i>	<i>2159</i>	<i>100</i>
<i>Total Percent</i>	<i>48.9</i>	<i>33.5</i>	<i>1.3</i>	<i>0.5</i>	<i>1.5</i>		<i>14.3</i>	<i>100</i>	

HLA – human leukocyte antigen, T1D – type 1 diabetes

Table 2**Recruitment Strategies used to Recruit Fathers with T1D and Eligible Pregnant Women**

<ul style="list-style-type: none"> • Interview pregnant women and their partners at antenatal 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 health care 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* in study advertisement posters.
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T1D – type 1 diabetes

* Permission was obtained to use photographs.

Table 3

Retention Strategies used in TRIGR

Communication	<ul style="list-style-type: none"> Means for families to contact the TRIGR coordinator at all times, e.g. 24-hour 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	<ul style="list-style-type: none"> Pain control, i.e., use of topical anesthetic creams and distraction techniques; e.g. 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	<ul style="list-style-type: none"> 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; e.g. books and games at annual visits Birthday/Christmas/Easter cards
Assisting Parents	<ul style="list-style-type: none"> 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 IDDM in the Genetically at Risk