EarLy Surveillance for Autoimmune diabetes

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EarLy Surveillance for Autoimmune diabetes: protocol for a qualitative study of general population and stakeholder perspectives on screening for type 1 diabetes in the UK (ELSA 1)

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ABSTRACT

Objective Type 1 diabetes (T1D) is the most common form of diabetes in children, accounting for 96% of cases, with 29 000 children affected in the UK. Studies have recently identified immunotherapies that safely delay the development of T1D for at least 3 years, and further therapies are in development. General population screening programs in other countries can now accurately identify children with presymptomatic T1D who can be entered into prevention studies. The UK does not have such a system in place. We aim to explore whether parents and children in the UK would want to be part of such a program of testing for T1D in the general population, how they would want to be informed and participate in such a program, and how any barriers to recruitment and participation can be addressed. Additionally, the views of stakeholders who would be involved in the testing program will be collected and analyzed.

Research design and methods We will interview parents/guardians and children aged 3–13 years about their views on screening for T1D. We will recruit purposefully to ensure representation across ethnicities and socioeconomic groups. Interviews will be transcribed, analyzed and used to inform iterative co-design work with additional families to address any issues raised. Similar qualitative work will be undertaken with professional stakeholders who would be involved in implementing any future screening program. Where possible, all aspects of this study will be performed remotely by phone or online to minimize infection risk.

Conclusions This qualitative study will provide the first insights into acceptability of testing and monitoring for T1D in the general population from the perspective of families and stakeholders in the UK. Co-design work will help establish the barriers and identify strategies to mitigate and overcome these issues, as an important step towards consideration of national testing for T1D.

Significance of this study

What is already known about this subject?

- General population and community-based screening programs for type 1 diabetes (T1D) have been successfully undertaken in a few countries around the world and have demonstrated that presymptomatic T1D can be accurately identified prior to the development of clinical disease.
- Presymptomatic children can then be offered participation in clinical trials for T1D prevention. No such screening program currently exists in the UK.

What are the new findings?

- We provide the study protocol for the ELSA 1 study, which will perform qualitative interviews with families, parents/guardians, children and professional stakeholders, to understand perspectives towards general population screening for T1D.
- We will also address barriers to a national screening program through co-design and co-production work.

How might these results change the focus of research or clinical practice?

- This study will provide the most comprehensive acceptability data for T1D general population screening in the UK and contribute to the development of a national screening program.

INTRODUCTION

Type 1 diabetes (T1D) is a common chronic disease, affecting around 29 000 children in the UK.[1] T1D is characterized by the destruction of insulin producing pancreatic islet beta cells by the body's immune system.[2] Once diagnosed, T1D is treated by insulin replacement therapy administered through subcutaneous injection.

T1D is one of the most challenging chronic conditions to manage, with <10% of individuals achieving the recommended target of 48 mmol/mol for glucose control.[3] Furthermore, even when nationally recommended glucose targets are achieved, T1D associates

with a threefold excess cardiovascular risk and twofold excess mortality.[4]

Predicting T1D

T1D risk can be predicted in asymptomatic children through measurement of pancreatic islet antibodies.[5] T1D is divided into 3 stages, of which stages 1 and 2 are presymptomatic and stage 3 is symptomatic T1D. Stage 1 is defined by autoimmunity with normoglycemia, stage 2 by progression to dysglycemia and stage 3 marks further progression towards beta cell failure and overt T1D as defined by standard American Diabetes Association glucose criteria, comprising fasting plasma glucose ≥7.0mmol/mol, 2-hour plasma glucose ≥11.1 mmol/mol or hemoglobin A1c (HbA1c) ≥48 mmol/mol.[6 7] Positive antibody tests indicate a greater than 80% likelihood of developing stage 3 T1D over the next 15 years. These children can subsequently be offered a glucose challenge test, which further stratifies their 5-year and 10-year risk. Processes for predicting progression to stage 3 T1D, according to antibody status, have been validated in population studies across Europe and the USA and are most accurate in children between preschool age to puberty.[8]

Preventing T1D

Investment into therapies that can delay or prevent the development of T1D has gained traction.[9] Herold *et al* showed in a phase 2 trial in children with presymptomatic T1D (seroconverted) that a 2-week infusion of teplizumab, a monoclonal antibody that modulates T cell immune responses, could halve the rate of progression to T1D from 36% per year down to 15% per year (HR 0.46), providing a mean delay of T1D onset by 3 years.[10 11] Importantly, teplizumab was well tolerated, and the long-term safety of teplizumab is supported by other studies where 7 years of safety follow-up is available.[12] Teplizumab recently underwent the Food and Drug Administration (FDA) review and is subject to rereview for approval following optimization of their manufacturing processes (FDA), while other therapies are also under investigation.

The development of algorithms that accurately predict progression to stage 3 T1D, combined with therapeutic agents to delay onset of T1D on the horizon, provide the justification to explore T1D testing and monitoring programs. The benefits of early testing and monitoring for T1D include reduction in rates of presentation with diabetic ketoacidosis (DKA),[13] facilitating entry into prevention trials and treatment cost-savings[14] if T1D onset is delayed.

Screening programs for T1D

Studies of T1D risk have previously relied on undertaking screening tests on first degree relatives (FDRs) of people with T1D. Here the genetic and shared environmental risk puts them at a 15-fold higher risk of T1D than people without a family history of T1D.[15] Several FDR screening programs currently exist in the UK,[16 17] and acceptability work in this cohort has previously shown preference for home testing (involving a capillary sample of blood collected on blotting paper and returned by post) rather than a visit to their general practitioner.[18] However, over 90% of people who develop T1D will not have a FDR with the condition.[19] Therefore, effective identification of children with stage 1–3 T1D requires general population screening.

There are currently several general population screening initiatives outside the UK. The FR1DA community screening program in Bavaria screened 90 632 children aged 2–5 years over a 4-year period through the Bavarian community paediatrician network.[13 20 21] They found 261 children were confirmed positive for islet antibodies of which 220 families agreed to undergo a glucose challenge test. Approximately 0.3% of children were found to be presymptomatic T1D and were offered referral into prevention studies. Formal qualitative studies of acceptability were not undertaken in this program, but psychological stress was lower for parents informed of the high risk compared with children diagnosed who had not undergone screening.

The Autoimmunity Screening for Kids (ASK) general population screening program in Colorado has screened 21 000 children aged 1–17 years for both T1D and celiac disease. Approximately 0.5% have been found to have presymptomatic T1D,[14 22] with ad hoc recruitment, for example, at community health fairs. This screening program has yet to report its full outcome but will also provide meaningful results and the feasibility of an alternative approach to general population screening.

There is currently no program of T1D general population screening in the UK. Prior to establishing such a program, it will be important to explore the acceptability of a screening program to UK parents, as well as gather thoughts on how any such program should be designed, and how the results of testing are fed back to parents and children. It will also be important to explore the views of professional stakeholders involved in the screening program, including general practitioners, community pharmacists, and nurses.

Aims and objectives

We aim to deliver the first formal qualitative study to understand acceptability for a national T1D general population screening program for children in the UK. We aim to explore whether parents and children in the UK would want to be part of a program of testing for T1D, how they would want to be informed and participate in such a program, and how any barriers to recruitment and participation can be addressed. Additionally, the views of healthcare professionals, school staff and other stakeholders who would be

involved in the testing program will be collected and analyzed.

RESEARCH DESIGN AND METHODS

Setting

Participants will initially be recruited from the West Midlands region of the UK but with the potential to subsequently recruit nationally. The study has been designed so that it can be entirely remote to mitigate risk from SARS-CoV-2. The study interviews will be held via video or telephone call,[23] but face-to-face interviews[24] will also be offered to families without access to these devices. There will be additional sets of focus groups,[25] held remotely and face-to face in schools, with parents and children. Stakeholder interviews will be held remotely.

Study population

Parents and guardians of children aged 3–13 years will be included and recruited through purposive sampling.[26] We will use a predesigned sampling grid to ensure there is adequate representation across socioeconomic groups, levels of deprivation, parental age, guardian status and ethnicities for the families participating in the study. We will also ensure that families with and without experience or knowledge of T1D are recruited. Finally, we will specifically target recruitment from schools comprising populations of lower socioeconomic groups and higher levels of deprivation, using the National Statistics Socio-economic Classification (NS-SEC).[27] The West Midlands is an ideal region to undertake this work due to the wide representation of different socioeconomic classes and ethnicities.[28] This is important because the complications of T1D and presentation with T1D in DKA disproportionately affect minority groups.[1 3]

Recruitment

Families, including parents, guardians and children, will be recruited in multiple ways to ensure diverse representation of opinions from the general population. Recruitment strategies are outlined in figure 1. There will be no financial incentives to participate in this study, but we will reimburse postage costs and provide prepaid return envelopes for postal consent. We will also reimburse reasonable travel expenses, but given the predominantly remote nature of this study, this will be required for a minority of participants.

General practice recruitment

First, we will engage with the National Institute for Health Research (NIHR) Clinical Research Networks (CRN) to support searches of general practice practice databases to identify suitable participants who will subsequently be contacted by mailing out an 'invitation to participate letter' and a participant information sheet. Other methods of contact will be used including text message if consent has previously been provided for this option. Also, the list of children requiring childhood vaccinations, which is provided by the Children's Immunisation Service, will be screened by the general practices for eligible children. A text message will be sent to those families who have previously consented to this method of contact to invite them to take part in the ELSA study. We will principally target the measles, mumps and rubella (MMR) vaccination at 3 years 4 months, the HPV and the influenza vaccination programs.

Social media and health research recruitment services

Online recruitment will be via the study website: www.elsadiabetes.nhs.uk. We will use social media to advertise the study to provide improved levels of awareness

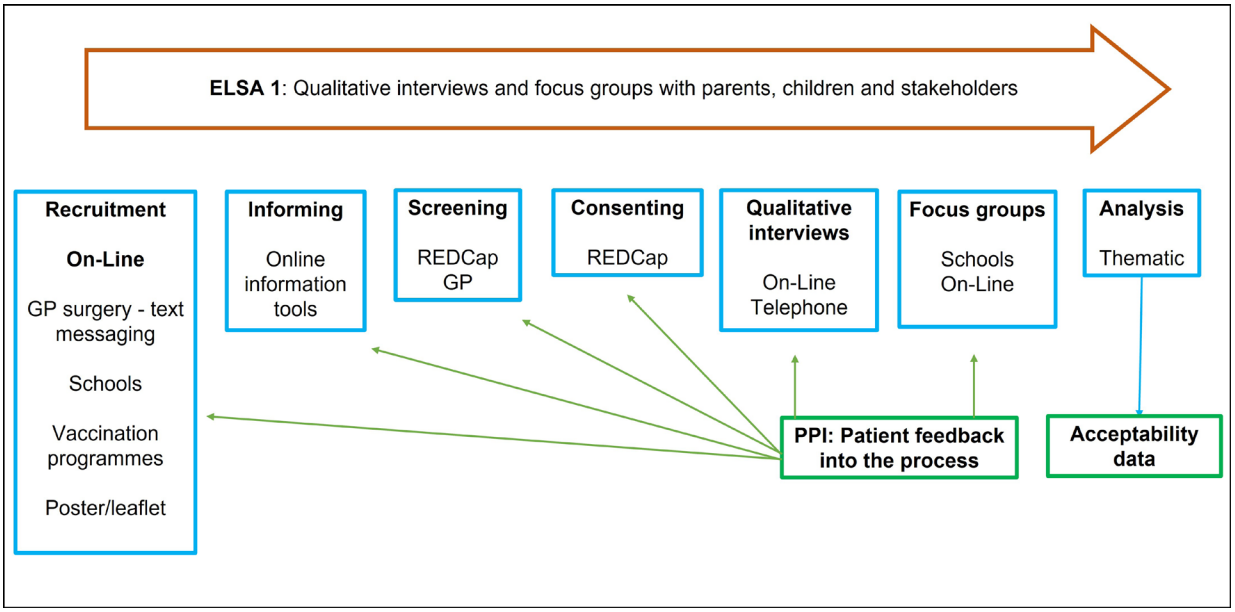

Figure 1 Qualitative study flow chart. A flow chart to depict how a participant will proceed through the ELSA 1 study. GP, general practitioner; PPI, patient and public involvement; REDCap, Research Electronic Data Capture.

and engagement between the study team and potential participants.[29] We will also engage with a health research recruitment service that uses social media to find eligible participants for clinical surveys and studies and who have previously engaged with other NIHR-funded research programmes to support recruitment to studies.

Community recruitment

In partnership with the Birmingham Community Healthcare NHS Trust (BCHC), we will approach mainstream primary headteachers and ask them to send email invitations to parents/guardians of all children on the school roll. We will also contact headteachers of primary and secondary schools asking them to consider hosting one parent or child focus group at their school. A similar method will be used by other trusts identified via the NIHR CRN, with the support of local authority public health where needed.

We will collaborate with community health engagement teams to recruit individuals from the general population from locations such as high streets and shopping malls. We will offer leaflets about the ELSA study and invite individuals to join our ELSA study mailing list to provide information about the study, eligibility and recruitment.

Inclusion and exclusion criteria

This is a broad community-based study. Parents or guardians of ≥1 child aged 3–13 years will be eligible for inclusion. The only exclusion criteria will be parents who are not willing or able to provide consent.

The lower age of 3 years was chosen because islet antibodies rarely develop before 2 years of age.[5] In consultation with our patient and public involvement (PPI) in research group, age 3 years was deemed acceptable for children to enter any future screening program that would include blood sampling for antibody measurement and oral glucose tolerance testing. The selection of this age would also facilitate integration of T1D testing and monitoring aligned with the preschool MMR vaccination program (aged 3–4 years).

Although T1D can develop at any age, the upper age of 13 years was chosen because there is significant evidence that the biology of T1D changes at or around this time.[8 30–32] Furthermore, our understanding of the natural history and the design of the prediction algorithms are all based on studies in children before the age of puberty. Also, including children aged 13 years aligns with the HPV vaccination program for boys and girls in schools, facilitating another recruitment route into testing programs in the future.

Consenting

Eligible participants interested in taking part in the study can access the study information and proceed to consent through an online process using the study website and Research Electronic Data Capture (REDCap) for data collection. A postal consent process is also available, and face-to-face, with social distancing measures, will be offered to families who are unable to proceed with online or postal consent. Informed consent will be obtained from all participants prior to participation in the study.

Qualitative methods and study flow

An overview of the qualitative study is provided in figure 2. Different topic guides will be used according to the participant type, with interviews and focus groups held, to sample parents, families, children and stakeholders, to be broadly representative of the general target population. At the start of the interview, the family or stakeholder will be shown a 4 min prerecorded presentation, which provides a definition of T1D and explains what our proposed general population antibody screening program involves, the eligibility criteria for participation, the factors to consider before taking part and the benefits of antibody screening. Following this, we will invite the interview participant to ask any questions and offer their first reactions to the proposed screening program.

An overview of the proposed screening program is provided in figure 3.

First, interviews will be held with individual parents, guardians or families (including their children),[24] lasting up to 60 min.[33] Parents will be asked to describe their previous experiences of T1D, their views on a T1D testing program, whether they would want their child to be tested and the reasons for or against this, and how they would want to be informed of the outcome. The children's view on the entire T1D testing and monitoring process will also be explored with the permission of the family and involving the entire family. This will include the design and flow of the website and in particular the children's adapted section of the website, which aims to inform about the study and the test. The family will also be asked to comment on what they understand about T1D, whether they know anyone with T1D and whether they would be willing to take part in any future study of T1D prevention.

Second, focus groups will be held with sets of parents and guardians for purposes of co-design and co-production, via video or telephone call[23 25] to explore barriers to a T1D testing and monitoring program. Furthermore, face-to-face focus groups will be held with parents and guardians either before school pick-up or after school drop-off. We will specifically target this work to socioeconomically deprived schools in the West Midlands to ensure that a wide spectrum of families are engaged. This will help further elucidate perspectives and barriers to T1D testing and monitoring.

Third, focus groups with children aged 9–11 years and 11–13 years will be held in school break times to minimize disruption to school lessons. The lower age of 9 years was deemed appropriate by PPI and pediatricians, because children at this age could begin to formulate their own views and could engage in a focus group setting. Focus groups with children were established because children may engage and respond differently, and perhaps more openly, to questions if they were interviewed in the

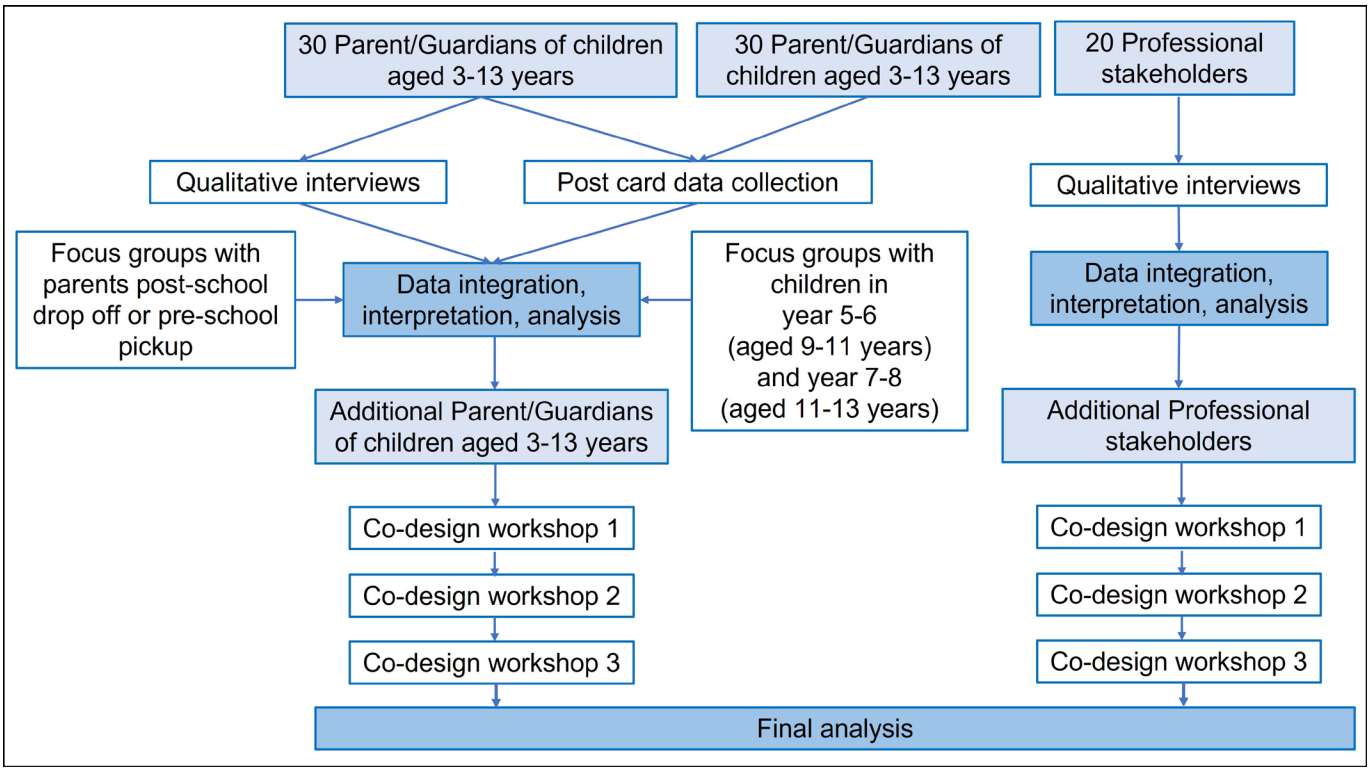

Figure 2 Qualitative study overview. A diagram to depict the qualitative methods used in the ELSA 1 study and how each stage will inform the next.

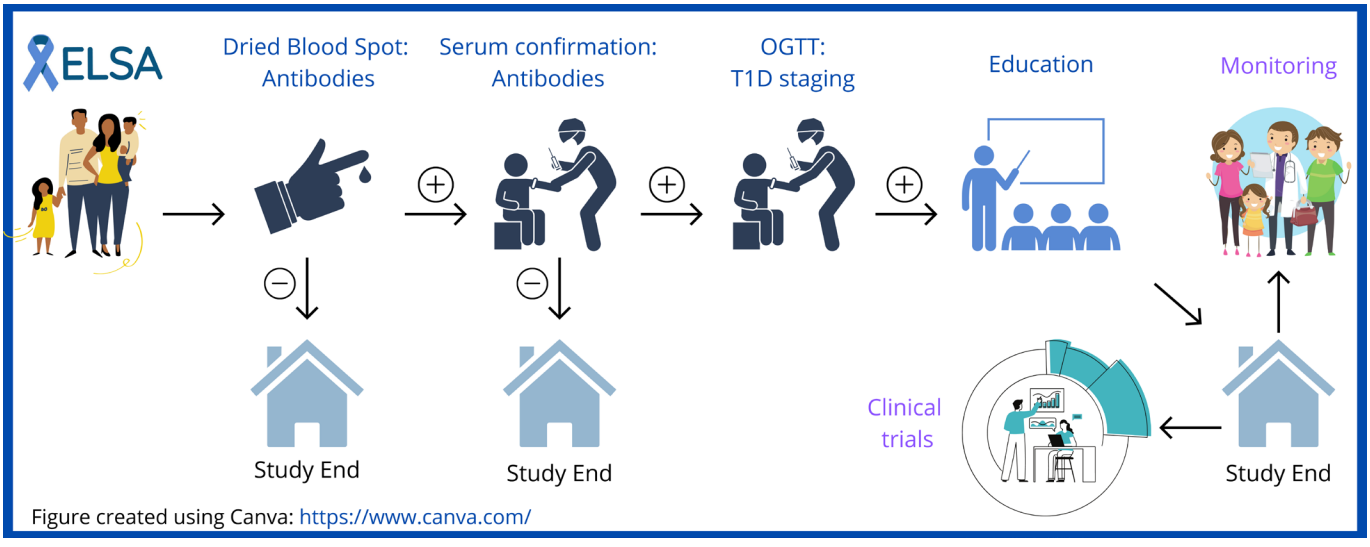

Figure 3 Summary of the proposed ELSA general population type 1 diabetes (T1D) antibody screening program (The ELSA Study). Children aged 3–13 years are eligible to take part. The child will first have a dried blood spot (DBS) performed to test for diabetes antibodies (islet antigen 2, anti-insulin, glutamic acid decarboxylase (GAD) and zinc transporter 8). If this is negative for antibodies, the child will not require further follow-up in ELSA. If the DBS is positive for antibodies, a venous collection for confirmation is arranged. If this is positive for 2 or more antibodies, the child will need to attend for an oral glucose tolerance test for staging of T1D. All antibody positive (single, double or more) children and their families will be invited to an education session. This will inform families about the signs and symptoms of T1D and advise about presymptomatic T1D and the risk of progression to stage 3 T1D over time. The family will also be informed about research studies their child may be eligible for, including monitoring programs and prevention studies, which they can pursue following completion of the ELSA study. https://www.canva.com/policies/free-media-license-agreement-2022-01-03/. No reproduction of this is image or any part of it is permitted. OGTT, oral glucose tolerance test.

absence of their parents (but with parental consent).[34] We will also work with BCHC to undertake community engagement with underserved communities through the regional minority ethnic research group to ensure satisfactory representation.

Finally, we will send out postcards to the families, seeking anonymously returned feedback about the study design and processes, allowing participants to comment informally and privately.[35] Postcards will be sent to families who have participated in the qualitative work, as well as to families who have expressed interest in the study but could not or were not available to take part in the interview to gather a balanced range of perspectives.

Sample size

In order to achieve thematic saturation and based on expectations around the different reasons for engaging with a testing program for T1D, we have estimated we will need up to 30 families to participate in this study.[36 37] We will also include approximately 20 children and 20 parents in the focus groups and 20 stakeholders in the individual interviews, or until thematic saturation is reached. For the co-design work, we will include up to 8 parents and 8 stakeholders per iteration, and sample until thematic saturation is met. We will as far as possible reflect the maximum demographic variety of the overall sample to understand their experiences of the study and to allow for theme saturation to be reached.[37] If we are not able to obtain saturation, we will recruit more families until we are able to do so.

Interviews and focus groups

Family interviews will include a maximum of 2 parents/guardians and up to 3 children. Focus groups will include up to 8 participants, and there will be 2 focus groups each for: (1) the parents, (2) children aged 9–11 years and (3) children aged 11–13 years (6 focus groups total). Additional sets of focus groups will be organized if required to obtain thematic saturation. We will also aim to obtain anonymous postcards from 60 families, 30 who completed the study interview and 30 families who expressed interest but did not participate.[35]

Interviews will be conducted using a topic guide that will explore families' views of the intervention, perceived value, timing, satisfaction with and understanding of information, the result delivery process and support, any potential harms and how the process might be improved in the future. We will include questions on parents' preference for blood collection to explore how this may differ from the studies of FDRs.[18] The topic guide has been developed from our current understanding of the literature as well from guidance from the PPI members and piloted with a few families. The topic guide will also be informed by the Theoretical Domains Framework (TDF). Some specific questions in the topic guide will be adapted to be appropriate for families or stakeholders. These groups will include FDRs and families where there is no history of T1D, representing different ages, ethnicities and demographics. We will also explore views on the recruitment and study procedure, including the quality of the participant information materials provided and how they would want the results of the T1D tests fed back to them. We will ensure that interpreters are available for families where English is not the first language and ensure this is also possible for online interviews.

Recruitment and study of professional (non-parent) stakeholders

We will also interview up to 20 professional stakeholders[33] who would be involved in implementing any future general population screening program. This will include healthcare professionals such as general practitioners and practice nurses from whose surgeries the recruitment and testing will occur, as well as stakeholders from schools, including headteachers and school nurses, where similar activities will take place. The purpose of the stakeholder interviews is primarily to ensure that the practical aspects of undertaking a large-scale community-based testing and monitoring program of children are explored and to gain their views on barriers and enablers to recruitment and testing.

Interviews with stakeholders will be held remotely, via video call or telephone and will last for 30 min (up to 60 min if required).[38]

Analysis of data

Interviews will be audio recorded and transcribed with the permission of participants and thematically analyzed using a constant comparative method.[29] Data management will be facilitated by the use of QSR NVivo. The interview topic guide will be informed by the TDF,[39] a behavioral framework that can help to reduce prior assumptions.[40] Freely emerging themes from the data will be mapped to the 14 TDF domains to provide a clear structure to identify the factors influencing families' decision-making processes and their eventual behavior around the screening process.

CO-DESIGN WORKSHOPS

Co-design workshops[41 42] will be held with parents and professional stakeholders to explore if the barriers identified in the previous interviews can be addressed and, if so, how best to do so. Up to 3 consecutive groups of new sets of parents will be recruited and informed of the qualitative results (and the results of the previous co-design group if this is relevant). We will employ diversity and rotation in families undertaking each iterative co-design workshop; community engagement through BCHC will be undertaken to ensure appropriate public representation.

Regulatory approval

The project will be hosted and embedded in BCHC who will facilitate links into primary care and schools. The University of Birmingham are the sponsors for this study and will provide support for any liability.

Patient and public involvement

PPI have been involved throughout the design of the ELSA study and have worked with us to inform the study process, findings, and direction. We will continue to work with PPI throughout the data collection and analysis phases to further inform the study design and interpretation and for dissemination of the results.

CONCLUSION

At the end of this study, we will have a comprehensive understanding of the views of parents, guardians, children, and professional stakeholders on the design and structure of a program for general population screening for T1D in children aged 3–13 years. We will also have insight into the barriers to participation and how these might be addressed.

This understanding will then be taken forward to design the most efficient T1D screening program in children. Specifically, knowledge of the barriers to recruitment will inform design of the study website, study materials, and recruitment processes. Understanding of the barriers to participation will inform the design of the T1D testing and monitoring program to ensure acceptability at the population level. Finally, understanding of the barriers to national implementation, from the perspectives of stakeholders, will optimize facilitation and integration of future screening programs into public health systems.

In this study, we seek to attain transferability and analytical generalization,[43] and our sample size is guided to facilitate thematic saturation. By employing qualitative methods, we aim to achieve a greater depth of understanding of families' viewpoints. One limitation is that we are interviewing families based on a hypothetical situation, and how families perceive they would react, or feel, could differ from the real-life scenario. However, with our qualitative approach, the findings are likely to be detailed, above what could be achieved by the use of quantitative methods alone, and the results may lend themselves to application in other clinical scenarios. For example, as this study is designed to understand families' perceptions of barriers to testing, the findings may be used to inform the setup of future UK testing and monitoring programs for diabetes and other conditions. Sampling minority populations is critical to the success of this study to ensure acceptability is being tested at the general population level; the study has been designed to facilitate this as far as possible.

Prevention (or long-term delay of T1D) has long been considered a 'holy grail' in medicine. With the advent of new therapies that can significantly delay T1D, we are on the cusp of realizing this goal, a goal that will have significant benefits to the physical and mental health of people who would otherwise develop T1D. Establishing a national system for early detection is the first major step in facilitating the testing of therapies and refining the treatment algorithm. This study will explore the acceptability of doing so.

Study status

This study is open for recruitment and will close by December 2022.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was reviewed by the North West national research ethics committee. The IRAS ID is 294654. Approval was issued in June 2021: 21/NW/0141. Participants gave informed consent to participate in the study before taking part.

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