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**Design of a prospective, longitudinal cohort of people living with type 1 diabetes
exploring factors associated with the residual cardiovascular risk and other diabetes-
related complications: the SFDT1 study**

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Abbreviations:

AJD : *Aide aux Jeunes Diabétiques*

CGM: continuous glucose monitoring

CV: cardiovascular

DCCT: Diabetes Control and Complications Trial

EDIC: Epidemiology of Diabetes Interventions and Complications

ENTRED: *Echantillon national témoin représentatif des personnes diabétiques traitées*

ePRO: electronic platform dedicated to patient-reported outcomes

FFD : *Fédération Française des Diabétiques*

FFRD : *Fédération Francophone pour la Recherche sur le Diabète*

GV: glucose variability

MACE: major adverse cardiovascular events

MI: myocardial infarction

QoL: quality of life

RIPH 2: *Recherche impliquant la personne humaine* (research involving human beings, rank 2) according to French law (Jardé)

SFD: *Société Francophone du Diabète*

T1DM: type 1 diabetes mellitus

ABSTRACT

Type 1 diabetes mellitus (T1DM) is associated with a high risk of cardiovascular (CV) complications, even after controlling for traditional CV risk factors. Therefore, determinants of the residual increased CV morbidity and mortality remain to be discovered. This prospective cohort of people living with T1DM in France (SFDT1) will include adults and children aged over six years living with T1DM, recruited throughout metropolitan France and overseas French departments and territories. The primary objective is to better understand the parameters associated with CV complications in T1DM. Clinical data and biobank samples will be collected during routine visits every three years. Data from connected tools, including continuous glucose monitoring, will be available during the 10-year active follow-up. Patient-reported outcomes, psychological and socioeconomic information will also be collected either at visits or through web questionnaires accessible via the internet. Additionally, access to the national health data system (Health Data Hub) will provide information on healthcare and a passive 20-year medico-administrative follow-up. Using Health Data Hub, SFDT1 participants will be compared to non-diabetic individuals matched on age, gender, and residency area. The cohort is sponsored by the French-speaking Foundation for Diabetes Research (FFRD) and aims to include 15,000 participants.

Keywords: Cardiovascular risk factors; Cohort; Glucose variability; Hypoglycaemia; Macroangiopathy; Quality of life; Type 1 diabetes

Introduction

Type 1 diabetes mellitus (T1DM) accounts for 5–10% of the total cases of diabetes worldwide. The incidence of all diabetes including T1DM is steadily increasing in all countries around the world [1]. Increased incidence in younger children [2, 3] leads to a longer duration of the disease and consequently prolonged exposure to hyperglycaemia throughout life and higher risk of developing macrovascular complications [4, 5]. In Sweden from 1998 through 2014, mortality and incidence of cardiovascular (CV) outcomes declined substantially among persons with diabetes, although fatal outcomes declined less among those living with T1DM than among controls [6]. A nationwide, population-based Finnish register of patients diagnosed with T1DM showed an excess of mortality mainly due to ischaemic heart disease [7]. Age at onset of T1DM is an important determinant of CV outcomes, with the highest excess risk in females [8].

The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study showed that intensive treatment of hyperglycaemia leads to reduced CV morbidity and mortality [9, 10]. However, hyperglycaemia per se only partly explains CV morbidity and mortality in T1DM as two-fold CV mortality has been observed even in the case of good glycaemic control [11]. Other CV risk factors are involved in this over-mortality including the most traditional ones, such as hypertension, dyslipidaemia, smoking, and family history of premature coronary artery disease. The presence of microangiopathic complications, especially nephropathy and subclinical CV disease, can be used to predict CV events in this population [12]. It has been shown that patients with T1DM with none of these traditional CV risk factors had about an 80% higher risk of CV events compared to non-diabetic individuals [13]. This indicates that other determinants of CV morbidity and mortality remain to be explored in T1DM, such as the role of hypoglycaemia [14], glucose variability (GV) [15], environment, new pathophysiological determinants, i.e. inflammatory pathways [16] or psychosocial factors [17-20]. Recent technological advances have provided new therapeutic options to patients with T1DM, especially insulin pumps, continuous glucose monitoring (CGM) systems, and hybrid closed-loop insulin pumps with CGM systems. These devices have many benefits for patients, including improved diabetes control, fewer hypoglycaemia events and diabetic ketoacidosis events, and improved quality of life (QoL) [21]. In this new context, evaluating macrovascular complications in this population is particularly relevant.

In order to explore these new determinants, the French-speaking Society of Diabetes (SFD) decided to create a large national cohort study in France, based on accurate T1DM phenotyping along with a detailed clinical database, an extensive biobank with multiple biospecimens, detailed information on hypoglycaemia, lifestyle, psychosocial factors, extensive structured data from CGM devices to assess GV, and during the follow-up, medico-administrative information from the French National Health Data System (Health Data Hub).

Objectives

The primary objective of SFDT1 is to evaluate the risk factors/determinants of major adverse CV events (MACE) in individuals with T1DM.

The secondary objectives are (1) to evaluate classical and non-classical risk factors associated with every component of incident MACE; (2) to assess the role of GV (including hypoglycaemia) in health events (complications, QoL, mortality); (3) to assess the relationship between microangiopathy and macrovascular complications; (4) to identify and characterise novel biomarkers and metabolic pathways associated with health events; (5) to identify psychosocial factors associated with health events; (6) to identify the impacts of therapeutic and care innovations on metabolic control and diabetic complications; (7) to identify the impact of medications on metabolic control and diabetic complications; and (8) to assess the economic burden of T1DM and its complications using various perspectives and according to both patients' clinical and socio-economic characteristics and their health care pathways.

Material and method

Study design

SFDT1 is a non-randomised, prospective, multicentre national real-life T1DM cohort study with limited intervention. A large set of clinical, biological, personal, lifestyle, environmental, social and CGM data will be collected. Data from the Health Data Hub (health events, mortality) will be compared with those of a control group of matched individuals without diabetes.

This cohort study involves minimal risks and constraints for individuals and – according to French law (Jardé) on research involving human beings (RIPH, *Recherche impliquant la personne humaine* – is ranked level 2, i.e. involving “interventional research with low

impact”. The data will also constitute a Health Data Warehouse. The ClinicalTrials.gov Identifier is NCT04657783.

Inclusion and non-inclusion criteria

The inclusion criteria of the SFDT1 cohort are: (1) the will to sign an informed consent form (by one of the parents in the paediatric population), (2) age ≥ 6 years, (3) T1DM defined as age at diabetes diagnosis > 1 year and ≤ 35 years, with insulin treatment initiated within the first 12 months following diabetes discovery; (4) affiliation to the French social security scheme (RIPH-2 constraint) and (5) ability to speak and read French. Adult patients under guardianship or protection for vulnerable people are excluded.

Recruitment and inclusion

In France, most patients with T1DM are followed by a diabetologist, either in a university hospital, a regional hospital, or a private structure [22]. Participants will be recruited by diabetologists in such places, considering that private diabetologist offices would be linked to hospital centres for biobanking. To date, 75 centres (51 dedicated to adults and 24 to children) over France, including overseas territories, have planned to participate in SFDT1 recruitment ([Figure S1; see supplementary materials associated with this article on line](#)).

Consent forms will be signed during the consultation. This written consent will include: (1) participation in the study (mandatory); (2) participation in the biobank (optional) with (3) genetic analyses (optional) and (4) link to the Health Data Hub (optional). For each part of the study, the participant will consent to data being used for specific research dealing with diabetes and, optionally, for research of additional topics (Health Data Warehouse, optional).

The collected data at enrolment will include email address and mobile phone number to be contacted via the electronic platform dedicated to patient-reported outcomes (ePRO); and personal healthcare system affiliation number (NIR) for the adult patients who consented to link to the Health Data Hub. The NIR is considered as sensitive personal data and will be stored under specific conditions.

Study Schedule

The first visit will include (1) a clinical visit including face-to-face questionnaires, (2) connection of devices such as CGM systems, (3) ePRO activation, (4) biobanking and (5) link to the Health Data Hub (4 and 5 upon the patient’s acceptance). Follow-up will include (1) clinical visits every three years during nine years including (2) bio banking at each visit,

(3) connected device data throughout the study, (4) monthly and annual self-reported questionnaires through the ePRO platform and (5) passive follow-up through the Health Data Hub. [Figure 1](#) shows the different parts of the study.

The inclusion period will last five years (from June 2020 to early 2026). The patient will actively participate during 10 years, with a subsequent 20-year passive follow-up through Health Data Hub (last extraction planned in 2042). The total duration of the study will therefore be 22 years.

Data collection at baseline

- Clinical data:

The data collected at baseline will include demographic data (gender, parents' birth countries, month / year of birth, place of birth) and T1DM characteristics (age at disease onset, presentation at onset, presence of specific antibodies, metabolic control, treatment, complications). At baseline and at each clinical visit, a routine standardised set of data will be collected. These data collected both at inclusion and during each follow-up visit are summarised in [Table I](#).

Furthermore, face to face questionnaires will be filled out during each clinical visit by the investigator or a clinical research associate and the patient. The questionnaires are listed in [Table II](#).

- Connected tools:

CGM data will be regularly uploaded anonymously from platforms, especially LibreView® currently used in France. CGM data will provide GV parameters (coefficient of variation and standard deviation of glucose measurement), glucose management index and time in different ranges (in/below/above) [23, 24]. The threshold of hypoglycaemia awareness will be explored using the Gold score [25] and the Clarke questionnaire [26]. Finally, the occurrence and the number of severe hypoglycaemia and diabetic ketoacidosis events will also be considered. When necessary and appropriate, other platforms and devices, such as connected insulin pens, will be used.

-Biobank:

Inflammation [16] and vascular endothelial injury occur early and could participate in accelerated atherosclerosis in T1DM [13, 27]. The mechanisms that lead to inflammation and by which inflammation operates in T1DM are likely to be multiple and may include GV (including hyperglycaemia and hypoglycaemia) [28, 29] excess adiposity or altered body fat

distribution, thrombosis, adipokines, and peripheral hyperinsulinism. Furthermore, the coagulation system is altered in T1DM due to changes in clotting factor levels and/or activity [27]. Genetic polymorphisms such as haptoglobin genotype [30] have also been found to be associated with the progression and prognosis of CV disease in T1DM [4].

In this context, SFDT1 includes an optional biobank. [Table III](#) shows the collected biological samples, and how storage will at the current time be centralised in two biological research centres: AP-HP, Bichat hospital, Paris and Lille, LIGAN platform, for DNA extraction and genetic analyses. After DNA samples extraction, genetic association analyses using DNA microarrays (comprising more than 1 million DNA polymorphisms, Illumina technology) will be performed. Moreover, studies for rare genetic variants by exome or whole genome sequencing will possibly be considered.

Participant timeline and data collection

- Clinical visit on site

Routine visits will be proposed every three years (\pm 6 months) for nine years during the active follow-up period of the study (inclusion (T0), T0+3, T0+6; T0+9; [Figure 1](#)). These visits will be similar to the inclusion visit and include collection of clinical data ([Table I](#)), face-to-face questionnaires ([Table II](#)) and biobanking ([Table III](#)).

- Data collected from devices

Participants' shared data (including CGM data) will be routinely extracted from platforms.

- Data from ePRO

Twelve monthly self-reported questionnaires, each one requiring 5 to 10 minutes to answer, will be repeated each year. Information on hypo- and hyperglycaemia will be evaluated yearly. These questionnaires will screen various dimensions such as QoL, nutrition, diabetes-related distress, burden, sleep quality, sexual function in men and women, and impact of disease on occupational activity ([Table S1](#); [see supplementary materials associated with this article on line](#)). A yearly questionnaire will be sent, dealing especially with putative change of residence, new centre of follow-up, and new events such as severe hypoglycaemia and MACE.

- Data from Health Data Hub

Health Data Hub records healthcare expenditures for nearly 66 million inhabitants, for whom information is individualised and anonymised at the individual level. Health Data Hub is an

exhaustive database and covers 99.8% of the French population. This database has been used to perform many epidemiological studies [31].

The database lists (1) socio-demographic beneficiary characteristics (such as beneficiary of the complementary Universal Health Coverage, health insurance plan, ICD-9 and ICD-10 codes in case of chronic severe illness-registration); (2) data on healthcare professionals; (3) data on healthcare utilisation (drug code with date of prescription and of delivery, Common Classification of Medical Procedure code for medical procedures, National Table of Biology for biological testing, List of Products and Services for medical devices) and (4) data on hospitalization.

Health Data Hub will be extracted considering a one-year time lag so that information can be recorded in the database. Extraction will include retrospective data from 2013. Three waves of extraction have been planned during the inclusion phase: *i*) in 2023 for participants included during the first 18 months of inclusion; *ii*) in 2025 for participants included during the following 24 months; and *iii*) in 2027 for the subsequent participants. Then, further data extractions have been planned, to be performed every three years with a last extraction in 2042, including 2041 data.

A control group will also be set up in a three-step process during the inclusion phase for collection of only Health Data Hub data and the same sequence of extractions of healthcare expenses every three years. This control group of individuals without diabetes at inclusion [32] will be matched by age group, gender and residence area (region); and monitored exclusively in the Health Data Hub. Three controls will be selected for each patient included to ensure sufficient power for comparative analyses in subgroups by age, treatment, etc.

Study outcomes

Primary outcome

The primary outcome is a composite of non-fatal myocardial infarction, non-fatal stroke, and CV-related death (defined as death occurring within 30 days after a diagnosis of myocardial infarction, stroke, unstable angina, heart failure, sudden cardiac arrest, cardiogenic shock, other cerebrovascular events, or other CV events recorded in a medical claim in any setting).

MACE will be collected during clinical visits or through the Health Data Hub. The codes identifying each event are shown in supplementary data [Table S2 \(see supplementary materials associated with this article on line\)](#). If a MACE is logged by a patient through ePRO, it will be checked by an investigator.

Secondary outcomes

Health events will be considered as secondary outcomes and will include the following:

- Macrovascular complications: every event composing the MACE and each event related to CV mortality;
- Microvascular complications, including retinopathy and maculopathy [33]; nephropathy [34]; neuropathy: routine physical examination, classification of symptoms according to Michigan score [35], simple routine questions about presence of autonomic neuropathy; foot deformities, wounding and history of amputation;
- Non-typical complications such as musculoskeletal disorders [36], periodontal disease, hearing loss and history of cancer;
- Mortality

These events will be collected during clinical visits or through the Health Data Hub (Table S2).

- QoL determinants will be evaluated. QoL will be determined using the EQ5DL face-to-face questionnaire at each clinical visit.

Finally, costs associated with health events will be evaluated and their determinants identified. All healthcare resources consumed by each patient will be extracted from Health Data Hub, including for example physician and pharmacy fees, laboratory tests, imaging studies, nursing care, physical therapy, other attendant care, medical devices, transportation fees, other non-hospital care, hospital stays, and daily allowance or disability pension. Each item of ambulatory healthcare resource consumption will be quantified and associated costs extracted. Detailed data will be collected for in-patients stays. Participants with T1DM will be compared to matched controls.

Statistical analyses

The analyses will be performed by the Clinical Research Unit of Hospital Fernand Widal, Assistance Publique – Hôpitaux de Paris, Paris, France. The sample size calculation was based on a dichotomous outcome (MACE yes/no) with the design of an independent prospective cohort and used the Power and Sample Size software developed by Vanderbilt University [37]. We expect the new risk factors to be associated with CV risk with a low-to-moderate magnitude, with relative risk between 1.10 and 1.50. Based on our minimal

assumption (risk ratio [RR]=1.10) and with an overall probability of MACE events set at 0.25 (adapted from [38]) for the unexposed group during the 20-year follow-up, a power set at 80%, an α risk of 5%, and the exposed group considered as the extreme quintile group of the exposure of interest (such as GV for instance), the required minimal number of patients is 15,080. Consequently, we finally decided to target the inclusion of 15,000 patients with T1DM. The patients who decide to withdraw will not be replaced, unless such withdrawal occurs close to inclusion.

RR estimations and their 95% confidence intervals (CI) will be derived from Cox proportional hazards regression models. RRs will be determined considering the lowest quintile of exposure as the reference category. Linear trends across categories for continuous variables will be tested by assigning the median value for each exposure category and modelling exposure as a continuous variable. In multivariable analyses, models will be stratified by 5-year interval birth cohorts and simultaneously adjusted for various cofactors (depending on the main exposure and outcomes of interest). Missing values will be studied and multiple imputations will be used if needed. For continuous variables, restricted cubic spline regression models, based on three knots, will also be performed. The knots will be located at the 25th (reference value), 50th, and 75th percentiles.

Governance and study management

The French-speaking Society of Diabetes (SFD: *Société Francophone du Diabète*), a society whose objective is to promote the development of research and good practices of diabetology in France, is the initiator of the SFDT1 cohort. The French-speaking Foundation for Diabetes Research (FFRD), founded by the SFD, is the sponsor. An executive committee composed of two professors OF diabetology (JPR and EC), an epidemiologist (GF) and a project manager (LS) will coordinate the cohort under the control of a steering committee composed of the directions of the SFD, the FFRD, the French association of patients (FFD, *Fédération Française des Diabétiques*) and the French association for young diabetics (AJD, *Aide aux Jeunes Diabétiques*). The executive committee will work in collaboration with a scientific council and a committee of industrial partners ([figure S2; see supplementary materials associated with this article on line](#)).

Discussion

To improve knowledge of T1DM and its complications, several large-scale initiatives including the Finnish Diabetic Nephropathy Study (FinnDiane) [39], the Swedish National Diabetes Register (NDR) [40], the German Diabetes Study (GDS) [41], and the American T1D Exchange [42] have been developed. All these cohorts or registers have specificities in terms of recruitment, age distribution, logistics, quality and quantity of biobanking, and follow-up (Table S3; see [supplementary materials associated with this article on line](#)). Some, such as the NDR study, which is one of the largest T1DM cohorts worldwide, including 30,000 participants, did not analyse biological specimens; others do not have any CGM data or detailed information on socioeconomic, lifestyle or psychological factors.

In France, there are few studies including individuals with T1DM, such as the ENTRED study [43] or “Constances” [44]. However, all these French databases present several limitations as they *i*) have a small sample size of individuals with T1DM; *ii*) do not use an accurate T1DM phenotyping; *iii*) do not systematically include biological analyses; *iv*) do not cover a wide range of patient ages; or *v*) do not have access to CGM data. Overall, SFDT1 is the first study covering all the key issues on a very large set of people living with T1DM.

As many research questions remain unanswered, we felt it was crucial to design an extensive and detailed hybrid cohort study dedicated to T1DM, combining, for each participant, biological, omics, digital real-world and ePROs data. It is expected that this will aid the identification of important new parameters and validate the results reported in other landmark studies.

The SFDT1 cohort is patient-centred and aims to actively engage participants in all the aspects of the research program and to create a large community of individuals with T1DM. Participants will contribute to research and be partners in the discovery processes.

To conclude, the SFDT1 cohort represents a unique opportunity to increase medical knowledge about T1DM and to improve, on a short-term basis, the health of persons living with T1DM. Thanks to our unique set of information (clinical, biological, genetics, medical devices, ePROs), collected from such a large population, we will primarily aim to explain the residual increased risk of CV events and mortality in individuals with T1DM, even in the absence of the main traditional risk factors. SFDT1 results should lead to key discoveries, interesting biomarkers and should ultimately lead to new treatment strategies. In addition, our secondary aims are to better understand, especially through ePROs, how regular changes involving elements such as environmental, regional or psychosocial factors, can make a difference both in daily T1DM management and in the long-term health status of people living with T1DM.

Therefore, our work will also enable us to suggest new intervention strategies to facilitate the life of persons living with T1DM and decrease the burden of the disease. The health data collected will be useful to improve outcomes in clinical practice. Such data will also be used to promote more efficient practices in diabetes centres to manage known risk factors. This should lead to better cardiovascular prevention through changes in risk management and the creation of new collaborations between French diabetes centres.

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- **Duality of Interest:**

JPR is an advisory panel member for Sanofi, MSD, Eli Lilly, Novo Nordisk, Abbott, Alphadiab, Air Liquide and Medtronic and has received research funding from and provided research support to Abbott, Air Liquide, Sanofi, and Novo Nordisk. BV is an advisory panel member for Astra Zeneca, Lilly, NovoNordisk and received speaker honoraria from Amgen, Astra Zeneca, Boehringer-Ingelheim, Lilly, NovoNordisk and Sanofi. BD is employed by CEMKA, a health economic and outcomes research team providing health studies and advisory services for private and public organisms. BD served as an advisor, consultant, or member of a speaker bureau for Merck Sharpe & Dohme Corp., Novo Nordisk, Pfizer Inc., Eli Lilly, Sanofi-Aventis, and Boehringer-Ingelheim. SP has received writing and consulting fees from Abbott, Air Liquide, Astra Zeneca, Lilly, Medtronic, Novo Nordisk, Roche Diabetes Care, Sanofi, and VitalAire. PYB has received speaker honoraria from Abbott, Roche, Eli Lilly, Novo Nordisk and Sanofi, and served on advisory board panels for Abbott, Diabeloop, Roche, Medtronic, Dexcom, Insulet, LifeScaen, Eli Lilly, Novo Nordisk and Sanofi. HS is the main share owner and full-time employee of e-health Services Sanoïa, a full service CRO providing digital and scientific services for real-world evidence studies promoted by private and public organizations. HH has received congress invitations, honoraria and consultancy fees from Abbott, Animas/Johnson & Johnson, Medtronic, Roche, Eli Lilly, Novo Nordisk and MSD, and served on advisory board panels for Diabeloop and Insulet. NJ has received speaker honoraria from Eli Lilly and Sanofi, served without fees on advisory boards for Defymed, Diabeloop and public services. J.-F.G. reports personal fees and nonfinancial support from Eli Lilly, personal fees and nonfinancial support from Novo Nordisk, personal fees and nonfinancial support from Gilead, and personal fees and nonfinancial support from AstraZeneca. GF is or has been a consultant, expert or invited speaker for the following companies: MSD, Lilly, Roche Diabetes Care, AstraZeneca, Danone Research, Diabeloop, Bristol Myers Squibb and L'Oréal R&D. MJ has received consulting/speaker fees and/or research grants from Abbott, Medtronic, Glooko, Lilly, Novonordisk, Sanofi, Dexcom, Astrazeneca, Amgen, MSD, BMS, Boehringer-Ingelheim, Pfizer, Roche Diabetes Care, Air Liquide Santé International, Nestle Home Care, and Vitalaire. LB has received congress invitations, honoraria and consultancy fees from Abbott, Astra Zeneca, Roche, Eli Lilly, Novo Nordisk, Boehringer Ingelheim, Janssen, Novartis, Sanofi, Bayer, BD and MSD. EB has received consulting / speaker fees from Abbott, Lilly, Medtronic, Novo Nordisk, Insulet, and Orkyn. R.R. is an advisory panel member for

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- **Author Contributions**

JPR, BV, BT, SP, PYB, EB, LB, NJ, MJ, RR, ASG, SC, FLV, JB, HH, PF, CT, JFG, EL, LS, GF and EC contributed to the planning, conception and design of the study. They contributed to reporting the work in this article which was first written by JPR, LS, GF and EC. JPR, BV, SP, EB, JB, CT, and EC participated in the first inclusion in the cohort. JPR and EC are the co-coordinators of the study. BD is the referent for Health Data Hub. AB is the expert in genetics and coordinates the DNA extraction and storage . ST is the referent for the biobank. HS is the head of CRO Sanoia. SL is in charge of the fundraising unit. EV is the methodology referent . GF is the epidemiology referent . All authors approved the final version of the manuscript

- **Study Website:** <https://sfdt1.fr/>
- **Twitter:** [@sfdt1_fr](https://twitter.com/sfdt1_fr)
- **Linkedin:** e-cohorte sfdt1

- **Ethics and dissemination**

The study has been approved by the ethics committee “*Comité de protection des personnes, CPP*” Ouest V-RENNES (N° ID-RCB : 2019-A01681-56) in December 2019.

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Figure Legend

Figure 1: Schedule of the Cohort SFDT1

Figure 1

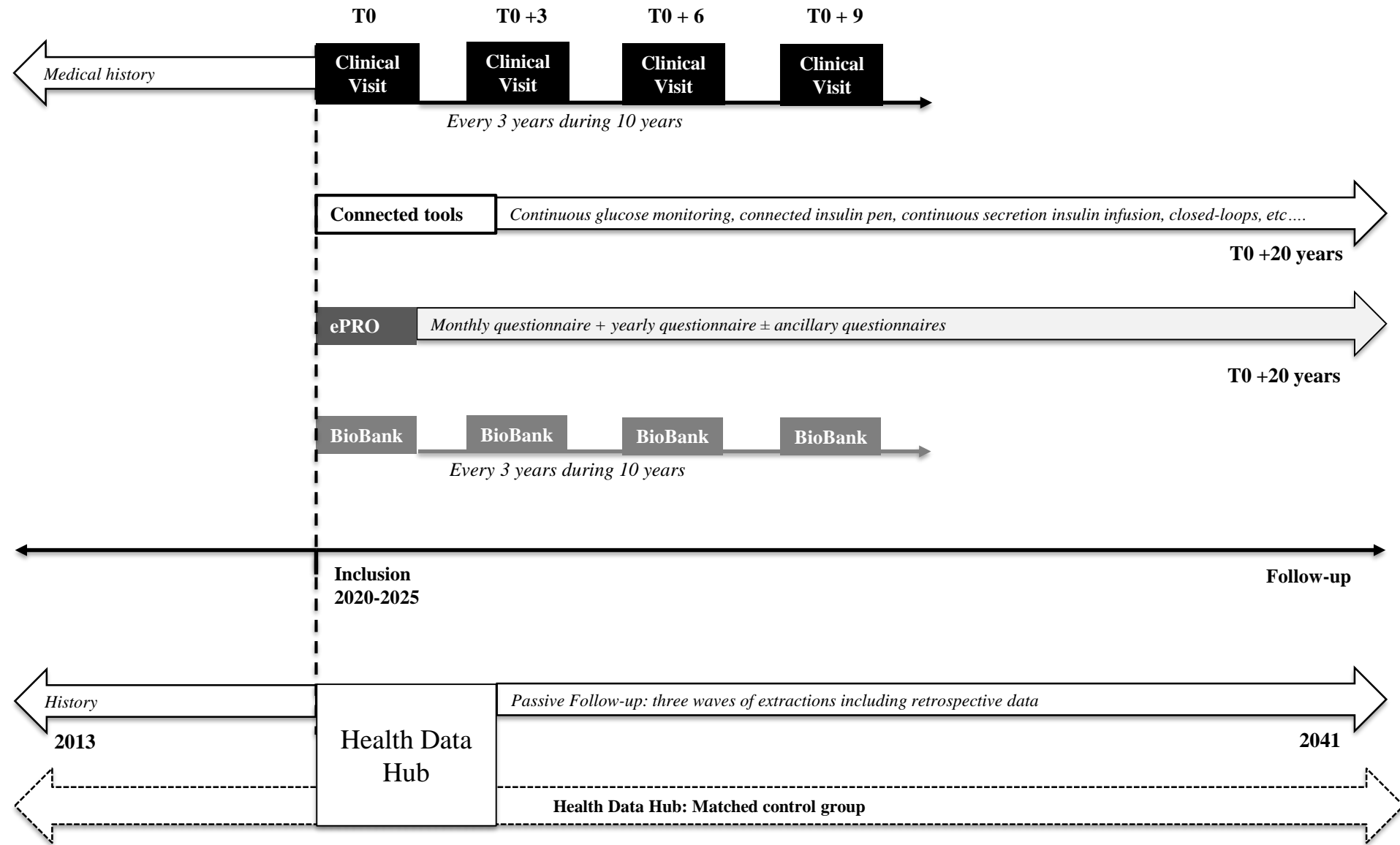


Table I: Routine data collected during each visit

Area of interest	Data collected
Contact details (for ePRO, messaging and motivation calls only)	Name, email, mobile for the messaging system
Health Data Hub	Personal Healthcare System affiliation number (NIR)
Inclusion characteristics	Date of inclusion / investigator Month/year of disease onset, Disease phenotype & antibody, Disease diagnostic circumstance, Country and department of residence Gender, Month / year and place of birth,
Family / housing status	Country of birth of parents, Marital status / Living alone
Occupational activity	Last diploma Socio professional category Working status Working hours (night or day) Missed work days due to T1DM Special workstation requests
Children	Number of school days missed due to T1DM Number of sport activities / week Activities supported by family Psychological support Use of therapeutic patient education use Burden of the disease for the parents Nocturnal disturbances during last 4 weeks
Cardiovascular factors	Body mass index, waist circumference Maximum weight and year of maximum weight Smoking status Hypertension Sleep apnoea Family history of cardiovascular disease Personal history of cardiovascular disease
Medical history	Family history of diabetes Personal history of autoimmune disease Bariatric surgery
Treatments and care	Treatment of diabetes (insulin and graft) All other current treatments Type of care facility (private, hospital, mixed) and frequency of consultation Remote-monitoring modalities
Cardiologic parameters	Sitting and standing blood pressure Cardiac frequency Summary of electrocardiogram (if available)

	Coronary artery calcium score (if available)
Ophthalmology	Personal history of ophthalmology events Source of data (patient or summary) Diabetic retinopathy classification Macular oedema status
Nephrology (adult only)	Diabetic nephropathy classification
Neurology / feet	Michigan score value Personal history of foot disorders
Other complications of diabetes	Personal history of other complications of diabetes (... cancer).
Gynaecologic history (women only)	Age at menarche Number of children/pregnancies Personal history of ovary-related disease Ever use of contraceptive pills Breastfeeding (cumulated number of months) Menopausal status and age at menopause
3-year laboratory results (upon availability)	Hb _{A1c} Fasting C peptide Glycaemia Liver enzymes Total cholesterol total, triglycerides, HDL-cholesterol, calculated LDL-cholesterol Thyroid function Creatininaemia Albuminuria / Creatinuria
Hypoglycaemia and hyperglycaemia (previous year)	Number of severe hypoglycaemia events Number of ketoacidosis events
Continuous glucose monitoring (CGM) practices and results (including legacy GM)	CGM adoption status CGM device: legacy, connected, etc. Practices of CGM / number of scans per day Data from ambulatory glucose profile
Death (if applicable)	Vital status from medical file Context of death

Table II: Face-to-face questionnaires at each clinical visit

Area of interest	Data collected
Educational cursus	Ad hoc question
Physical Activity	I-PAQ (International Physical Activity Questionnaire)
Psychosocial deprivation	EPICES (<i>Evaluation de la Précarité et des Inégalités de santé dans les Centres d'Examens de Santé</i>) (psychosocial deprivation questionnaire)
Quality of life	EQ5DL (standardised measure of health-related quality of life)
Eating disorders	mSCOFF 7Q (eating disorder questionnaire)
Fear of Hypoglycaemia	HSF II (Hypoglycaemia Fear Survey-II)
Hypoglycaemia unawareness	Impaired hypoglycaemia awareness: Gold score
Hypoglycaemia unawareness	Impaired hypoglycaemia awareness: Clark Score
Senior only (> 65 years old)	AGGIR rank (Autonomy, Gerontology, Iso-Resource Groups) ADL score (Activities of Daily Living) MNA (Mini Nutritional Assessment) MMSE (Mini-Mental State Examination)
Children only	EPICES (for parents) ETP: evaluation of therapeutic education (for parents) Socio-demographic characteristics of parents WHO-5: The World Health Organisation - Five Well-Being Index (for children and parents) HFS (for parents and children) Hvidøre questionnaire (quality of life for children and teenagers)

Table III: biological samples collected at each visit

Collection	Preparation	Storage	Purpose	Conservation duration	Future
Blood	One tube - 4-5 ml	-80°C	4 aliquots of Serum for biochemical analysis	30 years	Destruction
Blood	One EDTA tube - 5 ml	-80°C	4 aliquots of Plasma for biochemical analysis	30 years	Destruction
Blood	Two EDTA tubes - 5 ml	-80°C	2 aliquots for PBMCs Extraction	30 years	Destruction
Total blood	One EDTA tube - 5 ml	+4°C	1 aliquot for DNA extraction (genetic analysis)	30 years	Destruction
Urine	One tube - 5 ml	-80°C	Biochemical analyses	30 years	Destruction
Hair	Lock of hair	Ambient temperature	Drug exposure and toxin impregnation	30 years	Destruction
Saliva	1-2 ml	-80°C	Biochemical analyses	30 years	Destruction