BMJ Open

A randomized, prospective, medico-economic nationwide French study of islet transplantation in patients with type 1 brittle diabetes: the STABILOT study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013434
Article Type:	Protocol
Date Submitted by the Author:	13-Jul-2016

Complete List of Authors:	Lablanche, Sandrine; Centre Hospitalier Universitaire de Grenoble, Department of Diabetology; Universite Grenoble Alpes, LBFA - U1055 INSERM David-Tchouda, Sandra; Centre Hospitalier Universitaire de Grenoble, Cellule d'évaluation médico-économique des innovations CIC ; Universite Grenoble Alpes, CIC 1406 Grenoble, TIMC-Imag UMR Margier, Jennifer; Centre Hospitalier Universitaire de Grenoble, Cellule d'évaluation médico-économique des innovations, CHU Grenoble Alpes, CIC 1406 Grenoble, TIMC-Imag UMR 5525 Univ. Grenoble Alpes, F-38000 Grenoble, France; Universite Grenoble Alpes, CIC 1406 Grenoble, TIMC-Imag UMR Schir, Edith; Centre Hospitalier Universitaire de Grenoble, Centre régional de Pharmacovigilance Wojtusciszyn, Anne; Centre Hospitalier Regional Universitaire de Montpellier, Pôle Rein Hypertension Métabolisme, Service d'Endocrinologie Borot, Sophie; Centre Hospitalier Universitaire de Besancon, Service Endocrinologie-Métabolisme et Diabétologie-Nutrition Kessler, Laurence; Hopitaux universitaires de Strasbourg, Service d'Endocrinologie Diabète et Maladies Métaboliques, Pôle NUDE Morelon, Emmanuel; Centre Hospitalier Universitaire de Lyon, Service d'Urologie et de Chirurgie de la Transplantation, Pôle Chirurgie Pattou, François; INSERM U1190, Translational research for diabetes, 59000 Lille, European Genomic Institute for Diabetes, EGID; Centre Hospitalier Regional Universitaire de Lille, Endocrine Surgery, Hôpital Huriez Vantyghem, Marie-Christine; Centre Hospitalier Regional Universitaire de Lille, Endocrinology and metabolism; INSERM U1190, Translational research for diabetes, 59000 Lille, European Genomic Institute for Diabetes, EGID Berney, Thierry; Hopitaux Universitaires de Geneve, Department of Surgery, Islet Isolation, and Transplantation Center Benhamou, Pierre-Yves; Centre Hospitalier Universitaire de Grenoble, Department of Diabetology; Universite Grenoble Alpes, LBFA - U1055 INSERM
Primary Subject Heading:	Diabetes and endocrinology
Secondary Subject Heading:	Health economics

Keywords:	Brittle Type 1 Diabetes, HEALTH ECONOMICS, Sensor augmented pump therapy, Islet Transplantation

A randomized, prospective, medico-economic nationwide French study of islet transplantation in patients with type 1 brittle diabetes: the STABILOT study protocol

Sandrine Lablanche[1, 2], Sandra David-Tchouda[3], Jennifer Margier[3], Edith Schir[4], Anne Wojtusciszyn[5], Sophie Borot[6], Laurence Kessler[7], Emmanuel Morelon[8], François Pattou[9,10], Marie Christine Vantyghem[10,11], Thierry Berney[12], Pierre-Yves Benhamou[1,2]
on behalf of STABILOT Trial investigators

Keywords: Islet transplantation, medico-economic, brittle diabetes, trials

Abstract: 203 words

Main body: 2521 words

Table: 1

Corresponding author:
Sandrine LABLANCHE
Department of Endocrinology
CHU de Grenoble, BP217
38043 Grenoble, FRANCE
Phone: +33 (0)4 76 76 37 36 – Fax: +33 (0)4 76 76 50 42

E-mail: slablanche@chu-grenoble.fr

The STABILOT protocol was supported by grants from Projet de Recherche Medico Economique National 2014, DGOS (Grant number 14-0225) and by grant no. 3200B0-102134 from the Swiss National Foundation for Scientific Research.

The authors declare no conflicts of interest.

Authors Adresses

[1]Department of Diabetology, Pôle DigiDune, Grenoble University Hospital, Grenoble Alpes University, Grenoble, France

[2]Grenoble Alpes University, INSERM, U1055Laboratory of Fundamental and Applied Bioenergetics, F-38041, Grenoble, France

[3]Cellule d'évaluation médico-économique des innovations, CHU Grenoble Alpes, CIC 1406 Grenoble, TIMC-Imag UMR 5525 Univ. Grenoble Alpes, F-38000 Grenoble, France

[4]Centre régional de Pharmacovigilance, Grenoble, France

[5]Centre Hospitalier de Montpellier, Pôle Rein Hypertension Métabolisme, Service d'Endocrinologie, Montpellier, France.

[6]Centre Hospitalier Universitaire Jean Minjoz, Service d'Endocrinologie-Métabolisme et Diabétologie-Nutrition, Besançon, France.

[7]Hôpitaux Universitaires de Strasbourg, Service d'Endocrinologie Diabète et Maladies Métaboliques, Pôle NUDE, Strasbourg, France.

[8]Hospices Civils de Lyon, Service d'Urologie et de Chirurgie de la Transplantation, Pôle Chirurgie, Lyon, France.

[9]University Lille, CHRU Lille, Inserm U1190 Translational research for diabetes, 59000 Lille, France; European Genomic Institute for Diabetes, EGID, 59000 Lille, France

[10] Endocrine Surgery, Hôpital Huriez Lille University Hospital, 59037, Lille Cedex, France

[11]Endocrinology and Metabolism, Hôpital Huriez, Lille University Hospital, 59000, Lille Cedex, France

[12]Departement of Surgery, Islet Isolation, and Transplantation Center, Geneva University Hospitals, Geneva, Switzerland

ABSTRACT

Introduction: Islet transplantation may be proposed to patients with type 1 brittle diabetes experiencing major glucose variability with severe hypoglycemia despite intensive insulin therapy. Few data are available on islet transplantation costs in relationship with its benefits. The STABILOT study proposes to assess economic impact of islet transplantation in comparison with the current best medical treatment defined as sensor-augmented pump (SAP) therapy. **Methods:** The trial will adopt an open-label, randomized, multicentric design. The study will include 30 patients with type 1 brittle diabetes. Eligible participants will be 18-65 years old, with type 1 diabetes duration over 5 years, a negative basal or stimulated C-peptide and brittleness defined by persistent, recurrent and invalidant severe hypoglycemia, despite optimized medical treatment. Participants will be randomized in two groups: a group with immediate registration for islet transplantation and a group with delayed registration for one year while patients will benefit from SAP therapy. The primary endpoint will be the incremental cost-utility ratio at one year between islet transplantation and SAP therapy. Both perspectives of the French Health Insurance System and hospital will be retained. **Ethics and dissemination:** Ethical approval has been obtained at all sites. All participants will sign a free and informed consent form before randomization.

Principal Investigator :

Pr Pierre-Yves Benhamou

Department of Endocrinology

Grenoble University Hospital, CS10217

38043 Grenoble, France

Strengths and limits of the study

In our STABILOT study, we propose a health economic evaluation of islet transplantation in comparison with Sensor Augmented Pump therapy. The strength of the study is represented by its design: to the best of our knowledge, it is the first randomized health economic study in islet transplantation performed. Moreover, our study is the first randomized study comparing islet transplantation to the current best medical treatment for brittle type 1 diabetes mellitus represented by SAP therapy.

Annex 1. The STABILOT Trial Investigators

Main centres

- Grenoble University Hospital: Pierre Yves BENHAMOU, Sandrine LABLANCHE, Rachel TETAZ
- Besançon University Hospital: Sophie BOROT
- Clermont-Ferrand University Hospital: Igor TAUVERON, Béatrice ROCHE
- Geneva University Hospital: Thierry BERNEY
- Lille University Hospital : François PATTOU, Marie-Christine VANTYGHEM, Kanza BENOMAR, Christian NOEL
- Lyon University Hospital: Charles THIVOLET, Emmanuel MORELON, Lionel BADET, Fanny BURON
- Montpellier University Hospital: Anne WOJTUSCISZYN, Eric RENARD
- Nancy University Hospital: Luc FRIMAT, Sophie GIRERD
- Nantes University Hospital: Diego CANTAROVICH, Lucy CHAILLOUS
- Paris University Hospital: Pierre CATTAN, Jean-Pierre RIVELINE, Marie-Noelle PERALDI, Olivier BOURRON
- Strasbourg University Hospital: Laurence KESSLER, François MOREAU, Philippe BALTZINGER et Thibault BAHOUGNE

Islet Production Centres

- Geneva: Domenico Bosco, Nadine Pernin
- Grenoble: Harald Egelhofer, Anaick Moisan, Virginie Persoons
- Lille: Julie Kerr-Conte, Valery Gmyr, Rimed Ezzouaoui
- Paris: Mathieu Armanet

INTRODUCTION

Type 1 diabetes mellitus is a chronic disease characterized by autoimmune destruction of beta cell resulting, in absence of treatment, in hyperglycemia, ketoacidosis and death. Type 1 diabetes mellitus treatment is currently based on multi-daily subcutaneous insulin injections. Some patients with type 1 diabetes develop a particular form diabetes mellitus named brittle diabetes characterized by glucose variability, lack of predictability, unawareness of hypoglycemic episodes and occurrence of severe hypoglycemia. Severe hypoglycemia is associated with alteration in quality of life (1), a 3.2 increased risk of death (2; 3) and an increase in health-costs (4); glucose variability is associated with a higher risk of microangiopathy progression (5). If intensive insulin therapy and use of innovative technologies such as insulin pump therapy and real-time continuous glucose monitoring (RT-CGM) allow some patients to reduce glucose variability and prevent occurrence of severe hypoglycemia (6), other patients failed to restore glucose stability and described persistent severe hypoglycemia. For such patients, islet transplantation may be proposed. Currently, islet transplantation permits to improve glucose variability, to prevent the occurrence of severe hypoglycemia, to enhance glycemic control (7; 8) with a positive impact on quality of life (1) and on the progression of microangiopathy (9; 10).

Islet transplantation is costly and the question of its cost in relation to its benefits is important to address. Few data are available on islet transplantation costs in relationship with its benefits. For islet transplantation performed in France and Switzerland, the cost of islet transplantation (including the initial cost and the one-year follow-up) is estimated at € 78,000 and is slightly higher than the cost of whole-pancreas organ transplantation (11). Beckwith et al. performed (12) a health economic evaluation of islet transplantation showing that islet transplantation is cost-effective in the short term and cost-saving in the long term when

compared with standard insulin therapy : for standard insulin therapy, cumulative cost per patient during 20-year follow-up was $663,000 with a cumulative effectiveness of 9.3 QALY (quality-adjusted life years) and an average cost-effectiveness ratio of $71,000 per QALY. For islet transplantation, the cumulative cost was $519,000 with a cumulative effectiveness of 10.9 QALY and an average cost-effectiveness ratio of $ 47,800 per QALY. Nevertheless, the evaluation performed by Beckwith et al. was based on estimations and extrapolations from clinical data because actual trial data were lacking. Moreover, current best medical treatment for patients with brittle type 1 diabetes is nowadays suggested to be SAP therapy composed of continuous subcutaneous insulin infusion integrated with RT-CGM. To the best of our knowledge, no health economic evaluation of islet transplantation has been performed in comparison with SAP therapy. The primary objective of the STABILOT study is to perform a prospective cost-effectiveness analysis to compare islet transplantation versus SAP therapy in patients with type 1 brittle diabetes. The main secondary objectives are to assess clinical and economic benefits of islet transplantation in patients with brittle diabetes including short or long-term analysis.

POPULATION AND METHODS

Study Design

The STABILOT trial is an open-label, prospective, randomized, multicenter trial involving 10 clinical centers in France (Grenoble, Besançon, Clermont-Ferrand, Lille, Lyon, Nantes, Nancy, Montpellier, Paris, and Strasbourg).

Main inclusion Criteria

Patients aged between 18-65 years with a type 1 diabetes duration over 5 years, with an HbA1c < 12% (HbA1c < 108mmol/mol), insulin requirement < 0,85UI/kg/day, negative basal or stimulated C-peptide and describing brittle type 1 diabetes despite an optimized insulin treatment and educational training will be included. A patient will be considered as experiencing a brittle type 1 diabetes if at least two criteria are present among: persistence of severe hypoglycemia, occurrence of ketoacidosis events without obvious etiology, diagnosis of unaware hypoglycemic episodes < 3 mmol/L based on CGM or self-monitoring blood glucose data, a mean blood glucose standard deviation > 50% or > 40mg/dL (2.22 mmol/L) on CGM data, MAGE index (Mean amplitude of glucose excursions) > 60 mg/dl (3.33 mmol/L), LBGI index (low blood glucose index) > 5, Clarke score ≥ 4 or HYPOSCORE > 800 (13).

Main exclusion criteria

- Exclusion criteria related to islet infusion: hemostatic disorders, pre-existing liver disease (PAL, Gamma-GT, ASAT-ALAT >2N) or gallbladder lithiasis.
- Exclusion criteria related to diabetic complications: evolutive proliferative retinopathy, evolutive nephropathy (Glomerular filtration rate < 30 ml/min/1.73m^2 and/or proteinuria > 0.5g/day), evolutive cardiopathy or obliterative arteriopathy with trophic cutaneous lesions.
- Exclusion criteria related to immunosuppressant use: hemoglobin < 110 mg/dL in women and < 120 mg/dL in men, leuconeutropenia, thrombopenia, systemic infection including chronic hepatitis B, C and VIH, neoplasic disease and hypertension > 160/100 mmHg.
- Corticoid treatment (except for patient that benefited from a kidney graft with maintenance steroid therapy)

- Presence of anti-HLA antibody directed against the donor
- Positive B or T cells crossmatch
- Pregnant women, woman with an intention to conceive or breastfeeding woman

Trial intervention and visit schedule

Pre-inclusion visit

Participants meeting the inclusion criteria will be invited to give their inform consent. The pre-inclusion visit allows validating each putative inclusion via a selection and validation procedures by respective committees (i.e. paragraphs section committee and validation committee). Once approved by selection and validation procedures, patients will undergo the inclusion visit.

Inclusion visit

During the inclusion visit, patients eligible for islet transplantation will be randomized in two parallel-groups: the immediate islet transplantation group (IIT group) (n=15) or the delayed islet transplantation group (DIT group) (n=15). The randomization will be performed through a web-based central randomization system and by minimization. Minimization aims to ensure that treatment arms are balanced with respect to major confusion factors in case of low sample size (13). However, patients describing life-threatening brittle type 1 diabetes will be directly allocated to immediate islet transplantation without randomization.

Intervention

In the IIT group, patients will be immediately registered on the islet transplantation waiting list. When an islet graft will be available, participants will be transplanted. Islet isolation and

transplantation procedure as well as immunosuppressive therapy used in our consortium have been previously described in GRAGIL Network (14). In the IIT group, the reference date for the beginning of the follow-up will be the date of the first islet infusion.

In the DIT group, patients will be registered on the islet transplantation waiting list one year after the randomization. During the delayed period, a SAP therapy will be proposed to the patients. For patients refusing the SAP therapy, a multi-daily injection regimen will be adopted in association with RT-CGM. In the DIT group, the reference date for the beginning of the follow-up will be the date of the inclusion visit.

Follow-up

In the IIT group, during the waiting period, patients will attend for a study visit every 3 months until islet transplantation procedure. After islet transplantation, protocol requests a monthly supervision of patients by the diabetologist investigator during the first year following first infusion. After year 1, patients will be required to see the diabetologist investigator every 6 months. In the DIT group, patients will be required to see the diabetologist investigator every 3 months during the first year. At 12 months, DIT participants group will be registered on the waiting list and will attend for a study visit each three month until islet transplantation procedure. After islet transplantation, protocol will follow the same pattern than in the IIT group.

In each group and for each visit, a clinical and biological evaluation will be performed as detailed in Table 1. Serious adverse events in particular acute metabolic events (severe hypoglycemia and keto-acidosis) that occurred since the last follow-up visit will be reported prospectively. At 6 and 12 months, a one-month CGM recording will be performed for each participant. An EQ-5D and DQoL will be fulfilled as described in Table 1.

Table 1. Schedule visit table

Parameters recorded	All		IIT Group		DIT Group		
	Pre Inclusion visit	Inclusion visit	Waiting period	Post transplantation Period	Delayed period	Waiting period	Post transplantation Period
			Quaterly visit	Monthly visit	Quaterly visit	Quaterly visit	Monthly visit
Medical evaluation							
Height	x	x	x	x	x	x	x
Weight	x	x	x	x	x	x	x
Insulin requirement	x	x	x	x	x	x	x
Clarke score	x						
LBGI, MAGE index	x						
Hyposcore	x						
Adverse events			x	x	x	x	x
Biological evaluation							
HbA1c	x	x	x	x	x	x	x
C-peptide level	x	x		x			x
Creatinin level	x	x	x	x	x	x	x
Proteinuria	x	x	x	x	x	x	x
Anti-HLA Ab	x	x	x	x	x	x	x
Anti-GAD, anti-IA2 Ab	x	x	x	x	x	x	x
Complete Blood Count	x	x	x	x	x	x	x
ASAT/ALAT	x	x	x	x	x	x	x
CGM recording							
One-months CGM recording		x		x M6-M12 post-transplantation	x M6-M12 post-inclusion		x M6-M12 post-transplantation
Questionnaire							
DQOL		x		x M12 post-transplantation	x M12 post-inclusion		

EQ-5D		x	x	x M6-M12 post- transplantation	x	x	x M6-M12 post- transplantation

Endpoints

Primary endpoint

The primary endpoint will be the incremental cost-effectiveness ratio at one year for islet transplantation versus SAP therapy. Costs will be valued in the perspective of the French health care system and hospital. The effectiveness will be expressed as quality adjusted life years (QALYs) in a cost-utility analysis. QALYs are a composite measure of outcomes where utilities for health states (on 0-1 scale, where 0 corresponds to death and 1 to full health) act as qualitative weights to combine quantity and quality of life. The number of QALYs in each group will be assessed with the EuroQol 5 Dimensions questionnaire (EQ5D). The EQ-5D measures health status in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

Secondary endpoints

The secondary outcomes will allow to:

1. Assess the cost-effectiveness ratio at one year of islet transplantation and SAP therapy for patients with no life-threatening brittle type 1 diabetes. Two criteria of effectiveness will be used: the number of life years gained and the number of severe hypoglycemia.
2. Assess and compare the individual medical benefits in terms of quality of life (DQoL questionnaire), metabolic efficacy, hospitalizations and complications of islet transplantation and SAP therapy at 6 and 12 months.
3. Compare the clinical outcomes and costs of patients with life-threatening brittle type 1 diabetes before and after islet cell transplantation.

4. Implement a budget impact analysis
5. Perform a long-term evaluation of the clinical and economic impact of islet transplantation through modelisations.

Economic Evaluation

Cost measurement

To assess the total cost of each group, the number of resources consumed will be prospectively collected for each patient (drugs, medical devices, consultations, transportations, hospitalization…). The French health care prices will be used to cost out resource consumed during the follow-up period.

To the procedure costs for islets infusion, the microcosting approach will be used. This approach consists to measure by direct observation all relevant cost components of the procedure: duration of the procedure, composition of the staff, drugs and medical devices used, type of operating room and the duration of the hospital stays as variables and cost out each component with unit production cost or purchasing prices for drugs and medical devices.

QALYs estimation

The EQ-5D will be self-administered at baseline and every three months. The utility values are based on the French utility function (15; 16). Utility curves were obtained for each group by plotting average utility values at baseline and every 3 months. The difference in QALYs was estimated as the difference in the area between the utility curves for the 2 groups.

Statistics analysis

Sample size

The sample size was estimated upon the primary economic criterion and the secondary clinical criteria based on Glick's works (16). We describe here the clinical hypothesis requiring the most of subjects. We considered a two-tailed alpha of 5% and a study power of 90%. Considering a monthly mean of 25 hypoglycaemias ± 20 (SD) in the DIT group and 5 ± 10 in the IIT group (TRIMECO study preliminary results), it was necessary to include 15 patients per group (Calculated using Nquery 6.02 on 2014 july 31th).

Analysis

In this randomized controlled trial, an intention to treat analysis will be performed in line with arguments in the CONSORT statement (http://www.consort-statement.org/). A flow diagram will allow us to describe the studied population at each step of the study (Fig 1). Sociodemographic, clinical and economic data will be analysed per group.

Primary outcome

The costs and utilities will be estimated for a 1-year horizon. QALYs and costs will be described using means (with standard deviations or 95% confidence intervals) or medians (with interquartile ranges). Differences in costs and QALYs will be described as means (with 95% confidence intervals) and tested using standard parametric or nonparametric tests (t test or Mann-Whitney test) as appropriate. The incremental cost-effectiveness ratio will be calculated. To address uncertainty in cost and outcomes across both arms, sensitivity analysis will be performed.

Missing data will be considered using multiple imputation regression methods.

Secondary outcomes

1. The incremental cost-effectiveness ratios will be calculated and expressed as incremental cost per life years gained and the number of hypoglycemia avoided.

2. Comparison of clinical and biological data will be performed, in particular on metabolic events, insulin requirement, hospitalization or occurrence of complications. Continuous data will be compared using a t-test if the variable was normally distributed or Mann Whitney test for non-parametric variables. The Chi-square test will be used for categorical variables (Fisher's exact test if necessary).

3. Description and comparison of studied population with life-threatening brittle diabetes based on a data-paired analysis (before-after study) will be performed. Continuous data will be compared using a paired t-test if the variable was normally distributed or Wilcoxon test for non-parametric variables. The MacNemar test will be used for categorical variables (Fleiss test if necessary).

4. The economic burden at 1 and 5-years after islet transplantation in the management of severe forms of type 1 diabetes will be measured. The model will take into account especially the target population, the SAP therapy management cost versus islet transplantation cost, the assumptions about the maintenance or not of insulin-independence over the time but also assumptions about changes in unit costs

5. To simulate the long-term cost, effectiveness and cost effectiveness will be used a Markov model, we will use data from Stabilot study, from our TRIMECO cohort and from literature.

Statistical significance will be considered at p-value ≤ 0.05. All statistical analyses were performed using Stata SE version 12.0 software (StataCorp LP, 4905 Lakeway Drive, College Station, Texas 77845-4512, USA).

This study is under process for registration with ClinicalTrials.gov: Protocol ID 38RC14.453.

STUDY MANAGEMENT

Selection committee

A selection committee composed of investigators from each center will review the medical history and the indication of islet transplantation for each participant candidating for an inclusion in the STABILOT protocol. Half of the centers have to be represented in order to authorize the selection procedure. At the term of the selection procedure, the pre-inclusion of the participants is validated or not.

Validation committee

The validation committee is an independent committee composed of two members (Pr Penfornis, Diabetologist, Corbeil-Essonnes Hospital and Dr Schaepelynck-Belicar, Marseille Hospital) in charge to validate the islet transplantation indication and the inclusion in the STABILOT trial for pre-included participants.

Pharmacovigilance and safety

According to the Directive 2001/20/EC, all adverse events will be recorded and reported with the help of the "Terminology Criteria for adverse Events in Trials of adults pancreatic islet transplantation" (17). All serious adverse events will be reported prospectively to the Sponsor and to competent authority (ANSM) and ethic committee in case of Suspected Unexpected Serious Adverse Reactions. Complications related with the islet infusion will be closed

monitoring as well as adverse events related to immunosuppressive drugs or concomitant therapy.

An independent Data Safety Monitoring Board (DSMB) composed of 4 experts will be informed for all SUSAR and any safety signal and will receipted all Annual Safety Report. The DSMB will report to the Study Management Committee any safety concerns and recommendations for suspension or early termination of the investigation.

ETHICAL AND GOUVERNANCE APPROUVAL

Ethical approval for this study has been granted by the institutional review board (Person Protection Committee of Grenoble University Hospital (n° 15-CHUG-14) and Clinical Trial Authorization has been given by the French National Competent Authority (ANSM): n° idRCB 2015-00350-49.

AGENDA

It is expected that screening and recruitment will begin in June 2016 and the study will be completed by winter 2020.

Funding

Projet de Recherche Medico Economique National 2014, DGOS (Grant number 14-0225)

Contributorship statement

All the authors participated in the research design

Sandrine Lablanche, Sandra David-Tchouda, Jennifer Margier, Edith Schir, Laurence Kessler, Marie Christine Vantyghem, François Pattou, Pierre-Yves Benhamou participated in the writing paper.

Competing interests

No competing interest to declare

References

1. Benhamou PY, Milliat-Guittard L, Wojtusciszyn A, Kessler L, Toso C, Baertschiger R, Debaty I, Badet L, Penfornis A, Thivolet C, Renard E, Bayle F, Morel P, Morelon E, Colin C, Berney T, group G: Quality of life after islet transplantation: data from the GRAGIL 1 and 2 trials. Diabetic medicine : a journal of the British Diabetic Association 2009;26:617-621
2. Tanenberg RJ, Newton CA, Drake AJ: Confirmation of hypoglycemia in the "dead-in-bed" syndrome, as captured by a retrospective continuous glucose monitoring system. Endocr Pract 2010;16:244-248
3. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA: Increased mortality of patients with diabetes reporting severe hypoglycemia. Diabetes care 2012;35:1897-1901
4. Hammer M, Lammert M, Mejias SM, Kern W, Frier BM: Costs of managing severe hypoglycaemia in three European countries. J Med Econ 2009;12:281-290
5. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. Am J Ophthalmol 2000;129:704-705
6. Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, Slover RH, Ahmann AJ, Welsh JB, Lee SW, Kaufman FR, Group AI-HS: Threshold-based insulin-pump interruption for reduction of hypoglycemia. The New England journal of medicine 2013;369:224-232
7. Lablanche S, Borot S, Wojtusciszyn A, Bayle F, Tetaz R, Badet L, Thivolet C, Morelon E, Frimat L, Penfornis A, Kessler L, Brault C, Colin C, Tauveron I, Bosco D, Berney T, Benhamou PY, Network G: Five-Year Metabolic, Functional, and Safety Results of Patients With Type 1 Diabetes Transplanted With Allogenic Islets Within the Swiss-French GRAGIL Network. Diabetes care 2015;
8. Barton FB, Rickels MR, Alejandro R, Hering BJ, Wease S, Naziruddin B, Oberholzer J, Odorico JS, Garfinkel MR, Levy M, Pattou F, Berney T, Secchi A, Messinger S, Senior PA, Maffi P, Posselt A, Stock PG, Kaufman DB, Luo X, Kandeel F, Cagliero E, Turgeon NA, Witkowski P, Naji A, O'Connell PJ, Greenbaum C, Kudva YC, Brayman KL, Aull MJ, Larsen C, Kay TW, Fernandez LA, Vantyghem MC, Bellin M, Shapiro AM: Improvement in outcomes of clinical islet transplantation: 1999-2010. Diabetes care 2012;35:1436-1445
9. Thompson DM, Meloche M, Ao Z, Paty B, Keown P, Shapiro RJ, Ho S, Worsley D, Fung M, Meneilly G, Begg I, Al Mehthel M, Kondi J, Harris C, Fensom B, Kozak SE, Tong SO, Trinh M, Warnock GL: Reduced progression of diabetic microvascular complications with islet cell transplantation compared with intensive medical therapy. Transplantation 2011;91:373-378
10. Warnock GL, Thompson DM, Meloche RM, Shapiro RJ, Ao Z, Keown P, Johnson JD, Verchere CB, Partovi N, Begg IS, Fung M, Kozak SE, Tong SO, Alghofaili KM, Harris C: A

multi-year analysis of islet transplantation compared with intensive medical therapy on progression of complications in type 1 diabetes. Transplantation 2008;86:1762-1766

11. Guignard AP, Oberholzer J, Benhamou PY, Touzet S, Bucher P, Penfornis A, Bayle F, Kessler L, Thivolet C, Badet L, Morel P, Colin C, Group G: Cost analysis of human islet transplantation for the treatment of type 1 diabetes in the Swiss-French Consortium GRAGIL. Diabetes care 2004;27:895-900

12. Beckwith J, Nyman JA, Flanagan B, Schrover R, Schuurman HJ: A health economic analysis of clinical islet transplantation. Clin Transplant 2012;26:23-33

13. Scott NW, McPherson GC, Ramsay CR, Campbell MK: The method of minimization for allocation to clinical trials. a review. Control Clin Trials 2002;23:662-674

14. Lablanche S, Borot S, Wojtusciszyn A, Bayle F, Tetaz R, Badet L, Thivolet C, Morelon E, Frimat L, Penfornis A, Kessler L, Brault C, Colin C, Tauveron I, Bosco D, Berney T, Benhamou PY, Network G: Five-Year Metabolic, Functional, and Safety Results of Patients With Type 1 Diabetes Transplanted With Allogenic Islets Within the Swiss-French GRAGIL Network. Diabetes care 2015;38:1714-1722

15. Chevalier J, de Pouvourville G: Valuing EQ-5D using time trade-off in France. Eur J Health Econ 2013;14:57-66

16. Glick HA: Sample size and power for cost-effectiveness analysis (part 1). Pharmacoeconomics 2011;29:189-198

17. Consortium CIT: Terminology Criteria for adverse Events in Trials of adults pancreatic islet transplantation. 2011

BMJ Open

A randomized, prospective, medico-economic nationwide French study of islet transplantation in patients with severely unstable type 1 diabetes: the STABILOT study protocol

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013434.R1
Article Type:	Protocol
Date Submitted by the Author:	08-Nov-2016
Complete List of Authors:	Lablanche, Sandrine; Centre Hospitalier Universitaire de Grenoble, Department of Diabetology; Universite Grenoble Alpes, LBFA - U1055 INSERM David-Tchouda, Sandra; Centre Hospitalier Universitaire de Grenoble, Cellule d'évaluation médico-économique des innovations CIC ; Universite Grenoble Alpes, CIC 1406 Grenoble, TIMC-Imag UMR Margier, Jennifer; Centre Hospitalier Universitaire de Grenoble, Cellule d'évaluation médico-économique des innovations, CHU Grenoble Alpes, CIC 1406 Grenoble, TIMC-Imag UMR 5525 Univ. Grenoble Alpes, F-38000 Grenoble, France; Universite Grenoble Alpes, CIC 1406 Grenoble, TIMC-Imag UMR Schir, Edith; Centre Hospitalier Universitaire de Grenoble, Centre régional de Pharmacovigilance Wojtusciszyn, Anne; Centre Hospitalier Regional Universitaire de Montpellier, Pôle Rein Hypertension Métabolisme, Service d'Endocrinologie Borot, Sophie; Centre Hospitalier Universitaire de Besancon, Service Endocrinologie-Métabolisme et Diabétologie-Nutrition Kessler, Laurence; Hopitaux universitaires de Strasbourg, Service d'Endocrinologie Diabète et Maladies Métaboliques, Pôle NUDE Morelon, Emmanuel; Centre Hospitalier Universitaire de Lyon, Service d'Urologie et de Chirurgie de la Transplantation, Pôle Chirurgie Thivolet, Charles; Centre Hospitalier Universitaire de Lyon, Endocrinologie-Diabétologie-Maladie de la Nutrition Pattou, François; INSERM U1190, Translational research for diabetes, 59000 Lille, European Genomic Institute for Diabetes, EGID; Centre Hospitalier Regional Universitaire de Lille, Endocrine Surgery, Hôpital Huriez Vantyghem, Marie-Christine; Centre Hospitalier Regional Universitaire de Lille, Endocrinology and metabolism; INSERM U1190, Translational research for diabetes, 59000 Lille, European Genomic Institute for Diabetes, EGID Berney, Thierry; Hopitaux Universitaires de Geneve, Department of Surgery, Islet Isolation, and Transplantation Center Benhamou, Pierre-Yves; Centre Hospitalier Universitaire de Grenoble, Department of Diabetology; Universite Grenoble Alpes, LBFA - U1055 INSERM
Primary Subject	Diabetes and endocrinology

Heading:	
Secondary Subject Heading:	Health economics
Keywords:	HEALTH ECONOMICS, Sensor augmented pump therapy, Islet Transplantation, Unstable type 1 Diabetes

A randomized, prospective, medico-economic nationwide French study of islet transplantation in patients with severely unstable type 1 diabetes: the STABILOT study protocol

Sandrine Lablanche[1, 2], Sandra David-Tchouda[3], Jennifer Margier[3], Edith Schir[4], Anne Wojtusciszyn[5], Sophie Borot[6], Laurence Kessler[7], Emmanuel Morelon[8], Charles Thivolet[9], François Pattou[10,11], Marie Christine Vantyghem[11,12], Thierry Berney[13], Pierre-Yves Benhamou[1,2]

Keywords: Islet transplantation, medico-economic, brittle diabetes, trials

Abstract: 255 words

Main body: 2975 words

Table: 1

Corresponding author:
Sandrine LABLANCHE
Department of Endocrinology
CHU de Grenoble, BP217
38043 Grenoble, FRANCE
Phone: +33 (0)4 76 76 37 36 – Fax: +33 (0)4 76 76 50 42

E-mail: slablanche@chu-grenoble.fr

The STABILOT protocol (Version 2.3, 14/12/2015) was supported by grants from Projet de Recherche Medico Economique National 2014, DGOS (Grant number 14-0225) and by grant no. 3200B0-102134 from the Swiss National Foundation for Scientific Research.

The authors declare no conflicts of interest.

Authors Addresses

[1]Department of Diabetology, Pôle DigiDune, Grenoble University Hospital, Grenoble Alpes University, Grenoble, France

[2]Grenoble Alpes University, INSERM, U1055Laboratory of Fundamental and Applied Bioenergetics, F-38041, Grenoble, France

[3]Cellule d'évaluation médico-économique des innovations, CHU Grenoble Alpes, CIC 1406 Grenoble, TIMC-Imag UMR 5525 Univ. Grenoble Alpes, F-38000 Grenoble, France

[4]Centre régional de Pharmacovigilance, Grenoble, France

[5]Centre Hospitalier de Montpellier, Pôle Rein Hypertension Métabolisme, Service d'Endocrinologie, Montpellier, France.

[6]Centre Hospitalier Universitaire Jean Minjoz, Service d'Endocrinologie-Métabolisme et Diabétologie-Nutrition, Besançon, France.

[7]Hôpitaux Universitaires de Strasbourg, Service d'Endocrinologie Diabète et Maladies Métaboliques, Pôle NUDE, Strasbourg, France.

[8]Hospices Civils de Lyon, Service d'Urologie et de Chirurgie de la Transplantation, Pôle Chirurgie, Lyon, France.

[9]Hospices Civils de Lyon, Service de Diabétologie - Endocrinologie - Maladies Métaboliques et de Chirurgie de la Transplantation, Pôle Chirurgie, Lyon, France.

[10]University Lille, CHRU Lille, Inserm U1190 Translational research for diabetes, 59000 Lille, France; European Genomic Institute for Diabetes, EGID, 59000 Lille, France

[11] Endocrine Surgery, Hôpital Huriez Lille University Hospital, 59037, Lille Cedex, France

[12]Endocrinology and Metabolism, Hôpital Huriez, Lille University Hospital, 59000, Lille Cedex, France

[13]Departement of Surgery, Islet Isolation, and Transplantation Center, Geneva University Hospitals, Geneva, Switzerland

ABSTRACT

Introduction: Islet transplantation may be proposed to patients with severely unstable type 1 diabetes experiencing major glucose variability with severe hypoglycemia despite intensive insulin therapy. Few data are available on islet transplantation costs in relationship with its benefits. The STABILOT study proposes to assess economic impact of islet transplantation in comparison with the current best medical treatment defined as sensor-augmented pump (SAP) therapy. **Methods:** The trial will adopt an open-label, randomized, multicentric design. The study will include 30 patients with severely unstable type 1 diabetes. Eligible participants will be 18-65 years old, with type 1 diabetes duration over 5 years, a negative basal or stimulated C-peptide and severe unstability defined by persistent, recurrent and invalidant severe hypoglycemia, despite optimized medical treatment. Participants will be randomized in two groups: a group with immediate registration for islet transplantation and a group with delayed registration for one year while patients will benefit from SAP therapy. The primary endpoint will be the incremental cost-utility ratio at one year between islet transplantation and SAP therapy. Both perspectives of the French Health Insurance System and hospital will be retained. **Ethics and dissemination:** Ethical approval has been obtained at all sites. The trial has been approved by ClinicalTrials.gov (Trial registration ID NCT02854696). All participants will sign a free and informed consent form before randomization. Results of the study will be communicated during national and international meetings in the field of Diabetes and Transplantation. A publication will be sought in journals usually read by physicians involved in diabetes care, transplantation and internal medicine.

Principal Investigator:

Pr Pierre-Yves Benhamou

Department of Endocrinology

Grenoble University Hospital, CS10217, 38043 Grenoble, France

Strengths and limits of the study

The strengths of the trial are its design and the comparator used:

- It is the first randomized health economic study performed in islet transplantation.
- It is the first comparison between islet transplantation and SAP therapy.

The limitation of the study could be:

- The low sample size analysed in the trial; it is allowed by the expected strong efficacy of islet transplantation.

Annex 1. The STABILOT Trial Investigators

Main centres

- Grenoble University Hospital: Pierre Yves BENHAMOU, Sandrine LABLANCHE, Rachel TETAZ
- Besançon University Hospital: Sophie BOROT
- Clermont-Ferrand University Hospital: Igor TAUVERON, Béatrice ROCHE
- Geneva University Hospital: Thierry BERNEY
- Lille University Hospital: François PATTOU, Marie-Christine VANTYGHEM, Kanza BENOMAR, Christian NOEL
- Lyon University Hospital: Charles THIVOLET, Emmanuel MORELON, Lionel BADET, Fanny BURON
- Montpellier University Hospital: Anne WOJTUSCISZYN, Eric RENARD
- Nancy University Hospital: Luc FRIMAT, Sophie GIRERD
- Nantes University Hospital: Diego CANTAROVICH, Lucy CHAILLOUS
- Paris University Hospital: Pierre CATTAN, Jean-Pierre RIVELINE, Marie-Noelle PERALDI, Olivier BOURRON
- Strasbourg University Hospital: Laurence KESSLER, François MOREAU, Philippe BALTZINGER et Thibault BAHOUGNE

Islet Production Centres

- Geneva: Domenico Bosco, Nadine Pernin
- Grenoble: Harald Egelhofer, Anaick Moisan, Virginie Persoons
- Lille: Julie Kerr-Conte, Valery Gmyr, Rimed Ezzouaoui
- Paris: Mathieu Armanet

INTRODUCTION

Type 1 diabetes mellitus is a chronic disease characterized by autoimmune destruction of beta cell resulting, in absence of treatment, in hyperglycemia, ketoacidosis and death. Type 1 diabetes mellitus treatment is currently based on multi-daily subcutaneous insulin injections. Some patients with type 1 diabetes develop a particular form of diabetes mellitus with severe unstability, previously called brittle diabetes, characterized by glucose variability, lack of predictability, unawareness of hypoglycemic episodes and occurrence of severe hypoglycemia. Severe hypoglycemia is associated with alteration in quality of life (1), a 3.2 increased risk of death (2; 3) and an increase in health-costs (4); glucose variability is associated with a higher risk of microangiopathy progression (5). If intensive insulin therapy and use of innovative technologies such as insulin pump therapy and real-time continuous glucose monitoring (RT-CGM) allow some patients to reduce glucose variability and prevent occurrence of severe hypoglycemia (6), other patients failed to restore glucose stability and described persistent severe hypoglycemia. For such patients, islet transplantation may be proposed. Currently, islet transplantation permits to improve glucose variability, to prevent the occurrence of severe hypoglycemia, to enhance glycemic control (7; 8) with a positive impact on quality of life (1) and on the progression of microangiopathy (9; 10).

Islet transplantation is costly and the question of its cost in relation to its benefits is important to address. Few data are available on islet transplantation costs in relationship with its benefits. For islet transplantation performed in France and Switzerland, the cost of islet transplantation (including the initial cost and the one-year follow-up) is estimated at € 78,000 and is slightly higher than the cost of whole-pancreas organ transplantation (11). Beckwith et al. performed (12) a health economic evaluation of islet transplantation showing that islet transplantation is cost-effective in the short term and cost-saving in the long term when

compared with standard insulin therapy : for standard insulin therapy, cumulative cost per patient during 20-year follow-up was $663,000 with a cumulative effectiveness of 9.3 QALY (quality-adjusted life years) and an average cost-effectiveness ratio of $71,000 per QALY. For islet transplantation, the cumulative cost was $519,000 with a cumulative effectiveness of 10.9 QALY and an average cost-effectiveness ratio of $ 47,800 per QALY. Nevertheless, the evaluation performed by Beckwith et al. was based on estimations and extrapolations from clinical data because actual trial data were lacking. Moreover, current best medical treatment for patients with severely unstable type 1 diabetes is nowadays suggested to be SAP therapy composed of continuous subcutaneous insulin infusion integrated with RT-CGM. To the best of our knowledge, no health economic evaluation of islet transplantation has been performed in comparison with SAP therapy. The primary objective of the STABILOT study is to perform a prospective cost-effectiveness analysis to compare islet transplantation versus SAP therapy in patients with severely unstable type 1 diabetes. The main secondary objectives are to assess clinical and economic benefits of islet transplantation in patients with severe diabetes including short or long-term analysis.

POPULATION AND METHODS

Study Design

The STABILOT trial is an open-label, prospective, randomized, multicenter trial involving 10 clinical centers in France (Grenoble, Besançon, Clermont-Ferrand, Lille, Lyon, Nantes, Nancy, Montpellier, Paris, and Strasbourg).

Main inclusion Criteria

Patients aged between 18-65 years with a type 1 diabetes duration over 5 years, with an HbA1c < 12% (HbA1c < 108mmol/mol), insulin requirement < 0,85UI/kg/day, negative basal or stimulated C-peptide and describing severely unstable type 1 diabetes despite an optimized insulin treatment and educational training will be included. An optimized insulin treatment is defined by pump therapy (or MDI for patients refusing or failing to manage pump therapy). Pump therapy has to be supervised by a clinician expert in diabetes management warranting optimal insulin therapy adjustment. Patients have to be educated through the participation of structured psycho-educational programs, delivered in individual or group settings.

A patient will be considered as experiencing a severely unstable type 1 diabetes if at least two criteria are present among: persistence of severe hypoglycemia defined as the occurrence of at least one episode of severe hypoglycemia over the last year, occurrence of ketoacidosis events without obvious etiology, diagnosis of unaware hypoglycemic episodes < 3 mmol/L based on CGM or self-monitoring blood glucose data, a mean blood glucose standard deviation > 50% or > 40 mg/dL (2.22 mmol/L) on CGM data, MAGE index (Mean amplitude of glucose excursions) > 60 mg/dl (3.33 mmol/L), LBGI index (low blood glucose index) > 5, Clarke score ≥ 4 or HYPOSCORE > 800 (13).

Main exclusion criteria

- Exclusion criteria related to islet infusion: hemostatic disorders, pre-existing liver disease (PAL, Gamma-GT, ASAT-ALAT >2N) or gallbladder lithiasis.
- Exclusion criteria related to diabetic complications: evolutive proliferative retinopathy, evolutive nephropathy (Glomerular filtration rate < 30 ml/min/1.73m^2 and/or

proteinuria > 0.5g/day), evolutive cardiopathy or obliterative arteriopathy with trophic cutaneous lesions.

- Exclusion criteria related to immunosuppressant use: hemoglobin < 110 mg/dL in women and < 120 mg/dL in men, leuconeutropenia, thrombopenia, systemic infection including chronic hepatitis B, C and VIH, neoplasic disease and hypertension > 160/100 mmHg.
- Corticoid treatment (except for patient that benefited from a kidney graft with maintenance steroid therapy)
- Presence of anti-HLA antibody directed against the donor
- Positive B or T cells crossmatch
- Pregnant women, woman with an intention to conceive or breastfeeding woman

Trial intervention and visit schedule

Pre-inclusion visit

Participants meeting the inclusion criteria will be invited to give their informed consent. The pre-inclusion visit allows validating each putative inclusion via a selection and validation procedures by respective committees (i.e. paragraphs section committee and validation committee). Once approved by selection and validation procedures, patients will undergo the inclusion visit.

Inclusion visit

During the inclusion visit, patients eligible for islet transplantation will be randomized in two parallel-groups: the immediate islet transplantation group (IIT group) (n=15) or the delayed islet transplantation group (DIT group) (n=15). The randomization will be performed through a web-based central randomization system and by minimization. Minimization aims to ensure that treatment arms are balanced with respect to major confusion factors in case of low

sample size (13). However, patients describing life-threatening unstable type 1 diabetes will be directly allocated to immediate islet transplantation without randomization.

Intervention

In the IIT group, patients will be immediately registered on the islet transplantation waiting list. When an islet graft will be available, participants will be transplanted. Islet isolation and transplantation procedure as well as immunosuppressive therapy used in our consortium have been previously described in GRAGIL Network (14). Briefly, pancreases will be obtained from brain-dead multi organ donors through Swiss transplant and the French Biomedicine Agency (Agence de la Biomédecine). Islets will be isolated using the Ricordi automated method with local modifications. Islet preparations will be conditioned in gas-permeable transfer bags (Biorep, Miami, FL) in CMRL 1066 medium supplemented with human albumin (4%) and heparin (35 U/kg recipient body weight) and ship by ambulance to the transplant centers. Transit time will never exceed 4 hours. Islets will be transplanted intraportally. Patients are scheduled to receive up to a target islet mass of 11,000 IEQ/kg body weight. Consequently, when the first islet infusions does not permit to achieve the 11,000 IEQ/kg body weight threshold, a second infusion and third infusion may be performed ideally with a time frame of three months to acheive the total islet mass. In the IIT group, the reference date for the beginning of the follow-up will be the date of the first islet infusion.

In the DIT group, patients will be registered on the islet transplantation waiting list one year after the randomization. During the delayed period, a SAP therapy with Predictive Low-Glucose Suspend (Threshold: 60 mg/dL) will be proposed. For patients refusing SAP therapy, a multi-daily injection regimen will be adopted in association with RT-CGM. In the DIT group, the reference date for the beginning of the follow-up will be the date of the inclusion visit.

Follow-up

In the IIT group, during the waiting period, patients will attend for a study visit every 3 months until islet transplantation procedure. After islet transplantation, protocol requests a monthly supervision of patients by the diabetologist investigator during the first year following first infusion. After year 1, patients will be required to see the diabetologist investigator every 6 months. In the DIT group, patients will be required to see the diabetologist investigator every 3 months during the first year. In complement to the quarterly visit, patients will download pump and CGM data to clinician on a monthly basis. Based on these data, clinician can order insulin therapy adjustment through a phone call visit. At 12 months, DIT participants group will be registered on the waiting list and will attend for a study visit each three months until islet transplantation procedure. After islet transplantation, protocol will follow the same pattern than in the IIT group.

In each group and for each visit, a clinical and biological evaluation will be performed as detailed in Table 1. Serious adverse events in particular acute metabolic events (severe hypoglycemia and keto-acidosis) will be reported prospectively. At 6 and 12 months, a one-month CGM recording will be performed for each participant. An EQ-5D and DQoL questionnaire will be fulfilled as described in Table 1.

Table 1. Schedule visit table

Parameters recorded	All		IIT Group		DIT Group		
	Pre Inclusion visit	Inclusion visit	Waiting period	Post transplantation Period	Delayed period	Waiting period	Post transplantation Period
			Quaterly visit	Monthly visit	Quaterly visit	Quaterly visit	Monthly visit
Medical evaluation							
Height	x	x	x	x	x	x	x
Weight	x	x	x	x	x	x	x
Insulin requirement	x	x	x	x	x	x	x
Clarke score	x						
LBGI, MAGE index	x						
Hyposcore	x						
Adverse events			x	x	x	x	x
Biological evaluation							
HbA1c	x	x	x	x	x	x	x
C-peptide level	x	x		x			x
Creatinin level	x	x	x	x	x	x	x
Proteinuria	x	x	x	x	x	x	x
Anti-HLA Ab	x	x	x	x	x	x	x
Anti-GAD, anti-IA2 Ab	x	x	x	x	x	x	x
Complete Blood Count	x	x	x	x	x	x	x
ASAT/ALAT	x	x	x	x	x	x	x
CGM recording							
One-months CGM recording		x		x M6-M12 post-transplantation	x M6-M12 post-inclusion		x M6-M12 post-transplantation
Questionnaire							
DQOL		x		x M12 post-transplantation	x M12 post-inclusion		

EQ-5D		x	x	x M6-M12 post- transplantation	x	x	x M6-M12 post- transplantation

Endpoints

Primary endpoint

The primary endpoint will be the incremental cost-effectiveness ratio at one year for islet transplantation versus SAP therapy. Costs will be valued in the perspective of the French health care system and hospital. The effectiveness will be expressed as quality adjusted life years (QALYs) in a cost-utility analysis. QALYs are a composite measure of outcomes where utilities for health states (on 0-1 scale, where 0 corresponds to death and 1 to full health) act as qualitative weights to combine quantity and quality of life. The number of QALYs in each group will be assessed with the EuroQol 5 Dimensions questionnaire (EQ5D). The EQ-5D measures health status in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression.

Secondary endpoints

The secondary outcomes will allow to:

1. Assess the cost-effectiveness ratio at one year of islet transplantation and SAP therapy for patients with no life-threatening unstable type 1 diabetes. Two criteria of effectiveness will be used: the number of life years gained and the number of severe hypoglycemia.
2. Assess and compare the individual medical benefits in terms of quality of life (DQoL questionnaire), metabolic efficacy, hospitalizations and complications of islet transplantation and SAP therapy at 6 and 12 months.
3. Compare the clinical outcomes and costs of patients with life-threatening unstable type 1 diabetes before and after islet cell transplantation.

4. Implement a budget impact analysis
5. Perform a long-term evaluation of the clinical and economic impact of islet transplantation through modelisations.

Economic Evaluation

Cost measurement

To assess the total cost of each group, the number of resources consumed will be prospectively collected for each patient (drugs, medical devices, consultations, transportations, hospitalization…). The French health care prices will be used to cost out resource consumed during the follow-up period.

To the procedure costs for islets infusion, the microcosting approach will be used. This approach consists to measure by direct observation all relevant cost components of the procedure: duration of the procedure, composition of the staff, drugs and medical devices used, type of operating room and the duration of the hospital stays as variables and cost out each component with unit production cost or purchasing prices for drugs and medical devices.

QALYs estimation

The EQ-5D will be self-administered at baseline and every three months. The utility values are based on the French utility function (15; 16). Utility curves were obtained for each group by plotting average utility values at baseline and every 3 months. The difference in QALYs was estimated as the difference in the area between the utility curves for the 2 groups.

Statistics analysis

Sample size

The sample size was estimated upon the primary economic criterion and the secondary clinical criteria based on Glick's works (16). Regarding cost-utility analysis, we considered the less favourable following assumptions: difference in costs of 69,000 € ± 50,000 € (SD). The average cost for patients with unstable diabetes with delayed islet transplantation was assumed to rise from 6,700 to 25,000 € at 12 months (InVS report and data from (12)). The average cost for patients with unstable diabetes 12 months after islet transplantation was evaluated between 75,000 € (preliminary results from TRIMECO study) and 95,000 € (12). A difference in effects of 0.06 QALY ± 0.03 (12), a correlation between difference in costs and effects from -1 to 1, and a maximum willingness to pay of 20,000 € per QALY were used. Based on these data, 9 to 12 patients per group have to be included (calculated using Stata V11SE). Nevertheless, results on the medico-economic criteria have to be interpreted with caution because of many assumptions and because of high instability of the mathematical formula used. Consequently, we took also in account in the sample size calculation, the clinical hypothesis requiring the most of subjects. We considered a two-tailed alpha of 5% and a study power of 90%. Considering a monthly mean of 25 hypoglycaemias ± 20 (SD) in the DIT group and 5 ± 10 in the IIT group (TRIMECO study preliminary results), it was necessary to include 15 patients per group (Calculated using Nquery 6.02 on 2014 july 31th).

Analysis

In this randomized controlled trial, an intention to treat analysis will be performed in line with arguments in the CONSORT statement (http://www.consort-statement.org/). Sociodemographic, clinical and economic data will be analysed per group.

Primary outcome

The costs and utilities will be estimated for a 1-year horizon. QALYs and costs will be described using means (with standard deviations or 95% confidence intervals) or medians

(with interquartile ranges). Differences in costs and QALYs will be described as means (with 95% confidence intervals) and tested using standard parametric or nonparametric tests (t test or Mann-Whitney test) as appropriate. The incremental cost-effectiveness ratio will be calculated. To address uncertainty in cost and outcomes across both arms, sensitivity analysis will be performed.

Missing data will be considered using multiple imputation regression methods.

Secondary outcomes

1. The incremental cost-effectiveness ratios will be calculated and expressed as incremental cost per life years gained and the number of hypoglycemia avoided.

2. Comparison of clinical and biological data will be performed, in particular on metabolic events, insulin requirement, hospitalization or occurrence of complications. Continuous data will be compared using a t-test if the variable was normally distributed or Mann Whitney test for non-parametric variables. The Chi-square test will be used for categorical variables (Fisher's exact test if necessary).

3. Description and comparison of studied population with life-threatening unstable diabetes based on a data-paired analysis (before-after study) will be performed. Continuous data will be compared using a paired t-test if the variable was normally distributed or Wilcoxon test for non-parametric variables. The MacNemar test will be used for categorical variables (Fleiss test if necessary).

4. The economic burden at 1 and 5-years after islet transplantation in the management of severe forms of type 1 diabetes will be measured. The model will take into account especially the target population, the SAP therapy management cost versus islet transplantation cost, the

assumptions about the maintenance or not of insulin-independence over the time but also assumptions about changes in unit costs

5. To simulate the long-term cost, effectiveness and cost effectiveness will be used a Markov model, we will use data from Stabilot study, from our TRIMECO cohort and from literature.

Statistical significance will be considered at p-value ≤ 0.05. All statistical analyses were performed using Stata SE version 12.0 software (StataCorp LP, 4905 Lakeway Drive, College Station, Texas 77845-4512, USA).

STUDY MANAGEMENT

Selection committee

A selection committee composed of investigators from each center will review the medical history and the indication of islet transplantation for each participant candidating for an inclusion in the STABILOT protocol. Half of the centers have to be represented in order to authorize the selection procedure. At the term of the selection procedure, the pre-inclusion of the participants is validated or not.

Validation committee

The validation committee is an independent committee composed of two members (Pr Penfornis, Diabetologist, Corbeil-Essonnes Hospital and Dr Schaepelynck-Belicar, Marseille Hospital) in charge to validate the islet transplantation indication and the inclusion in the STABILOT trial for pre-included participants.

Safety

According to the Directive 2001/20/EC, all adverse events will be recorded and reported with the help of the "Terminology Criteria for adverse Events in Trials of adults pancreatic islet transplantation" (17). All serious adverse events will be reported prospectively to the Sponsor and to competent authority (ANSM) and ethic committee in case of Suspected Unexpected Serious Adverse Reactions. Complications related with the islet infusion will be closed monitoring as well as adverse events related to immunosuppressive drugs or concomitant therapy. An independent Data Safety Monitoring Board (DSMB) composed of 4 experts will be informed for all SUSAR and any safety signal and will receipted all Annual Safety Report. The DSMB will report to the Study Management Committee any safety concerns and recommendations for suspension or early termination of the investigation.

Study management and monitoring

The study coordinator will ensure that the study is conducted in accordance to ICH GCP standards through site monitoring visit. A monitoring plan will be written and agreed before first randomization. An independent data-monitoring committee will monitor 100% of the data. A data-monitoring report will be edited.

Data management

Confidentiality of participant data will be observed at all times during the study. Personal details for each participant taking part in the research study and linking them to a unique identification number will be held locally on a study-screening log in the Trial Master File at each of the investigation centers. All results will remain anonymous. The study identification number will be used on the case report form. Paper copies of the data will be stored for 15 years in line with the Data Protection Act 1998. Direct access to the source data will be

provided for monitoring, audits, ethical committee review and regulatory authority inspections during and after the study.

ETHICAL AND GOVERNANCE APPROUVAL

Ethical approval for this study has been granted by the institutional review board (Person Protection Committee of Grenoble University Hospital (n° 15-CHUG-14) and Clinical Trial Authorization has been given by the French National Competent Authority (ANSM): n° idRCB 2015-00350-49. The trial has been approved by ClinicalTrials.gov (Trial registration ID NCT02854696). Each important protocol modifications will be communicated to Person Protection Committee, to ANSM, to ClinicalTrials.gov and to each study center.

AGENDA

It is expected that screening and recruitment will begin in June 2016 and the study will be completed by winter 2020.

Funding

« Projet de Recherche Medico Economique National 2014 », DGOS (Grant number 14-0225)

Contributorship statement

All the authors participated in the research design

Sandrine Lablanche, Sandra David-Tchouda, Jennifer Margier, Edith Schir, Laurence Kessler, Marie Christine Vantyghem, François Pattou, Pierre-Yves Benhamou participated in the writing paper.

Competing interests

No competing interest to declare

References

1. Benhamou PY, Milliat-Guittard L, Wojtusciszyn A, Kessler L, Toso C, Baertschiger R, Debaty I, Badet L, Penfornis A, Thivolet C, Renard E, Bayle F, Morel P, Morelon E, Colin C, Berney T, group G: Quality of life after islet transplantation: data from the GRAGIL 1 and 2 trials. Diabetic medicine : a journal of the British Diabetic Association 2009;26:617-621
2. Tanenberg RJ, Newton CA, Drake AJ: Confirmation of hypoglycemia in the "dead-in-bed" syndrome, as captured by a retrospective continuous glucose monitoring system. Endocr Pract 2010;16:244-248
3. McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA: Increased mortality of patients with diabetes reporting severe hypoglycemia. Diabetes care 2012;35:1897-1901
4. Hammer M, Lammert M, Mejias SM, Kern W, Frier BM: Costs of managing severe hypoglycaemia in three European countries. J Med Econ 2009;12:281-290
5. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. Am J Ophthalmol 2000;129:704-705
6. Bergenstal RM, Klonoff DC, Garg SK, Bode BW, Meredith M, Slover RH, Ahmann AJ, Welsh JB, Lee SW, Kaufman FR, Group AI-HS: Threshold-based insulin-pump interruption for reduction of hypoglycemia. The New England journal of medicine 2013;369:224-232
7. Lablanche S, Borot S, Wojtusciszyn A, Bayle F, Tetaz R, Badet L, Thivolet C, Morelon E, Frimat L, Penfornis A, Kessler L, Brault C, Colin C, Tauveron I, Bosco D, Berney T, Benhamou PY, Network G: Five-Year Metabolic, Functional, and Safety Results of Patients With Type 1 Diabetes Transplanted With Allogenic Islets Within the Swiss-French GRAGIL Network. Diabetes care 2015;
8. Barton FB, Rickels MR, Alejandro R, Hering BJ, Wease S, Naziruddin B, Oberholzer J, Odorico JS, Garfinkel MR, Levy M, Pattou F, Berney T, Secchi A, Messinger S, Senior PA, Maffi P, Posselt A, Stock PG, Kaufman DB, Luo X, Kandeel F, Cagliero E, Turgeon NA, Witkowski P, Naji A, O'Connell PJ, Greenbaum C, Kudva YC, Brayman KL, Aull MJ, Larsen C, Kay TW, Fernandez LA, Vantyghem MC, Bellin M, Shapiro AM: Improvement in outcomes of clinical islet transplantation: 1999-2010. Diabetes care 2012;35:1436-1445
9. Thompson DM, Meloche M, Ao Z, Paty B, Keown P, Shapiro RJ, Ho S, Worsley D, Fung M, Meneilly G, Begg I, Al Mehthel M, Kondi J, Harris C, Fensom B, Kozak SE, Tong SO, Trinh M, Warnock GL: Reduced progression of diabetic microvascular complications with islet cell transplantation compared with intensive medical therapy. Transplantation 2011;91:373-378
10. Warnock GL, Thompson DM, Meloche RM, Shapiro RJ, Ao Z, Keown P, Johnson JD, Verchere CB, Partovi N, Begg IS, Fung M, Kozak SE, Tong SO, Alghofaili KM, Harris C: A multi-year analysis of islet transplantation compared with intensive medical therapy on progression of complications in type 1 diabetes. Transplantation 2008;86:1762-1766
11. Guignard AP, Oberholzer J, Benhamou PY, Touzet S, Bucher P, Penfornis A, Bayle F, Kessler L, Thivolet C, Badet L, Morel P, Colin C, Group G: Cost analysis of human islet transplantation for the treatment of type 1 diabetes in the Swiss-French Consortium GRAGIL. Diabetes care 2004;27:895-900
12. Beckwith J, Nyman JA, Flanagan B, Schrover R, Schuurman HJ: A health economic analysis of clinical islet transplantation. Clin Transplant 2012;26:23-33

13. Scott NW, McPherson GC, Ramsay CR, Campbell MK: The method of minimization for allocation to clinical trials. a review. Control Clin Trials 2002;23:662-674
14. Lablanche S, Borot S, Wojtusciszyn A, Bayle F, Tetaz R, Badet L, Thivolet C, Morelon E, Frimat L, Penfornis A, Kessler L, Brault C, Colin C, Tauveron I, Bosco D, Berney T, Benhamou PY, Network G: Five-Year Metabolic, Functional, and Safety Results of Patients With Type 1 Diabetes Transplanted With Allogenic Islets Within the Swiss-French GRAGIL Network. Diabetes care 2015;38:1714-1722
15. Chevalier J, de Pouvourville G: Valuing EQ-5D using time trade-off in France. Eur J Health Econ 2013;14:57-66
16. Glick HA: Sample size and power for cost-effectiveness analysis (part 1). Pharmacoeconomics 2011;29:189-198
17. Consortium CIT: Terminology Criteria for adverse Events in Trials of adults pancreatic islet transplantation. 2011

ETUDE STABILOT
FORMULAIRE d'INFORMATION
Impact médico-économique de la stabilisation des formes sévères de diabète de type 1 par transplantation d'îlots pancréatiques

Investigateur coordonnateur : Pr Pierre-Yves BENHAMOU
Clinique d'Endocrinologie, Diabète et Maladies de la Nutrition
CHU de Grenoble
CS 10217 - 38043 GRENOBLE CEDEX 09

Promoteur : CHU de Grenoble
Délégation à la Recherche Clinique et à l'Innovation (DRCI)
CS 10217 - 38043 GRENOBLE Cedex 9
Tél.04.76.76.84.55 - Fax.04.76.76.52.21

Le Dr/Pr ..... vous propose de participer à une recherche biomédicale. Elle est organisée par le CHU de GRENOBLE.

Vous êtes libre d'accepter ou de refuser de participer à cette recherche. Si vous acceptez, vous pourrez retirer à tout moment votre consentement sans encourir aucune responsabilité ni aucun préjudice.

Afin d'éclairer votre décision, voici des informations concernant cette recherche

SOMMAIRE :

TITRE de la RECHERCHE

« Impact médico-économique de la stabilisation des formes sévères de diabète de type 1 par transplantation d'îlots pancréatiques »

Titre court : étude STABILOT

OBJECTIF de la RECHERCHE

Vous êtes diabétique de type 1 ou insulinoprive. Votre glycémie est très instable malgré une insulinothérapie conduite selon les règles de l'art, ou bien vous êtes porteur d'un greffon rénal fonctionnel depuis au moins six mois et votre équilibre glycémique sous insulinothérapie est susceptible de compromettre la survie de votre greffon rénal.

Votre diabétologue vous propose de bénéficier d'une greffe d'îlots pancréatiques dans le cadre de l'étude STABILOT.

Le diabète de type 1 est une maladie causée principalement par la destruction des cellules bêta des îlots du pancréas par le système immunitaire. Cela entraine l'incapacité de la personne atteinte à sécréter de l'insuline.

Pour les personnes diabétiques de type 1 présentant une grave détérioration de leur qualité de vie en raison d'une instabilité majeure et irréductible de leur diabète, la greffe d'ilots pancréatiques constitue une alternative thérapeutique à l'insulinothérapie traditionnelle.

L'objectif de cette étude est d'évaluer la stratégie de transplantation d'îlots pancréatiques dans le cadre du traitement du diabète sucré de type 1, du point de vue de l'efficacité thérapeutique d'une part, et du point de vue des coûts induits par cette stratégie d'autre part. Quarante (40) patients seront recrutés pour l'étude sur 10 centres hospitaliers.

TRAITEMENT à l'ETUDE

Le traitement à l'étude est une transplantation ou greffe d'îlots pancréatiques.

La greffe se fera par injection des îlots pancréatiques dans la veine porte du foie :
- soit par radiologie interventionnelle sous contrôle échographique,
- soit par voie chirurgicale (mini laparotomie)

lors d'une hospitalisation de 8 jours maximum.

Un protocole d'immunosuppression sera mis en place pour empêcher votre corps de rejeter la greffe. Ce protocole nécessite la pose d'un cathéter veineux profond, ainsi qu'une corticothérapie transitoire.
La prise d'immunosuppresseurs sera à vie.

Des prélèvements sanguins seront effectués pendant votre hospitalisation pour la greffe pour procéder aux analyses nécessaires.

La greffe est réalisée :
- soit après l'inclusion dans l'étude (plus ou moins 7 mois)
- soit 1 an après l'inclusion (plus ou moins 7 mois).

7 mois correspondent au délai médian d'attente après mise en liste, délai observé lors d'une étude précédente.
Pour garantir les meilleures chances de succès, il vous faut recevoir une quantité d'îlots suffisante : ce seuil n'est le plus souvent pas obtenu avec un seul donneur, et il vous faudra probablement recevoir 2 voire 3 injections (provenant donc de 2 voire 3 donneurs distincts).

Les alternatives médicales possibles à la greffe d'îlots sont :
- la greffe de pancréas (organe entier) ;
- l'insulinothérapie dont vous bénéficiez déjà.

DEROULEMENT de l'ETUDE

7 visites sont prévues dans le cadre de cette recherche.

A chaque visite, vous aurez :

- Un examen clinique avec le diabétologue ;
- Un bilan biologique (prises de sang de 40 ml maximum) ;
- Deux questionnaires de Qualité de vie à compléter.

1ère VISITE : SELECTION

Lors de cette consultation, votre diabétologue réalisera une première synthèse clinique pour vérifier si vous êtes éligible à la greffe d'îlots pancréatiques. Il vous remettra cette lettre d'information sur l'étude STABILOT.

Il répondra également à toutes vos questions.

2ème VISITE : PRE-INCLUSION

Lors de cette consultation, un bilan pré greffe sera réalisé, qui consistera à rechercher les contre-indications d'ordre infectieux et cardiovasculaire, à évaluer les complications de votre diabète, à réaliser un bilan immunologique et à rechercher les contre-indications à la procédure de greffe.

Ce bilan comportera les examens suivants : pose d'un holter glycémique (3 à 6 jours), échocardiographie, dépistage d'une ischémie myocardique, écho-doppler des membres inférieurs et des vaisseaux du cou, examen ophtalmologique, consultation dermatologique, consultation dentaire, dosage des PSA chez les hommes de plus de 40 ans, consultation gynécologique chez les femmes, échographie abdominale, groupage HLA, recherche d'anticorps lymphocytotoxiques, sérologie virale, exploration de la coagulation sanguine, protéinurie, microalbuminurie, créatininémie, enzymes hépatiques, numération formule sanguine, recherche d'anticorps anti-pancréas, C-peptide à jeun et stimulé, profil lipidique, HbA1c.

Votre diabétologue répondra également à toutes vos questions sur cette étude.

S'il n'existe aucune contre-indication à la greffe, votre dossier sera présenté à un comité de sélection puis à un comité indépendant de validation qui validera ou non votre pré-inclusion.

3ème VISITE : INCLUSION

Après avis favorable* du comité de validation, le diabétologue vous reverra en consultation, dans un délai de 2 mois environ après la visite de pré-inclusion.

*(*Dans le cas où vous ne seriez pas sélectionné, vous continueriez à être pris en charge par votre diabétologue habituel qui veillera à vous faire bénéficier des soins les plus actualisés).*

Après avoir relu la présente lettre d'information et après un délai de réflexion suffisant, si vous acceptez de participer, vous signerez le formulaire de consentement.

Si votre pronostic vital n'est pas engagé, le diabétologue procèdera au tirage au sort et vous serez inclus :

- Soit dans le groupe *Greffe Différée*
- Soit dans le groupe *Greffe immédiate*

Si votre pronostic vital est engagé, vous serez inscrit immédiatement sur la liste d'attente greffe sans tirage au sort.

Lors de cette visite, vous aurez un examen clinique, un bilan biologique, un enregistrement continu de votre glycémie par capteur pendant un mois et des questionnaires Qualité de vie à compléter.

VISITES DE SUIVI

Quel que soit votre groupe, vous bénéficierez de deux enregistrements continus de votre glycémie par capteur pendant un mois : un entre le 5ème et le 6ème mois et un autre entre le 11ème et le 12ème mois.

En fonction de votre groupe, le suivi sera différent :

1. Groupe « GREFFE IMMEDIATE »

Si vous êtes dans le groupe *Greffe immédiate* : vous serez inscrit immédiatement en liste d'attente.

Vous reverrez votre diabétologue tous les 3 mois jusqu'à ce que soit réalisée votre greffe. Lors de ces visites, vous aurez un examen clinique ainsi qu'un bilan biologique.

Une fois greffé, vous reverrez votre diabétologue de façon obligatoire à 6 mois, 1 an, 1 an et demi, et 2 ans après la greffe. Lors de ces visites, vous aurez un examen clinique, un bilan biologique. Vous remplirez les questionnaires sur votre qualité de vie.

Dans le cadre du suivi normal de votre greffe, vous effectuerez des visites régulières avec un bilan biologiques (mensuelles la 1ère année puis tous les 3 mois). Ces visites ne rentrent pas dans le cadre de l'étude.

2. Groupe « GREFFE DIFFEREE »

Si vous êtes dans le Groupe *Greffe Différée*, vous poursuivrez votre traitement insulinique optimal associé à un équipement par capteur de glucose. L'inscription en liste d'attente aura lieu 1 an après cette visite d'inclusion.

Vous reverrez votre diabétologue de façon obligatoire à 6 mois, 1 an, 1 an et demi, et 2 ans.

Lors de ces visites, vous aurez un examen clinique, un bilan biologique. Vous remplirez les questionnaires sur votre qualité de vie.

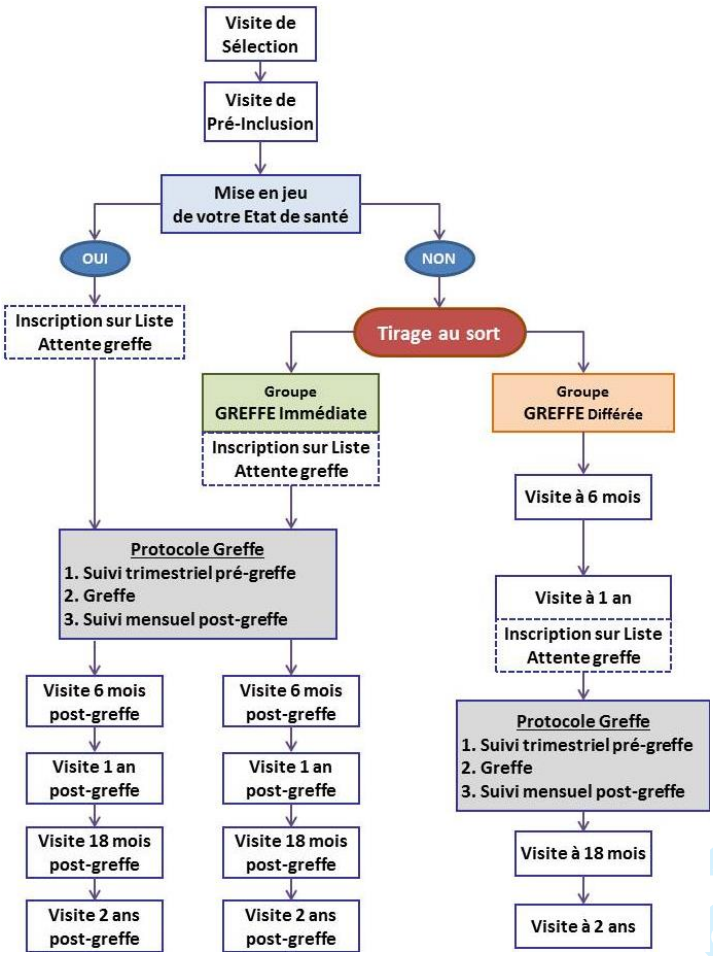
Lors de la visite à 1 an, vous serez inscrit sur la liste d'attente de greffe.

Dès l'inscription sur cette liste, vous aurez un suivi médical identique à celui du groupe « *Greffe immédiate* ».

3. Si votre pronostic vital est engagé

Si votre pronostic vital est engagé (survenue dans l'année précédente d'au moins 1 hypoglycémie sévère, avec coma et/ou convulsions, ayant nécessité une injection de glucagon ou de glucose IV et/ou une hospitalisation, ou ayant entrainé un accident domestique, professionnel (chute avec traumatisme) ou de la voie publique (accident de voiture), vous serez inscrit d'emblée sur la liste d'attente de greffe, sans tirage au sort, et vous bénéficierez du même suivi que les patients du groupe « *Greffe immédiate* ».

SCHEMA de l'ETUDE :



CONTACT

Au cours de l'étude, et en cas de nécessité, vous pourrez joindre à tout moment le Dr/Pr ..... au : __-__-__-__-__

DUREE de l'ETUDE

Vous serez inclus dans l'étude pour une durée de **2 à 4 ans en fonction de votre groupe soit greffe immédiate, soit greffe différée.**

BENEFICES ATTENDUS

Un succès total de la greffe d'îlots pancréatiques se traduit par :

- l'arrêt de la dépendance vis-à-vis des injections d'insuline ;
- la disparition des accidents métaboliques aigus (hypoglycémie ou acidocétose) ;
- la normalisation prolongée de la glycémie (réduction du risque d'apparition de complications micro-angiopathiques (rétine, rein), cardio-vasculaires et neuropathiques, stabilisation ou régression de ces dernières si elles étaient présentes avant la greffe ;
- enfin l'amélioration de la qualité de vie.

Un succès partiel se traduit par la restauration d'une insulino-sécrétion insuffisante pour autoriser l'insulino-indépendance, mais qui contribue cependant à :

- à améliorer le contrôle métabolique du diabète par des doses réduites d'insuline,
- à réduire le risque de complications aiguës et chroniques,
- enfin à améliorer la qualité de vie.

CONTRAINTES

Les contraintes sont liées à la greffe :

- Hospitalisation d'une durée de 8 jours maximum afin d'effectuer la transplantation ;
- Disponibilité pour les visites médicales de l'étude : visites trimestrielles avant la greffe, puis visites de suivi après la greffe (semestrielles obligatoires, mensuelles recommandées) jusqu'à 2 ans après la 1ère injection ;
- Prises de sang pour bilan biologique ;
- Examens d'imagerie médicale (échographie et radiographie) ;
- Prise d'immunosuppresseurs à vie ;
- Pose de capteur glycémique pour la mesure continue du glucose (3 périodes de 1 mois minimum).

Vous ne pourrez pas participer à une autre étude clinique pendant toute cette période. Toutefois, vous êtes autorisé(e) à participer à des protocoles de suivi immunologique de votre greffe qui consistent en des prélèvements sanguins avant et après greffe.

RISQUES

Les risques prévisibles liés à la greffe d'îlots pancréatiques sont :

- <u>risques immédiats liés à la procédure de transplantation</u> : hématomes périhépatiques, thrombose de branches de la veine porte, blessures des voies biliaires, montée enzymatique hépatique, hémorragie intra abdominale. L'hémorragie intra abdominale peut entrainer un choc hémorragique pouvant conduire dans les cas extrêmes au décès du patient. L'hémorragie intra abdominale peut nécessiter le recours à une transfusion sanguine et/ou intervention chirurgicale ;

- <u>risques consécutifs liés à l'immunosuppression inhérente à la greffe</u> : toxicité des immunosuppresseurs (anémie, leucopénie avec risque infectieux), digestive (aphtose) et néphrologique. A long terme, après plusieurs années, les effets de l'immunosuppression prolongée sont de nature oncologique (principalement carcinomes cutanés baso-cellulaires, et lymphomes par réactivation virale de type EBV) justifiant là aussi une surveillance spécialisée régulière.

C'est pourquoi un suivi médical régulier est prévu dans le cadre de l'étude, notamment afin de détecter la survenue d'effets indésirables.

Dans le cas où un arrêt de la recherche est envisagé (survenue d'effet indésirable grave lié à la procédure ou votre impossibilité à respecter les règles liées à la procédure et au suivi), la décision fera intervenir le Comité de surveillance de l'étude.

Votre suivi sera néanmoins poursuivi pendant la période prévue par l'étude (2 ans), en excluant les examens rendus inutiles.

INDEMNITES et PERIODE D'EXCLUSION

Aucun frais supplémentaire ne vous sera facturé du fait de votre participation à l'étude. Il n'y a pas d'indemnités prévues.

PROTECTION des PERSONNES

Cette recherche biomédicale a reçu un avis favorable du Comité de Protection des Personnes **Sud-Est V** le **08/04/2015.** Elle a été autorisée par l'Agence Nationale de Sécurité des Médicaments et des produits de santé (ANSM) le **12/11/2015.**

Le CHU de Grenoble a pris toutes les dispositions prévues par la loi sur la protection des personnes (contrat d'assurance SHAM n°**135751**).

Un exemplaire de cette fiche d'information vous est destiné.

Pour participer à cette recherche, vous devez être affilié(e) à un régime de sécurité sociale.

A l'issue de cette recherche, vous pourrez être informé de ses résultats globaux par courrier si vous en exprimez la demande auprès de votre médecin.

DONNEES INFORMATISEES

Dans le cadre de cette recherche, un traitement de vos données personnelles va être mis en œuvre pour permettre d'analyser les résultats de la recherche au regard de l'objectif de cette dernière. A cette fin, les données médicales vous concernant, seront transmises au Promoteur de la recherche ou aux personnes ou sociétés agissant pour son compte, en France.

Ces données seront identifiées par un numéro et vos initiales (1ère lettre de votre nom et 1ère lettre de votre prénom). Ces données pourront aussi, dans des conditions assurant leur confidentialité, être transmises aux autorités de santé françaises, à d'autres entités du CHU de Grenoble. Le promoteur et l'investigateur coordonnateur devront donner leur accord.

Conformément aux dispositions de la Loi relatives à l'Informatique et Liberté du 6 janvier 1978 (CNIL), vous avez un droit d'accès et de rectification. Vous disposez également d'un droit d'opposition à la transmission des données couvertes par le secret professionnel susceptibles d'être utilisées dans le cadre de cette recherche et d'être traitées.

Vous pouvez aussi accéder directement ou par l'intermédiaire d'un médecin de votre choix à l'ensemble de vos données médicales en application des dispositions de l'article L1111-7 du Code de la Santé Publique. Ces droits s'exercent auprès du médecin qui vous suit dans le cadre de la recherche et qui connaît votre identité.

En cas de retrait de consentement, vous acceptez que les données récoltées jusqu'ici soient utilisées (dans le cas contraire, il faudra le signaler à l'investigateur pour qu'elles soient détruites).

Nous vous remercions pour l'attention portée à la lecture de ce document

ETUDE STABILOT
CONSENTEMENT DE PARTICIPATION

Titre identifiant la recherche : Impact médico-économique de la stabilisation des formes sévères de diabète de type 1 par transplantation d'îlots pancréatiques

Médecin investigateur responsable de l'étude : **Pr Pierre-Yves BENHAMOU** Clinique d'Endocrinologie, Diabète et Maladies de la Nutrition - CHU de Grenoble CS 10217 - 38043 GRENOBLE CEDEX 09	**Promoteur :** CHU de Grenoble Délégation à la Recherche Clinique et à l'Innovation (DRCI) CS 10217 - 38043 Grenoble cedex 09 Tel : 04 76 76 84 55

J'ACCEPTE DE PARTICIPER A CETTE RECHERCHE DANS LES CONDITIONS PRECISEES DANS LA LETTRE D'INFORMATION.

Le Pr/Dr ..... m'a proposé de participer à une étude organisée par CHU de Grenoble. Cette étude est intitulée : « Impact médico-économique de la stabilisation des formes sévères de diabète de type 1 par transplantation d'îlots pancréatiques »

Si je le désire, j'ai le droit de refuser de participer à cette recherche ou de retirer mon consentement à tout moment sans encourir aucune responsabilité ni aucun préjudice de ce fait.
J'en informerai le médecin.

Les données qui me concernent resteront strictement confidentielles. Je n'autorise leur consultation que par des personnes soumises au secret professionnel et collaborant à cette recherche.
Je pourrais joindre à tout moment mon médecin pour des informations complémentaires.

Je dispose d'un délai de réflexion si je le désire avant de donner mon accord pour ma participation à cette étude.

J'accepte que les données enregistrées à l'occasion de cette étude puissent faire l'objet d'un traitement informatisé, après l'anonymat, par le promoteur ou pour son compte. J'ai bien noté que mon droit d'accès prévu par la loi informatique et liberté s'exerce à tout moment. En cas de retrait de consentement, j'accepte que mes données récoltées jusqu'au retrait soient utilisées, dans le cas contraire, je le signalerai à l'investigateur pour qu'elles soient détruites.

J'ai reçu une fiche d'information détaillée (version 2.1 du 19/03/2015). J'ai reçu une copie du présent document, j'ai été informé(e) qu'une copie sera également conservée par les organisateurs dans des conditions garantissant la confidentialité. J'y consens.

J'ai été informé(e) que conformément à la réglementation sur les recherches biomédicales : le Comité de Protection des Personnes Sud-Est V a donné un avis favorable le 08/04/2015 ; et l'Agence Nationale de Sécurité des Médicaments et des produits de santé (ANSM) a donné son autorisation le 12/11/2015 pour la réalisation de cette recherche.

Je suis bien affilié(e) à un régime de sécurité sociale.

Je m'engage à suivre toutes les consignes et instructions qui me seront données par l'investigateur ou son équipe, dont celles qui sont détaillées dans la notice d'information. Par ailleurs si je présente un symptôme anormal en cours d'étude je m'engage à contacter l'investigateur dans les délais les plus brefs. En cas d'urgence, je peux également appeler le 15 (SAMU).

Coordonnées des personnes du Centre Investigateur à contacter pendant et/ou après l'étude :	
Nom, prénom	.....
N° téléphone	___ . ___ . ___ . ___ . ___

Partie à compléter par le PATIENT :	**Partie à compléter par l'INVESTIGATEUR :**
Je soussigné (e) ..... *A remplir **par le patient** nom et prénom en majuscules.* Ai lu et reçu un exemplaire de la notice d'information et du consentement. Je déclare donner librement mon consentement de participation à cette étude en accord avec les informations mentionnées ci-dessus. Date : Signature	Je soussigné (e) ..... *A remplir par l'investigateur nom, prénom en majuscules.* confirme avoir personnellement expliqué au patient le contenu de la notice d'information et m'être assuré qu'il bénéficiait d'un régime de Sécurité Sociale. Date : Signature

ETUDE STABILOT
CONSENTEMENT DE PARTICIPATION

Titre identifiant la recherche : Impact médico-économique de la stabilisation des formes sévères de diabète de type 1 par transplantation d'îlots pancréatiques

Médecin investigateur responsable de l'étude : **Pr Pierre-Yves BENHAMOU** Clinique d'Endocrinologie, Diabète et Maladies de la Nutrition - CHU de Grenoble CS 10217 - 38043 GRENOBLE CEDEX 09	**Promoteur :** CHU de Grenoble Délégation à la Recherche Clinique et à l'Innovation (DRCI) CS 10217 - 38043 Grenoble cedex 09 Tel : 04 76 76 84 55

J'ACCEPTE DE PARTICIPER A CETTE RECHERCHE DANS LES CONDITIONS PRECISEES DANS LA LETTRE D'INFORMATION.

Le Pr/Dr ..... m'a proposé de participer à une étude organisée par CHU de Grenoble. Cette étude est intitulée : « Impact médico-économique de la stabilisation des formes sévères de diabète de type 1 par transplantation d'îlots pancréatiques »

Si je le désire, j'ai le droit de refuser de participer à cette recherche ou de retirer mon consentement à tout moment sans encourir aucune responsabilité ni aucun préjudice de ce fait.

J'en informerai le médecin.

Les données qui me concernent resteront strictement confidentielles. Je n'autorise leur consultation que par des personnes soumises au secret professionnel et collaborant à cette recherche.

Je pourrais joindre à tout moment mon médecin pour des informations complémentaires.

Je dispose d'un délai de réflexion si je le désire avant de donner mon accord pour ma participation à cette étude.

J'accepte que les données enregistrées à l'occasion de cette étude puissent faire l'objet d'un traitement informatisé, après l'anonymat, par le promoteur ou pour son compte. J'ai bien noté que mon droit d'accès prévu par la loi informatique et liberté s'exerce à tout moment. En cas de retrait de consentement, j'accepte que mes données récoltées jusqu'au retrait soient utilisées, dans le cas contraire, je le signalerai à l'investigateur pour qu'elles soient détruites.

J'ai reçu une fiche d'information détaillée (version 2.1 du 19/03/2015). J'ai reçu une copie du présent document, j'ai été informé(e) qu'une copie sera également conservée par les organisateurs dans des conditions garantissant la confidentialité. J'y consens.

J'ai été informé(e) que conformément à la réglementation sur les recherches biomédicales : le Comité de Protection des Personnes Sud-Est V a donné un avis favorable le 08/04/2015 ; et l'Agence Nationale de Sécurité des Médicaments et des produits de santé (ANSM) a donné son autorisation le 12/11/2015 pour la réalisation de cette recherche.

Je suis bien affilié(e) à un régime de sécurité sociale.

Je m'engage à suivre toutes les consignes et instructions qui me seront données par l'investigateur ou son équipe, dont celles qui sont détaillées dans la notice d'information. Par ailleurs si je présente un symptôme anormal en cours d'étude je m'engage à contacter l'investigateur dans les délais les plus brefs. En cas d'urgence, je peux également appeler le 15 (SAMU).

Coordonnées des personnes du Centre Investigateur à contacter pendant et/ou après l'étude :	
Nom, prénom	.....
N° téléphone	___ . ___ . ___ . ___ . ___

Partie à compléter par le PATIENT :	**Partie à compléter par l'INVESTIGATEUR :**
Je soussigné (e) ..... *A remplir **par le patient** nom et prénom en majuscules.* Ai lu et reçu un exemplaire de la notice d'information et du consentement. Je déclare donner librement mon consentement de participation à cette étude en accord avec les informations mentionnées ci-dessus. Date : Signature	Je soussigné (e) ..... *A remplir par l'investigateur nom, prénom en majuscules.* confirme avoir personnellement expliqué au patient le contenu de la notice d'information et m'être assuré qu'il bénéficiait d'un régime de Sécurité Sociale. Date : Signature

ETUDE STABILOT CONSENTEMENT DE PARTICIPATION	
Titre identifiant la recherche : Impact médico-économique de la stabilisation des formes sévères de diabète de type 1 par transplantation d'îlots pancréatiques	
Médecin investigateur responsable de l'étude : **Pr Pierre-Yves BENHAMOU** Clinique d'Endocrinologie, Diabète et Maladies de la Nutrition - CHU de Grenoble CS 10217 - 38043 GRENOBLE CEDEX 09	**Promoteur :** CHU de Grenoble Délégation à la Recherche Clinique et à l'Innovation (DRCI) CS 10217 - 38043 Grenoble cedex 09 Tel : 04 76 76 84 55

J'ACCEPTE DE PARTICIPER A CETTE RECHERCHE DANS LES CONDITIONS PRECISEES DANS LA LETTRE D'INFORMATION.

Le Pr/Dr ..... m'a proposé de participer à une étude organisée par CHU de Grenoble. Cette étude est intitulée : « Impact médico-économique de la stabilisation des formes sévères de diabète de type 1 par transplantation d'îlots pancréatiques »

Si je le désire, j'ai le droit de refuser de participer à cette recherche ou de retirer mon consentement à tout moment sans encourir aucune responsabilité ni aucun préjudice de ce fait.

J'en informerai le médecin.

Les données qui me concernent resteront strictement confidentielles. Je n'autorise leur consultation que par des personnes soumises au secret professionnel et collaborant à cette recherche.

Je pourrais joindre à tout moment mon médecin pour des informations complémentaires.

Je dispose d'un délai de réflexion si je le désire avant de donner mon accord pour ma participation à cette étude.

J'accepte que les données enregistrées à l'occasion de cette étude puissent faire l'objet d'un traitement informatisé, après l'anonymat, par le promoteur ou pour son compte. J'ai bien noté que mon droit d'accès prévu par la loi informatique et liberté s'exerce à tout moment. En cas de retrait de consentement, j'accepte que mes données récoltées jusqu'au retrait soient utilisées, dans le cas contraire, je le signalerai à l'investigateur pour qu'elles soient détruites.

J'ai reçu une fiche d'information détaillée (version 2.1 du 19/03/2015). J'ai reçu une copie du présent document, j'ai été informé(e) qu'une copie sera également conservée par les organisateurs dans des conditions garantissant la confidentialité. J'y consens.

J'ai été informé(e) que conformément à la réglementation sur les recherches biomédicales : le Comité de Protection des Personnes Sud-Est V a donné un avis favorable le 08/04/2015 ; et l'Agence Nationale de Sécurité des Médicaments et des produits de santé (ANSM) a donné son autorisation le 12/11/2015 pour la réalisation de cette recherche.

Je suis bien affilié(e) à un régime de sécurité sociale.

Je m'engage à suivre toutes les consignes et instructions qui me seront données par l'investigateur ou son équipe, dont celles qui sont détaillées dans la notice d'information. Par ailleurs si je présente un symptôme anormal en cours d'étude je m'engage à contacter l'investigateur dans les délais les plus brefs. En cas d'urgence, je peux également appeler le 15 (SAMU).

Coordonnées des personnes du Centre Investigateur à contacter pendant et/ou après l'étude :	
Nom, prénom	.....
N° téléphone	___ . ___ . ___ . ___ . ___

Partie à compléter par le PATIENT :	**Partie à compléter par l'INVESTIGATEUR :**
Je soussigné (e) ..... *A remplir **par le patient** nom et prénom en majuscules.* Ai lu et reçu un exemplaire de la notice d'information et du consentement. Je déclare donner librement mon consentement de participation à cette étude en accord avec les informations mentionnées ci-dessus. Date : Signature	Je soussigné (e) ..... *A remplir par l'investigateur nom, prénom en majuscules.* confirme avoir personnellement expliqué au patient le contenu de la notice d'information et m'être assuré qu'il bénéficiait d'un régime de Sécurité Sociale. Date : Signature

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	1
	2b	All items from the World Health Organization Trial Registration Data Set	1 (See ClinicalTrail.gov)
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	18
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	2
	5b	Name and contact information for the trial sponsor	1/18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	NA

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	17_18
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6-7
	6b	Explanation for choice of comparators	6-7
Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	7
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	*8*-9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	NA
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	NA

	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	NA
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5-16
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	9-12
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	9
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11-15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11-15
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	18
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14_15_
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	NA
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	14-15

Methods: Monitoring

Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	17
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	17
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17

Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	19
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	18
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	3
	31b	Authorship eligibility guidelines and any intended use of professional writers	19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary data
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.