## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | A randomized, prospective, medico-economic nationwide French study of islet transplantation in patients with severely unstable type 1 diabetes: the STABILOT study protocol |
| **AUTHORS** | Lablanche, Sandrine; David-Tchouda, Sandra; Margier, Jennifer; Schir, Edith; Wojtusciszyn, Anne; Borot, Sophie; Kessler, Laurence; Morelon, Emmanuel; Thivolet, Charles; Pattou, François; Vantyghem, Marie-Christine; Berney, Thierry; Benhamou, Pierre-Yves |

## VERSION 1 - REVIEW

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| **REVIEWER** | Camillo Ricordi<br>University of Miami, USA |
| **REVIEW RETURNED** | 07-Sep-2016 |

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| **GENERAL COMMENTS** | The primary objective of the STABILOT multicenter trial is to perform a prospective analysis of the cost effectiveness of islet transplantation versus sensor-augmented pump (SAP) therapy. The study is timely and very important for the field and could also provide a useful model for other countries to adopt and assess their own cost-effectiveness of the strategies evaluated, especially in the USA where the cost of islet transplantation is significantly higher compared to France and other European countries. |

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| **REVIEWER** | James Shaw<br>Institute of Cellular Medicine,<br>Newcastle University,<br>UK<br><br>Member of the UK Medtronic Advisory Board<br>Previous support from Novo Nordisk to attend American Diabetes association Conference |
| **REVIEW RETURNED** | 13-Sep-2016 |

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| **GENERAL COMMENTS** | In this planned trial, the investigators propose prospective medico-economic nationwide study of islet transplantation versus optimised medical therapy. This is undoubtedly a worthwhile initiative given the growing evidence base for optimised medical therapy for type 1 diabetes complicated by recurrent severe hypoglycaemia and absence of previous studies directly comparing sensor-augmented pump therapy with islet transplantation.<br><br>In its current form, however, weaknesses in the study description diminish my enthusiasm. |

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| | The description ‘brittle diabetes’ is no longer favoured and, in my opinion, should be avoided throughout, replaced by specific phenotypic characterisation. It should be clarified whether ‘persistence of severe hypoglycaemia’ (define more precisely) is necessary for study inclusion or whether solely having glycaemic variability (SD on CGM and MAGE) is sufficient? I am concerned that broadening the inclusion criteria will preclude most meaningful economic analysis given small numbers overall. Can the investigators justify why basal C-peptide negativity is deemed sufficient, as opposed to C-peptide after a clearly defined and standardised stimulus? The inclusion criterion of ‘despite optimised insulin treatment and educational training’ should be more clearly defined.<br><br>I understand the desire to include participants ‘refusing’ SAP to ensure that those who may benefit from islet transplantation but who cannot manage pump therapy are not excluded, but given the very small numbers, this requires further justification.<br><br>The medical comparator SAP intervention should be more clearly defined, particularly given the evidence-base for structured education in management of recurrent severe hypoglycaemia and the growing evidence that greatest impact can be achieved specifically through SAP including low glucose insulin suspend capability. It appears that there may be greater attention provided post-islet transplant than post-SAP and – equivalence in support for diabetes self-management should be demonstrated. Clarity here will be particularly important given the low numbers and multiple sites.<br><br>I would like to see more detail on number of transplants to be performed and protocol for islet transplant management although note that this is referenced.<br>I am concerned about the choice and timing of patient reported outcome measures given lack of face validity for DQOL in this patient group and the possibility that EQ-5D will be insufficient to measure important impacts (for example on hypoglycaemia-related outcomes). Should hypoglycaemia questionnaires not all be repeated at the 12 month time-points in addition to pre-intervention?<br><br>The proposed careful prospective collection of data regarding resource use / overall costs is a strength.<br><br>Further clarification of the power calculation and statistical review would be worthwhile.<br><br>Overall I am supportive of this trial proceeding but recommend careful reconsideration and refinement of all aspects prior to commencement. I suggest consideration of only recruiting those with recurrent severe hypoglycaemia (life-threatening and supported by baseline economic analysis of associated direct and indirect costs) with confirmed C-peptide negativity following standard challenge who have already trialled insulin pump therapy without CGM, who are prepared to explore SAP (including predictive low glucose suspend (PLGS)). SAP with PLGS to be augmented by a validated hypoglycaemia-targeted structured education programme. Include range of validated patient-reported outcome measures and seek further health economist and statistician input regarding optimal design. |

**VERSION 1 – AUTHOR RESPONSE**

Reviewer: 1
Reviewer Name: Camillo Ricordi
Institution and Country: University of Miami, USA Competing Interests: None declared

The primary objective of the STABILOT multicenter trial is to perform a prospective analysis of the cost effectiveness of islet transplantation versus sensor-augmented pump (SAP) therapy. The study is timely and very important for the field and could also provide a useful model for other countries to adopt and assess their own cost-effectiveness of the strategies evaluated, especially in the USA where the cost of islet transplantation is significantly higher compared to France and other European countries.

We warmly thank Pr Ricordi for the comments.

Reviewer: 2 Reviewer Name: James Shaw Institution and Country: Institute of Cellular Medicine, Newcastle University, UK Competing Interests: Member of the UK Medtronic Advisory Board; Previous support from Novo Nordisk to attend American Diabetes association Conference

In this planned trial, the investigators propose prospective medico-economic nationwide study of islet transplantation versus optimised medical therapy. This is undoubtedly a worthwhile initiative given the growing evidence base for optimised medical therapy for type 1 diabetes complicated by recurrent severe hypoglycaemia and absence of previous studies directly comparing sensor-augmented pump therapy with islet transplantation.

In its current form, however, weaknesses in the study description diminish my enthusiasm.

The description ‘brittle diabetes’ is no longer favoured and, in my opinion, should be avoided throughout, replaced by specific phenotypic characterisation.

We agree that the denomination of brittle diabetes has been controversial. Therefore we have replaced it with the term of “severely unstable” or “unstable” diabetes, keeping in mind that the extreme and unpredictable glucose fluctuations are the common phenotypic characterisation of these patients.

It should be clarified whether ‘persistence of severe hypoglycaemia’ (define more precisely) is necessary for study inclusion or whether solely having glycaemic variability (SD on CGM and MAGE) is sufficient?

Regarding study inclusion, as described in the inclusion criteria in the manuscript, at least two criteria among the following are required to consider patients for inclusion:

- Persistence of severe hypoglycemia defined as occurrence of at least one severe hypoglycemia over the last year (added in the main manuscript)
- 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
- A MAGE index (Mean amplitude of glucose excursions) > 60 mg/dl (3.33 mmol/L)
- A LBGI index (low blood glucose index) > 5
- A Clarke score ≥ 4

- An HYPOSCORE > 800
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Consequently, a patient describing glucose variability without persistent severe hypoglycemic episodes may be a candidate for the study. This will allow to include patients with a broad history of severe hypoglycaemia for whom glycemic targets have been raised to avoid severe hypoglycaemia. Moreover, persistence of severe hypoglycemia alone is not sufficient for the patient to be included in the study. Another criterion has to be associated with severe hypoglycemia to authorize the inclusion of the patient.

I am concerned that broadening the inclusion criteria will preclude most meaningful economic analysis given small numbers overall.

We understand the concern of the reviewer and we recognize that the spectrum of inclusion criteria is apparently large. However, from a clinical and economical perspective, the vast majority of the targeted population will be an homogenous group of patients, corresponding to a small number of patients, characterised by extreme glucose variability, and vulnerability to hypoglycemic episodes.. This assumption is based upon our previous experience of multicentric trials in the field of islet transplantation (Trimeco trial)

Can the investigators justify why basal C-peptide negativity is deemed sufficient, as opposed to C-peptide after a clearly defined and standardised stimulus?

The rationale for measuring C-peptide before and after transplantation is to provide evidence that the improvement in metabolic control is related with the restoration of endogenous insulin secretion. We set a C-peptide threshold of <0.3 ng/ml for basal C_peptide or <0.5 ng/ml for stimulated C-peptide, based upon DCCT data establishing that patients with stimulated C-peptide ≥0.2nm/l had reduced prevalence of severe hypoglycemia. For practical and empirical reasons, pre-transplant basal C-peptide negativity was deemed sufficient. Indeed, a recent study (A.K. Davis, Diabetes Care 2015; 38: 476) showed that the prevalence of unfasting C-peptide >0.2nmol/l after a duration of diabetes of 20 years or more (the expected duration of disease in our trial based upon our previous experience) is 0% in patients with onset < 18 y.o. and 7% in patients with onset >18 y.o. In patients with unfasting C-peptide <0.2 nmol/l, the prevalence of stimulated C-peptide >0.2 nmol/l is only 14%. Therefore it is unlikely that patients with a long duration of disease screened with a negative basal C-peptide actually present with positive stimulated C-peptide.

The inclusion criterion of ‘despite optimised insulin treatment and educational training’ should be more clearly defined.

Patients experiencing severely unstable type 1 diabetes despite an optimised insulin treatment and educational training will be included.

An optimised insulin treatment is defined by CSII (or MDI for patients refusing CSII treatment or failing to manage CSII). CSII has to be supervised by a clinician expert in diabetes management warranting optimal insulin therapy adjustment. Patients have to be educated through the participation in structured psycho-educational programs delivered in individual or group settings.

This clarification has been added to the main manuscript.

I understand the desire to include participants 'refusing' SAP to ensure that those who may benefit from islet transplantation but who cannot manage pump therapy are not excluded, but given the very small numbers, this requires further justification.

In France, islet transplantation is available for patients only through clinical research program. Currently, in France, the STABILOT study is the unique opportunity for patients to benefit from islet transplantation. In this context, we decided to also include patients who cannot manage insulin pump therapy. Even though, from a statistical point of view, these patients increase the heterogeneity of the population, from a clinical point of view, islet transplantation remains the unique therapeutic option for these patients with unstable type 1 diabetes. We assume that the expected strong efficiency efficacy of islet transplantation would counterbalance for the heterogeneity of the population.

The medical comparator SAP intervention should be more clearly defined, particularly given the evidence-base for structured education in management of recurrent severe hypoglycaemia and the growing evidence that greatest impact can be achieved specifically through SAP including low glucose insulin suspend capability. It appears that there may be greater attention provided post-islet transplant than post-SAP and – equivalence in support for diabetes self-management should be demonstrated. Clarity here will be particularly important given the low numbers and multiple sites.

This is an important point. SAP therapy with Predictive Low-Glucose Suspend (Threshold: 60 mg/dL) will be proposed to DIT group. In complement to the quarterly visit, patients from DIT group 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.

This clarification has been added to the main manuscript.

I would like to see more detail on number of transplants to be performed and protocol for islet transplant management although note that this is referenced.

Pancreases will be obtained from brain-dead multi organ donors through Swiss transplant and the French Biomedicine Agency (Agence de la Biomédecine). Islets are isolated using the automated method described by Ricordi et al. with local modifications as previously reported. 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 shipped by ambulance to the transplant centers. Transit time will never exceed 4 hours. Patients are scheduled to receive up to a target islet mass of 11,000 IEQ/kg body weight. Consequently, when the first islet infusion 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 achieve the total islet mass. These details have been provided in previous publications from the investigators.

I am concerned about the choice and timing of patient reported outcome measures given lack of face validity for DQOL in this patient group and the possibility that EQ-5D will be insufficient to measure important impacts (for example on hypoglycaemia-related outcomes). Should hypoglycaemia questionnaires not all be repeated at the 12-month time-points in addition to pre-intervention?

We agree on the fact that DQOL exhibit lack of validation in our patient group.

Nevertheless, to the best of our knowledge, no QOL questionnaire is fully validated in our specific population. In our group, previous study on QOL after islet transplantation (Benhamou PY, Diabet

Metab, 2009) using DQOL has been performed and exhibited a good sensibility of DQOL in this population.

EQ-5D questionnaire is used first to describe primary endpoint: the economic utility (QALY). In this field, 2 questionnaires only are validated (HUI and EQ5D). However, EQ-5D questionnaire is widely validated to explore health-related utility in various pathologies and appears to be sensitive enough to measure evolution of health-related utility in patients experiencing non-severe and severe hypoglycaemia. (Currie CJ, 2009). EQ-5D questionnaire will be repeated every 3 months until the end of the study (M24).

The proposed careful prospective collection of data regarding ressource use / overall costs is a strength.

Further clarification of the power calculation and statistical review would be worthwhile.

Regarding cost-utility analysis (primary endpoint), we considered the less favourable following assumptions: difference in costs of 69,000 € ± 50,000 € (SD) [average cost without islet transplantation rising from 6,700 to 25,000 € at 12 months for brittle diabetes patients (InVS report and data from Beckwith, 2012) and between 75,000 € (preliminary results of TRIMECO study) and 95,000 € (Beckwith, 2012) for patients with islet transplantation at 12months]. Difference in effects of 0.06 QALY ± 0,03 (Beckwith, 2012), Correlation between difference in costs and effects from -1 to 1, and a maximum willingness to pay of 20,000 € par QALY. Using these data, we have to include 9 to 12 patients per group (calculated using Stata V11SE and based on Glick's works (16)). This number of subjects remains consistent with those written in the article (p14, at the top of the Statistical analysis section): “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)”. Nevertheless, the results on the medico-economic criteria have to be interpreted with caution because of many assumptions and the mathematical formula used is still very unstable (Glick 2011). That is why we choose the highest number of subjects (clinical criteria): 15 per group.

These precisions have been added in the main manuscript.

Overall I am supportive of this trial proceeding but recommend careful reconsideration and refinement of all aspects prior to commencement. I suggest consideration of only recruiting those with recurrent severe hypoglycaemia (life-threatening and supported by baseline economic analysis of associated direct and indirect costs) with confirmed C-peptide negativity following standard challenge who have already trialled insulin pump therapy without CGM, who are prepared to explore SAP (including predictive low glucose suspend (PLGS)). SAP with PLGS to be augmented by a validated hypoglycaemia-targeted structured education programme. Include range of validated patient-reported outcome measures and seek further health economist and statistician input regarding optimal design.

We warmly thank Pr Shaw for the comments that permit to enhance the methodology of our protocol. Hoping that our arguments and responses will permit to clarify the different points underlined.

## VERSION 2 – REVIEW

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| **REVIEWER** | James Shaw<br>Institute of Cellular Medicine<br>Newcastle University<br>UK<br><br>Travel support from Novo Nordisk to attend American Diabetes Association Conference |
| **REVIEW RETURNED** | 11-Dec-2016 |

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| **GENERAL COMMENTS** | The authors have carefully reflected on all of my previous comments and have sought to address all of these in the revised manuscript. I am now supportive of publication and progression with this valuable and unique trial. |