THE BIOARTIFICIAL PANCREAS

A CLINICAL CASE SCENARIO ANALYSIS TO ASSESS AND SUPPORT THE DEVELOPMENT OF A DEVICE TO IMPROVE TYPE 1 DIABETES CARE

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ABSTRACT

OBJECTIVE: A new bioartificial pancreas (BAP) is being developed to improve conventional islet of Langerhans transplantation. The objective of this study is to prospectively evaluate if, and particularly when, the new BAP becomes an alternative for patients and endocrinologists in comparison to conventional transplantation methods in the treatment of the uncontrollable diabetes type 1 patient eligible for conventional islet and pancreas transplantation.

METHODS: Based on literature research, semi-structured interviews and focus groups the key characteristics that determine clinical decision making between the conventional transplantation methods and the new BAP were identified and weighted by conventional type 1 diabetes patients (T1DM patients) (n=17), type 1 diabetes patients on the waiting list for islet transplantation or those that already received an islet transplant (T1DM IT/IT-WL patients) (n=4) and endocrinologists (n=12) using the Analytic Hierarchy Process. Subsequently, these weights were used to compute the relative preference of three scenarios: a negative, positive and most likely future BAP scenario and the conventional transplantation methods, both whole organ pancreas transplantation and islet of Langerhans transplantation, to evaluate whether type 1 diabetics and endocrinologists are willing to consider the new BAP in the treatment of uncontrollable type 1 diabetes. Between the included scenarios there was varied in the transplantation site for the BAP, the necessary intervention for BAP placement and the amount of donor material and dose immunosuppressive agents necessary for a successful transplantation.

RESULTS: The most important transplantation characteristics of BAP design are the effectiveness of the transplant, patient safety with emphasis on long-term patient safety, and the technique for BAP placement. From the T1DM patient perspective, the effectiveness of the transplant is seen as the most important criterion (0,458), followed by patient safety (0,336) and long term patient safety (0,212). The effectiveness of the transplant is, from their point of view, mainly determined by the reduction in progression and potential regeneration of long term complications (relative importance of 0,311). When it concerns a T1DM IT/IT-WL patient, the effectiveness of the transplant receives an importance weight of even 0,524, followed by patient safety (0,308) and a relative importance of 0,204 for the long term patient safety. For the endocrinologist patient safety (0,423) is seen as the most important criterion, followed by the effectiveness of the transplant (0,257) and long term patient safety receiving a relative importance weight of 0,261. The intervention for BAP placement is an important characteristic because of the interdependence between the intervention, the follow-up care and the safety of the procedure which together provide a relative importance weight of 0,127 for the T1DM IT/IT-WL patient, 0,188 for the T1DM patient and even 0,258 for the endocrinologist.

Of all transplant alternatives assessed pancreas transplantation is the most preferred by the T1DM patient and T1DM IT/IT-WL patient gaining an overall preference weight of respectively 0,279 and 0,320, followed by the positive BAP scenario (T1DM patient: 0,251; T1DM IT/IT-WL patient:0,233), the most likely BAP scenario (T1DM patient: 0,195; T1DM IT/IT-WL patient: 0,174), the negative BAP scenario (T1DM patient: 0,150; T1DM IT/IT-WL patient: 0,154) and conventional islet of Langerhans transplantation (T1DM patient: 0,125; T1DM IT/IT-WL patient: 0,119). For the endocrinologist the positive BAP scenario scores highest (0,298), followed by pancreas transplantation (0,223), the most likely BAP scenario (0,206), the negative BAP scenario (0,139) and islet of Langerhans transplantation (0,134).

CONCLUSION: According to this study it may be concluded that the BAP can be seen as an alternative in current treatment provided that the future BAP is going to perform equally or better than the defined negative future BAP scenario. Enlargement of the clinical market for the BAP can be achieved by either improvements in performance or a radical change in BAP design focus from the promotion of revascularisation towards immunological protection. To improve BAP performance it is recommended to focus on both the effectiveness of the transplant from the type 1 diabetic perspective and to focus on patient safety and mainly on immunosuppressive agent reduction from the endocrinologist's perspective.

ABBREVIATIONS:

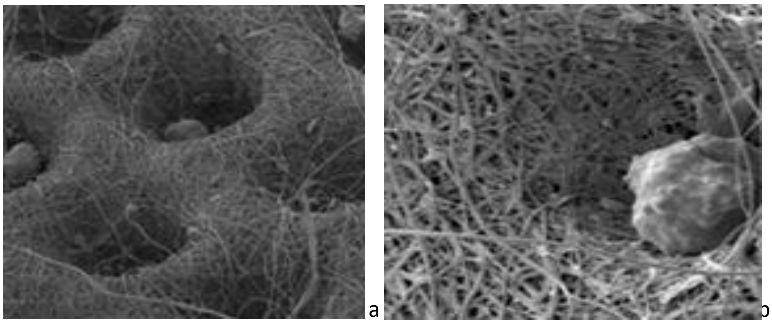
AHP: analytic hierarchy process, **BAP:** bioartificial pancreas, **CIPII:** continuous intraperitoneal insulin infusion, **CSII:** continuous subcutaneous insulin infusion, **eMTA:** early medical technology assessment, **HbA1c:** glycated haemoglobin, **IAK:** islet after kidney transplantation, **ITA:** islet transplantation alone, **MCDA:** multi criteria decision analysis, **PAK:** pancreas after kidney transplantation, **PTA:** pancreas transplantation alone, **SIK:** simultaneous islet kidney transplantation, **SPK:** simultaneous pancreas kidney transplantation, **T1DM IT/IT-WL patient:** type 1 diabetes patient that already received an islet transplantation of is waiting on the waiting list to receive one, **T1DM patient:** type 1 diabetes.

1.0 INTRODUCTION

Type 1 diabetes mellitus is a major health problem affecting increasing numbers of patients all over the world [1]. The disease is caused by an inadequate insulin secretion attributable to a progressive autoimmune destruction of beta cells [1–7] Restoration of this deficiency by beta cell replacement or regeneration might be the solution for the treatment of type 1 diabetes[2,8,9]. Islet transplantation is an accepted beta cell replacement method to re-establish and maintain physiological normoglycemia in type 1 diabetics [10]. The transplantation of allogeneic islets is seen as a treatment alternative for those individuals with severe glycemic lability, refractory episodes of hypoglycaemia and hypoglycaemia unawareness. However, the islets isolated from one donor organ are often insufficient to establish normoglycemia because of a reasonable amount of islet loss before, during and after transplantation [11].

THE BAP

Recently, the department of Tissue Regeneration of the University of Twente started with a new research project to improve islet transplantation by creating a carrier (figure 1) to ameliorate the survival of transplanted donor islets [12]. For now, this research performed by the University of Twente focuses on shifting the transplantation site away from the liver and the promotion of islet revascularisation, to pursue normal β cell function and viability. The ultimate aim of carrier development in the short term is the creation of a bioartificial pancreas (BAP), a combination of the new developed carrier with isolated allogenic islets, which is capable to realize a long-term physiologic glucose regulation with the islets of only one donor organ despite the presence of type 1 diabetes.



a b

Figure 1. The carrier comprises of stacked polymer films in which microwells (a) (~400 micron in diameter and 350 micron in depth) are inprinted which should provide a safe environment for the transplanted islets. (b) A close-up of one islet.

The creation of this BAP has the potential to improve current type 1 diabetes care. Yet, little is known so far about the clinical performance and, hence, the potential success of this new technology. In vivo animal tests with the prototype of the BAP need to be done to explore the potential transplantation sites, the related benefits and disadvantages of these places, the islet viability and functionality improvements and the necessary changes to scaffold design. Until the first results of the clinical trials are known it remains uncertain how the technology is going to perform and whether this performance is sufficient to be seen as a treatment to improve type 1 diabetes care.

Even though the clinical benefit is uncertain during early development, it is interesting to investigate how the BAP will resonate in the medical field; whereas it is still possible to adjust the BAP during early development. A lot of money is invested in BAP research and development and the BAP may contribute to better and sustainable healthcare. It is however difficult to predict the potential impact of a new technology. The potential impact of the BAP is closely related to the future performance of the BAP and the extent to which this performance is corresponding to consumer preferences taking into account the performances of other treatment alternatives. In case of the BAP, it is beneficial for the developers to assess their BAP already during early development to evaluate the potential impact of the BAP and to fine-tune further development to the requirements of clinical practice. Although this type of research has been performed on a limited scale, researchers have begun to recognize the importance of analysis methods that address uncertainties during the design and development process of a new medical technology [13]. In addition, investigating consumer preferences which can be used for health care optimization is becoming more and more popular[14–20].

Early medical technology assessment (figure 2) is a "toolbox" containing a set of formal approaches which can be applied to evaluate the potential impact of a new medical technology, like the BAP, during early development [13,20]. In this study an early assessment of the new BAP is performed to provide valuable information on the potential impact of the new BAP which subsequently can be used to support future product development. The objective of this study is to prospectively evaluate if and particularly when the new BAP becomes an alternative for patients and endocrinologists in comparison to conventional transplantation methods in the treatment of the diabetes type 1 patients eligible for conventional islet and pancreas transplantation.

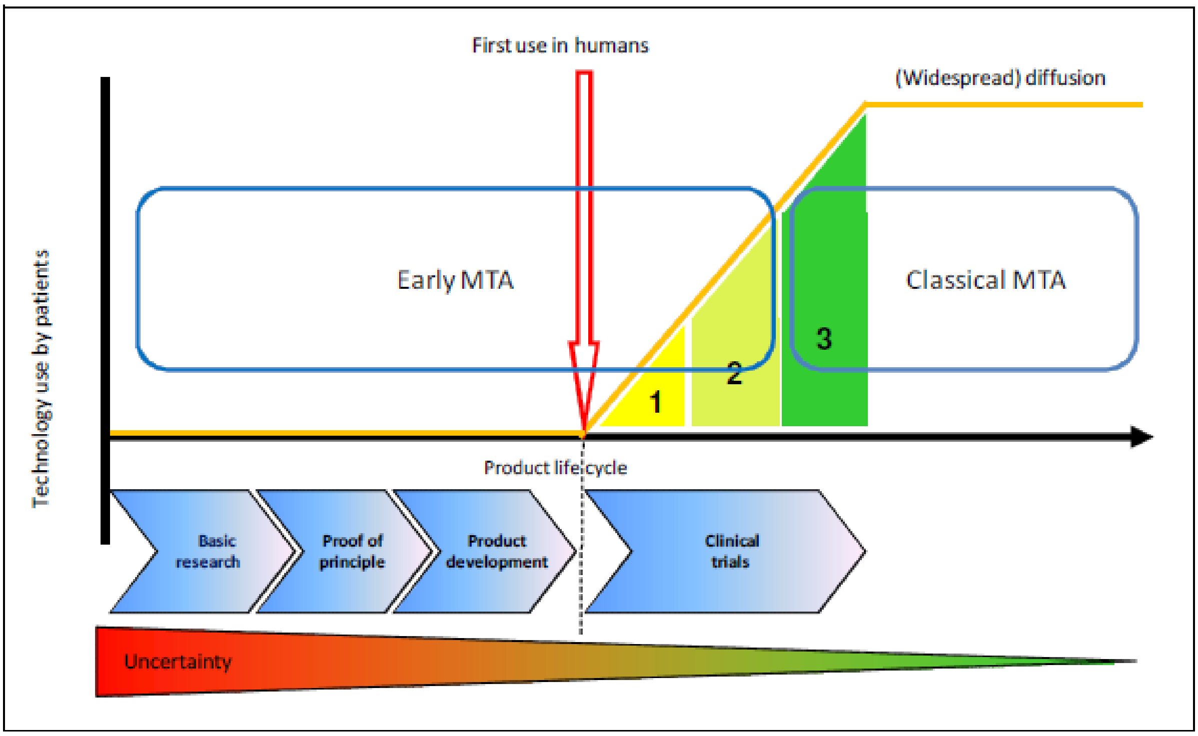


Figure 2. Diagrammatic representation of the life cycle of a medical technology. The term "Medical Technology Assessment" (MTA) is used as an umbrella term to describe a collection of formal approaches to assess a new medical technology in terms of efficacy, safety, its impact or future impact on the treatment of patients, as well as the technology's effect on economic, social, legal and ethical aspects of care. Traditionally, MTA is applied when new medical technologies first come onto the market. Early MTA, on the other hand, is focuses on the earlier stages of development which contributes to better outcomes for medical treatments, better investment decisions and prevention of social and ethical conflicts. [13,20]

In order to understand patient' and endocrinologist' judgement in decision making for a transplantation method, a multi criteria decision analysis (MCDA) method is used for quantifying the relative contribution of a transplant characteristic (decision criterion) in the overall preference for a transplantation method. MCDA methods are methods which help decision makers to clarify complex decisions by quantitatively supporting the evaluation of a finite number of transplant alternatives under a finite number of performance criteria[21,22]. As the complex choice for any transplantation method involves multiple decision criteria, a formal assessment of the impact and added value of the future BAP should take a prioritized set of criteria into account.

In this study, at first the most important criteria for decision making between transplantation therapies are identified, second MCDA is used to analyse how patients and endocrinologists trade-off the different treatment characteristics (decision criteria) and last the expected benefits of three scenarios for the use of the BAP are evaluated. Based on these results, recommendations are given to improve BAP design.

2.0 METHODS

2.1 MCDA/AHP ANALYSIS

The Analytic Hierarchy Process (AHP) - the multi criteria decision analysis (MCDA) method used in this study- is a frequently used method for measuring preferences[18,19] and structures the complex decision between transplant alternatives into a hierarchy of factors. The AHP analysis of this study was based on the hierarchical structure visualized in figure 4. The structure contains a goal, the determined (sub) decision criteria and the treatment alternatives that are compared.

2.2 CLINICAL CASE ANALYSIS TO CLARIFY BAP'S POTENTIAL

A clinical case analysis[20] was performed to see whether the BAP has clinical potential. Based on literature research, semi-structured interviews and focus groups (figure 3) the intended clinical application, expected clinical outcomes and the potential advantages of the BAP in comparison to current treatment were exposed. Ten researchers of the tissue regeneration department of the University of Twente and one physician involved in BAP development were approached to identify the intended BAP application and potential clinical outcomes and advantages of the BAP. In addition, several endocrinologists, type 1 diabetes patients and diabetes specialist nurses were randomly approached to give their opinion on current type 1 diabetes care. Eventually, 4 physicians, 3 patients and 6 nurses -unfamiliar with BAP development- were questioned to clarify advantages and disadvantages bound to current type 1 diabetes care. In addition, substance was given to the definition of transplant performance and the key transplant characteristics that determine the decision between transplant alternatives. Subsequently, a patient profile eligible for both the conventional transplantation methods and the new developed BAP was selected (see paragraph 2.3.2 identification treatment alternatives). The patient profile selected as the hypothetical patient is a relatively young person with severe glycemic liability, refractory episodes of hypoglycaemia and hypoglycaemia unawareness eligible for PTA, ITA and BAP.

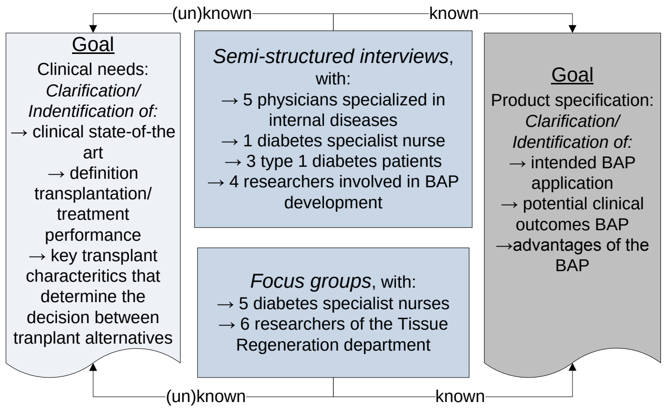


Figure 3. In total, 13 semi-structured interviews and two focus groups were conducted in support of this study. At first, a clinical case analysis was done [20]. Those individuals known with the BAP were asked on the intended application, the expected clinical outcomes and the advantages of the BAP in comparison to current treatment. Based on these answers three future BAP scenarios were created. Interviews and focus groups with both known and unknown individuals were used to visualize the clinical state of the art, to clarify the definition of the performance of a treatment/transplantation method, to identify the decision criteria (those key characteristics that determine the decision between transplant alternatives) and to inquire the potential adoption of the BAP by the consumer.

2.3 AHP HIERARCHY STRUCTURE

2.3.1 IDENTIFICATION DECISION CRITERIA

To identify the decision criteria included in the hierarchic structure (figure 4), literature research was performed to expose preferences in diabetes care and to find criteria that influence decision making for transplantation. A list of treatment characteristics was constructed and corrected and supplemented with the information retrieved from the semi-structured interviews and focus groups. Eventually, all aspects of the list were divided into four overarching criteria resulting in the four top-level criteria; transplant effectiveness, amount of donor material necessary for a successful transplantation, impact of the treatment for the patient and patient safety. The criteria 10 years partial transplant function and 1,5 or 10 years full transplant function were included in this research to determine the importance of insulin independence in the choice between transplant alternatives. A detailed description of all decision criteria can be found in appendix A.

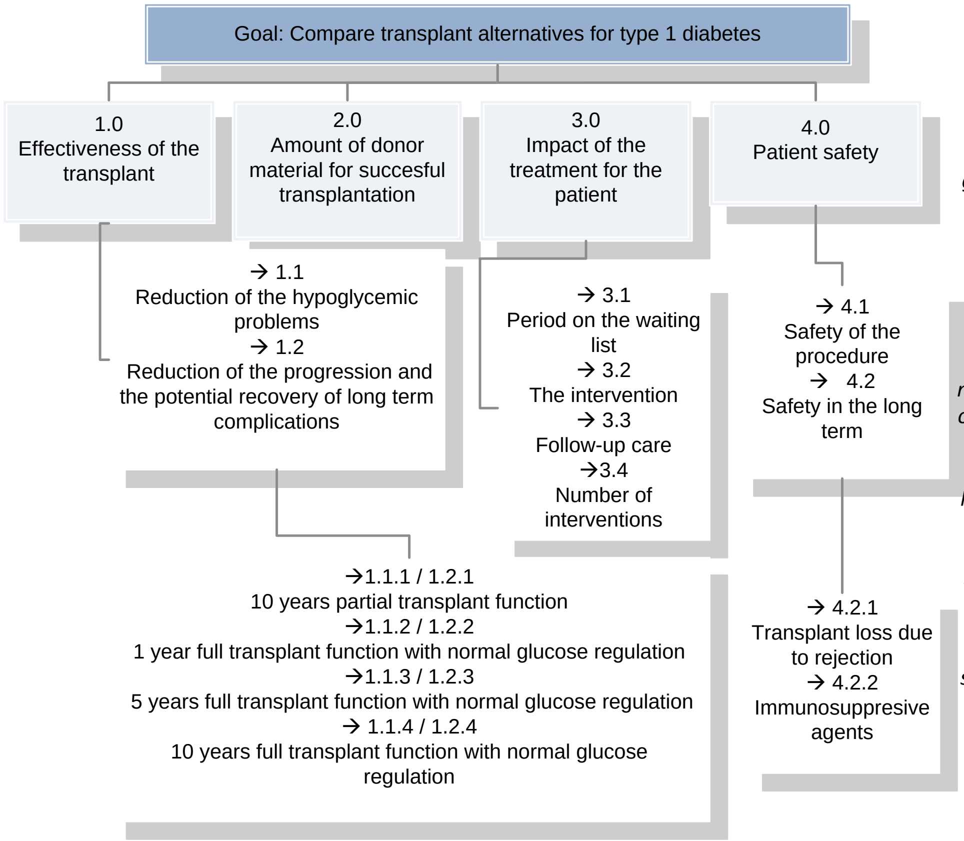


Figure 4. The AHP hierarchy structure to compare transplantation methods for type 1 diabetes patients. The structure consists of the goal, decision criteria and the treatment alternatives. The goal of this AHP analysis is to compare the expected performance of the developed BAP with current transplantation methods for the treatment of type 1 diabetes patients eligible for both conventional islet and pancreas transplantation. An extensive description of the criteria can be found in appendix A. The alternatives included in this AHP analysis are (1,2,3) three future BAP scenarios, (4) coventional islet transplantation and (5) conventional whole organ pancreas transplantation.

<u>2.3.2 IDENTIFICATION TREATMENT ALTERNATIVES</u>

Figure 5 provides an overview of the conventional insulin therapies used in type 1 diabetes management. In general, the subcutaneous insulin injection functions as a first-line treatment. When clinical goals aren't achieved adaptations to current treatment can be made, including a switch to another insulin administration technology.
The current focus of BAP development is the amelioration of transplanted donor islets by shifting the transplantation site away from the liver and promoting islet revascularisation to pursue normal β cell function and viability. Allogenic islet transplantation is already used and accepted as a treatment for type 1 diabetics and is therefore the most suitable opportunity for the carrier to prove itself in the short term. In the long term the BAP could also be combined with other potential beta-cell sources. In figure 5, the BAP could potentially make its appearance as an alternative or substitute for conventional islet or/and pancreas transplantation (see appendix D&E for additional information on the conventional transplantation methods).

Nevertheless, it depends on the future performance of the BAP, patient characteristics and consumer needs to select the right type of patient eligible for BAP. If BAP performance exceeds islet transplantation performance, the BAP may be used as an alternative to/or replacement of islet transplantation alone (ITA), islets after kidney transplantation (IAK) and the less performed simultaneous islet kidney (SIK) transplantation. When BAP performance is going to exceed even pancreas performance, the BAP may be used as a pancreas transplant replacement in simultaneous pancreas kidney (SPK) transplantation, pancreas after kidney (PAK) and pancreas transplantation alone (PTA). Currently, it is most likely that the BAP will be used for those type 1 diabetics with severe glycemic liability, refractory episodes of hypoglycaemia and hypoglycaemia unawareness. This patient profile is eligible for PTA, ITA and BAP and was therefore used in this study in the assessment of three future BAP scenarios in comparison to the conventional transplantation alternatives ITA and PTA.

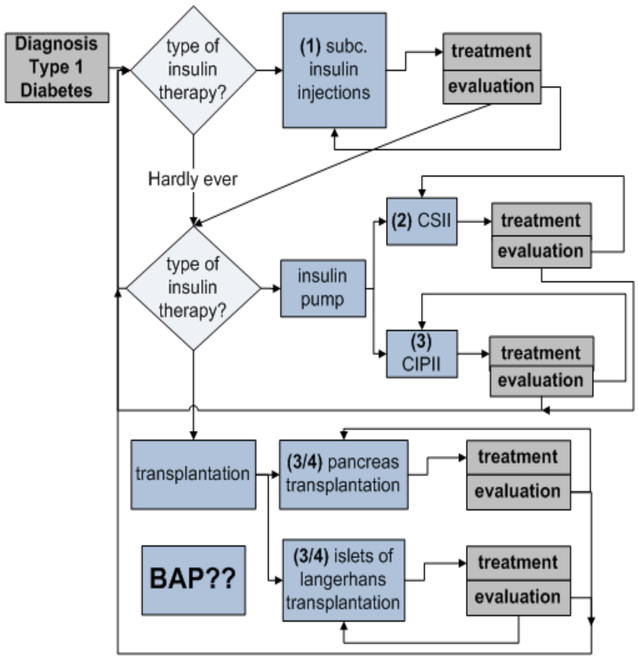


Figure 5. Flow diagram representing the choices made for insulin therapy. After the type 1 diabetes diagnosis the subcutaneous insulin injection functions as the first-line treatment. When clinical goals aren't achieved adaptations to current insulin therapy can be made, including a switch to another insulin administration technology. In general, the switch is made to continuous subcutaneous insulin infusion (CSII). Continuous intraperitoneal insulin infusion(CIPII) offers a more physiological route for insulin administration, though, both CIPII and islet transplantation, are no routinely available strategies [49]. The pancreas transplantation is performed more often but both performed islet and pancreas transplantations are limited by the number of donor organs available. The BAP is an alternative transplantation method developed with the aim to improve conventional islet transplantation and may make its appearance as an alternative or substitute for conventional islet or/and pancreas transplantation.

2.4 DETERMINATION OF THE IMPORTANCE OF DECISION CRITERIA

2.4.1 QUESTIONNAIRE

Two questionnaires, one for the patient and one for the physician, were developed using AHP weighting, to determine the importance of the defined decision criteria relevant in the decision making process for a transplantation method by type 1 diabetes patients and endocrinologists (appendix F).

The relative contribution of a decision criterion (transplant characteristic) in the overall preference for a transplantation method was computed based on pairwise comparisons of sets of two (sub-) criteria. The relative importance of one criterion in comparison to the other was appointed on a nine-point ordinal scale in which one reflects equal importance or preference and nine extremely higher importance or preference[18,23–25]

In the questionnaires a clinical vignette was used to fix clinical circumstances to ensure all participants made pairwise comparisons for the same hypothetical patient. The patient profile selected as the hypothetical patient is a relatively young person with severe glycaemic liability, refractory episodes of hypoglycaemia and hypoglycaemia unawareness eligible for PTA, ITA and BAP. The T1DM patient was asked to consider a situation in which they would experience the same burden as the hypothetical patient when assigning weights. The endocrinologist was asked to consider a situation in which they are responsible for the hypothetical patient's treatment.

In addition to the weightings, the T1DM patient questionnaire inquired demographic data including age, gender, level of education, marital status, nationality, age of T1DM diagnosis, the level of glycated haemoglobin (HbA1c), the presence of both hypo as hyperglycaemic episodes, the presence of hypoglycaemia unawareness, the presence of a high cholesterol or high blood pressure, potential micro and macrovascular long term complications, the insulin administration technology, their quality of life, treatment satisfaction and disease knowledge satisfaction.

Additional demographic data obtained of the endocrinologists were age, gender, specialism, start year specialty, type of diabetes patients under treatment, familiarity with the hypothetical patient and the involvement in scientific research.

The questionnaire was designed for completion within 30 minutes. A pilot of the questionnaire was conducted to test the questionnaire and to determine whether the method, questionnaire language and the chosen criteria were appropriate and clear.

2.4.2 SELECTION OF PATIENTS AND EXPERTS

27 endocrinologists operating in hospitals in the west, mid and east of the Netherlands were randomly approached per mail to participate in this research project. In addition, 38 type 1 diabetes patients were approached in the hospital face to face, by phone, or trough the universities group mail to participate in this study. Of those approached 12 (44%) endocrinologists and 27 (71%) T1DM patients completed and returned the questionnaire. Questionnaires were sent per email or by letter and in addition participants received a letter of introduction, instructions for questionnaire fulfilment and an information sheet to describe the decision criteria. To improve response rates, reminders by mail or phone were given to non-responders two weeks after they received the questionnaire.

2.5 SCENARIO DESIGN

In consultation with those involved in BAP development three scenarios: a negative, positive and most likely future BAP scenario were created and assessed in comparison to conventional transplantation methods to evaluate whether type 1 diabetics and endocrinologists are willing to consider the new BAP in the treatment of uncontrollable type 1 diabetes. Table 1 provides an overview of the transplant alternatives included in this study.

TABLE 1. THE TRANSPLANT ALTERNATIVES INCLUDED IN THIS STUDY

TRANSPLANT ALTERNATIVES: DESIGN CHOICES:	① Positive future BAP scenario	② Negative future BAP scenario	③ Likely future BAP scenario	④ ITA	⑤ PTA
Transplantation site	*Subcutaneous*	*Greater omentum*	*Subcutaneous*	*Intrahepatic*	*Intraperitoneal*
Intervention	*Minimal incision*	*Laparoscopic intervention*	*Minimal incision*	*Portal vein catheterization*	*Open surgery*
Number of donor organs	*1/2*	*2*	*1*	*2 or 3*	*1*
Amount of immunosuppressive agents	*Halved dose*	*Conventional dose*	*Conventional dose*	*Conventional dose*	*Conventional dose*

2.5.1 DESIGN CHOICES

For the creation of the scenarios variations were made in the design choices BAP developers could make, including the choice for the transplantation site, the potential choice for the necessary intervention for BAP placement, the amount of donor material to use and the dose immunosuppressive agents necessary for successful transplantation.

Extra-hepatic opportunities for BAP placement, with clinical relevance, are seen subcutaneously, intramuscularly and intraperitoneally [2]. A subcutaneous and an intraperitoneal site (placement of the BAP in the greater omentum) are included in the created future BAP scenarios (table 1). Subcutaneous BAP placement can be done with a minimal incision, though, for BAP placement in the greater omentum either a laparoscopic or open procedure is required. Both the minimal incision as the laparoscopic procedure are included in the future BAP scenarios.

Concerning the number of donor organs necessary for a successful transplantation the assumption is made that BAP reduces this amount requiring respectively two, one or only half a donor organ. For the immunosuppressive agents it is expected that the patient needs to take a conventional amount of immunosuppressive agent when they receive a BAP. Current BAP design focuses on revascularisation instead of immunological protection. This latter focus in design may cause a reduction in the amount of immunological agents necessary. Though, because of the named impact of immunosuppressive agents use on the decision to proceed to transplantation the dose immunosuppressive agents needed is halved in the positive future BAP scenario.

2.6 DETERMINATION OF COMPETITIVE ADVANTAGE OF THREE CLINICAL APPLICATIONS

The second part where AHP was used was the calculation of the priorities for the decision alternatives. Three future BAP scenarios were compared with the conventional transplantation methods based on their overall performance in order to learn whether this new BAP would be an alternative for current treatment in uncontrollable diabetics. Based on the importance weights assigned and the relative performance of the transplantation alternatives on every decision criterion, the overall preferences for the defined transplantation alternatives were calculated and the minimal requirements for the BAP to be accepted by patients and endocrinologists to consider the treatment were identified.

2.6.1 PERFORMANCE ASSESSMENT TREATMENT ALTERNATIVES

Up till now, no data is available on future BAP performance and so far only a prototype is available. In addition, large variability in research design and chosen outcome parameters was found in literature, describing the outcomes of the conventional transplantation methods, and there was a lack of randomised controlled trials describing conventional islet transplantation outcomes [11]. Expert opinion was therefore used to score the alternatives on their relative performance per criterion. The performance assessment was done using a nine-point ordinal scale method (also used for the determination of the importance of decision criteria) in which one reflects equal performance and nine extreme better performance of one transplantation alternative in comparison to the other. The expert used for the performance assessment is known with all transplant alternatives included in this study. Assigning the performance weights, the expert had to consider the interdependence between the transplant characteristics.

2.7 CONSISTENCY TESTS

For a correct interpretation of the results it is important to test for consistency of responses to assess the reliability of the responses. An advantage of the use of the AHP is the included measure of the ratio of inconsistency. This ratio indicates the degree to which each pairwise comparison is consistent with the remainder of the comparisons [22]. In this way individual consistency was assessed. It is advised that the consistency ratio should not exceed the value of 0,1, [26] though, because of the large inconsistency of the received questionnaires this limit for inclusion was set on 0,3. Eventually, 12 endocrinologists and 21 T1DM patients were included in the analysis. The pairwise comparisons made by both T1DM patients and endocrinologists to determine the importance of insulin independence in the choice for a transplant option all had an >0,3 inconsistency. Results are shown; however the outcomes were excluded from further statistical analysis and discussion in this article.

2.8 CALCULATIONS AND STATISTICS

In this study a subdivision is made between those patients that already received an islet transplant or were waiting to receive one and those patients unfamiliar with transplantation. Therefore three study groups can be distinguished; 1) the normal diabetes type 1 patient unfamiliar with transplantation (indicated by T1DM patient), 2) the diabetes type 1 patient already confronted with islet transplantation (indicated by T1DM IT/IT-WL patient) and 3) the endocrinologist.

At first the group averages of the assigned weights to every criterion were calculated. Subsequently, statistical analyses were performed to statistically confirm the intergroup variability in importance between the decision criteria, to identify potential correlations and to significantly confirm differences in assigned importance weights for the same criterion between the participant groups. All statistical analysis were performed using SPSS 16.0. Because the results were not normally distributed, the non-parametric Mann-Whitney and the non-parametric Wilcoxon signed-rank test were performed to demonstrate respectively 1) significant differences in the weights assigned between the endocrinologist and the T1DM patient and 2) significant differences between the weights assigned by the same participant group. The spearman's correlation coefficient was used to identify potential relationships between participant characteristics and assigned weights.

After statistically evaluating the assigned weights in comparison to each other, the group averages per criterion were combined with the performance weights of every transplant alternative at the criteria to obtain the overall preferences for the transplant alternatives. Finally, the relative importance weights of the different performance levels of the transplant alternatives on the transplant characteristics (or decision criteria) were calculated.

Overall, p values less than 0.05 were considered to be statistically significant. **Nevertheless, found significant differences in this study can only be explorative interpreted.** Because of the few participants included in the T1DM IT/IT-WL patient group it was difficult to statistical confirm differences in the weights assigned. Unless indicated otherwise, the average weighting factors per participant group for every decision criterion (+ standard deviation (σ)) or transplant alternative are presented.

3.0 RESULTS

3.1 DEMOGRAPHICS INCLUDED PARTICIPANTS

The T1DM patients included in this study (n=21) were almost evenly split in terms of gender (52% female) with a mean age of 40 years and an average number of diabetes years of 21, 2 years. All were of Dutch origin and between the age of 18 and 69 years old. The average age of diagnosis was 18, 8 years old and the HbA1c of the participants was in 62% of all that participated between the 6.0% (42 mmol/mol) and 8.0% (64 mmol/mol). All T1DM patients included, except for one, were known with low blood sugar levels of less than 3,5 mmol/L and seven indicated to have difficulty recognizing these hypoglycaemic episodes. Three T1DM participants already received an islet transplant and one T1DM patient that participated was on the waiting list at the time of participation in this study. Table 2 in appendix B provides an overview of the demographic data on theT1DM patients included in this research.

The endocrinologists included (n=12) (83% male) in this research were between the age of 36 and 63 years old, with an average age of 49 years old. All endocrinologists were familiar with the type 1 diabetes patients and the hypothetical patient. They were all involved or had been involved in scientific research and the average number of years of experience with their specialism was 14 years.

3.2 OBTAINED IMPORTANCE WEIGHTS OF THE DECISION CRITERIA

3.2.1 TOP LEVEL CRITERIA

Of the four top level criteria effectiveness of the transplant and patient safety are by far the two most important criteria for both the T1DM patient, the T1DM IT/IT-WL patient and the endocrinologist (figure 6). From the T1DM patient perspective, effectiveness of the transplant (T1DM patient: 0,458; T1DM IT/IT-WL patient: 0,524) is seen as the most important criterion, followed by patient safety (T1DM patient: 0,336; T1DM IT/IT-WL patient: 0,306). Subsequently, the impact of the treatment for the patient (0,140) is seen by the T1DM patient as the third most important criterion followed by the amount of donor material necessary for a successful transplantation (0,066). From the T1DM IT/IT-WL patient perspective the assigned importance weights of these last two criteria are reversed. The amount of donor material (0,100) is the third most important criterion and the impact of the treatment is least important (0,069). Another relevant difference is the difference in the assigned weights to effectiveness of the transplant and patient safety by the endocrinologist in comparison to the type 1 diabetes patient. In contrast to the diabetes type 1 patient, patient safety (0,423) is seen by the endocrinologist as the most important criterion, followed by both the effectiveness of the transplant (0,257) and the impact of the treatment for the patient (0,249). Again in accordance with the T1DM patient the amount of donor material (0,071) is seen as the least important criterion.

Despite the relatively small groups of participants and the large variability in the assigned weights, a significant discrepancy between the endocrinologist and the T1DM patient could be found on the criterion effectiveness of the transplant ($p<0,05$) and impact of the treatment for the patient($p<0,001$). Focussing on those T1DM patients included in this study that already received an islet transplantation (n=3) or those waiting to receive a transplantation (n=1) (T1DM IT/WL-IT) a clear increase in the importance of the effectiveness of the transplant is visible where patient safety seems to be less important in comparison to both the 'conventional' T1DM patient and the endocrinologist. A significant difference between this patient population and the endocrinologist could again be found for the effectiveness of the transplant ($p<0,05$) and the impact of the treatment for the patient ($p<0,05$). These discrepancies indicate that the effectiveness of the transplant is significant more important for the T1DM patient and that the impact of the treatment is significant more important for the endocrinologist.

Significant differences between the weights assigned to the top level criteria by the endocrinologist could be found between patient safety and effectiveness of the transplant ($p<0,05$), patient safety and the impact of the treatment for the patient ($p<0,001$), patient safety and the amount of donor material ($p<0,001$), effectiveness of the transplant and the amount of donor material ($p<0,001$) and the impact of the treatment for the patient against the amount of donor material ($p<0,001$). For the T1DM patient significant differences could be found between the effectiveness of the transplant and the quantity of organ tissue necessary ($p<0,001$), patient safety and the quantity of organ tissue necessary ($p<0,001$), impact of the treatment and the amount of donor material necessary for a successful transplantation ($p<0,05$), effectiveness of the transplant and the impact of the treatment for the patient ($p<0,001$) and patient safety and the impact of the treatment for the patient ($p<0,05$). Because of the small T1DM IT/IT-WL patient population no significant differences between the weights assigned to the top-level criteria could be confirmed.

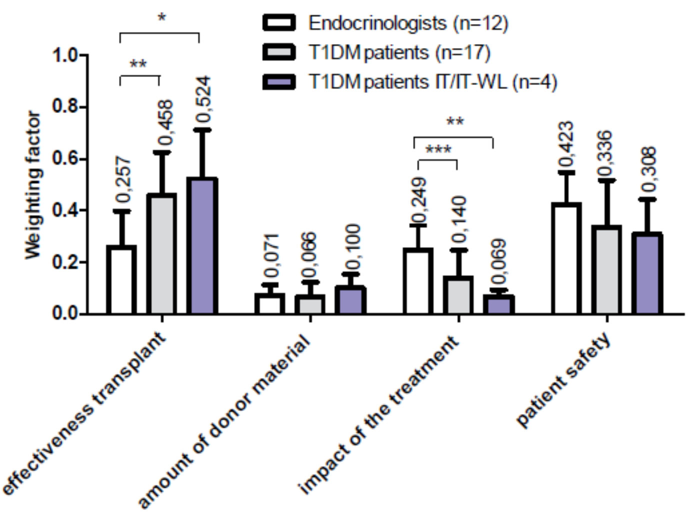


Figure 6. *The average weights assigned by the T1DM patients and the endocrinologists to the four top level criteria that determine the decision for a transplantation method. Between groups significant differences were found for the effectiveness of the transplant (p<0,05) and the impact of the treatment for the patient (p<0,001) between the T1DM patient and the endocrinologist and for the effectiveness of the transplant (p<0,05) and impact of the treatment for the patient (p<0,05) between the T1DM IT/IT-WL patient and the endocrinologist. Standard deviation (σ) is indicated by the black bars. For an extensive description of the criteria see appendix A. The average inconsistency between the pairwise comparisons of the top-level criteria was 0.20 (T1DM patients), 0,15 (T1DM IT/IT-WL patients) and 0.18 (endocrinologists).*

3.2.2. SUBCRITERIA

Observing the weights assigned to the subcriteria that determine the effectiveness of the transplant (figure 7) the ability of the transplant to reduce the progression and the potential regeneration of long term complications receives the largest weights of all participant groups evaluated (the T1DM patient (0,678); the T1DM IT/IT-WL patient (0,517); the endocrinologist (536)). The reduction of the hypoglycaemic problems seems to be less important receiving a weight of 0,322 of the T1DM patient, 0,483 of the T1DM IT/IT-WL patient and 0,465 of the endocrinologist. A significant preference for the reduction in progression and potential regeneration of long term complications could only be demonstrated for the T1DM patient (p<0,05).

Between the subcriteria that determine the top-level criterion impact of the treatment for the patient (figure 7) less clear preferences could be demonstrated. An exception, however, is the weight of the period on the waiting list assigned by the T1DM IT/IT-WL patient (0,533). The 'conventional' T1DM patient assigned a weight of 0,156 and the endocrinologist assigned a weight of 0,228 to this same criterion. The second most important criterion for the T1DM IT/IT-WL patient is the follow-up care bound to the transplantation, receiving a weight of 0,190, closely followed by the intervention (0,140) and the number of interventions needed (0,138). For the 'conventional' T1DM patient the period on the waiting list was seen as least important and therefore the follow-up care (0,224), the intervention necessary for transplantation (0,236) and the number of interventions (0,384) all score higher. In accordance to the 'conventional' T1DM patient again the criterion number of interventions is most important for the endocrinologist (0,388). Nevertheless, follow-up care (0,233) is seen as the second most important criterion by the endocrinologist and the intervention needed for transplant placement as the least important (0,152). Significant differences could only be demonstrated between the number of interventions and the intervention self (p<0,05) for the endocrinologist and between the number of interventions and the period on the waiting list (p<0,05) for the T1DM patient.

Of the subcriteria that determine patient safety (figure 7) both groups share the opinion that safety in the long term is more important, receiving a weight of 0,681 from the endocrinologist, 0,631 of the T1DM patient and 0,662 of the T1DM IT/IT-WL patient. The safety of the procedure seems to be less important receiving respectively 0,382 of the endocrinologist, 0,369 of the T1DM patient and 0,338 of the T1DM IT/IT-WL patient. Of those subcriteria that determine the safety in the long term a discrepancy is visible between the endocrinologist and both types of T1DM patients. The endocrinologist assigns a larger importance weight to the use of immunosuppressive agents (0,645) in comparison to the risks bound to the transplant loss due to rejection (0,355). While the T1DM patients believes transplant loss due to rejection (T1DM patient: 0,527; T1DM IT/IT-WL patient: 0,727) is more important in comparison to the use of immunosuppressive agents (T1DM patient: 0,473; T1DM IT/IT-WL patient: 0,273).

Significant differences could be found between the endocrinologist and both types of T1DM patients for the assigned weight to transplant loss due to rejection ($p<0,05$) and immunosuppressive agents ($p<0,05$). Subsequently, a significant difference was found between the T1DM patient weights assigned to the safety of the procedure and the safety in the long term ($p<0,05$). However, no significant differences could be found between the importance weights assigned to both transplant loss due to rejection and immunosuppressive agents use for either both types of T1DM patients or the endocrinologist.

3.2.3 OBTAINED IMPORTANCE WEIGHTS FOR ACHIEVING INSULIN INDEPENDENCE

Four different criteria were included in this study to investigate the importance of achieving insulin independence in the choice for a transplant alternative. The results are visible in figure 8. From the results in this study it becomes clear that

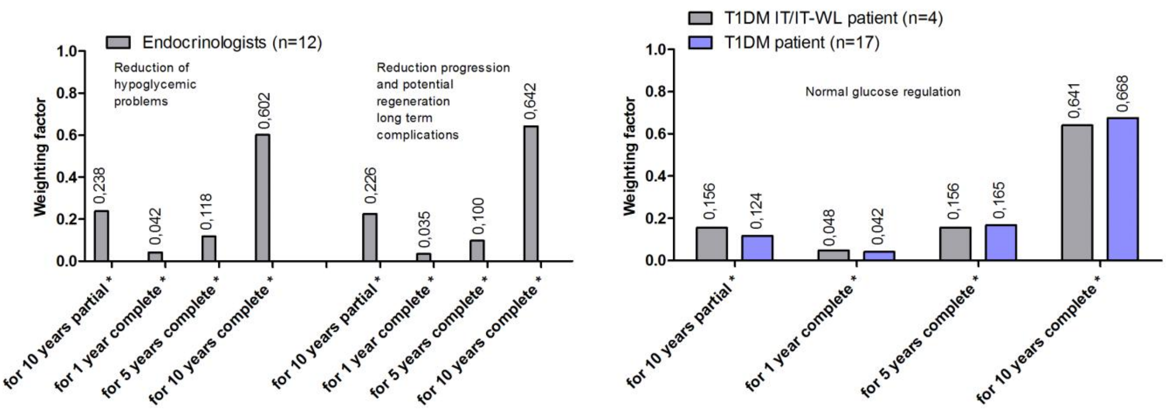


Figure 8. *Importance weight assigned to the criteria that represent a certain period of total or partial transplant functionality. During the time of total graft functionality the patient is insulin independent. The endocrinologist was asked whether he or she would prefer a certain period of total/partial graft functionality against another period of total/partial graft functionality to gain the most beneficial reduction in hypoglycaemic problematic or reduction of progression and potential regeneration in long term complications. The same pairwise comparisons were made by both T1DM patients. Nevertheless, they had to decide what transplant functionality they in general life would prefer. Because of an extreme average inconsistency of 0,28 for the T1DM IT/IT-WL patient, 0,31 for the T1DM patient and even 0,33 and 0,35 for the endocrinologist these result are excluded from further statistical analysis. Abbreviations: *=transplant functionality.*

10 years of complete transplant functionality is strongly preferred by everyone asked (T1DM patient: 0,668; T1DM IT/IT-WL patient: 0,641; endocrinologist:0,602 or 0,642). Less clear differences are however seen between the weights assigned to 10 years of partial transplant functionality and 5 years of complete transplant functionality. It seems that the endocrinologist has a slight favour for longer partial transplant functionality (0,238/0,226) in comparison to 5 years of full transplant functionality (0,118/0,100) were the T1DM patient prefers 5 years of insulin independence (0,165) in comparison to 10 years of additional insulin administration (0,124). For the T1DM IT/IT-WL patient no difference in weights assigned to these two criteria can be discovered (both: 0,156). Logically, one year of total graft function is the least preferred alternative, obtaining a weight of 0,042/0,035 of the endocrinologist, 0,048 of the T1DM IT/IT-WL patient and 0,042 of the T1DM patient.

3.3 RELATIVE PERFORMANCES OF THE TREATMENT ALTERNATIVES

In this study it was assumed, based on expert opinion, that placement of the BAP in the greater omentum will result in a slightly better reduction of hypoglycaemic problems in comparison to a subcutaneously BAP placement or conventional islet transplantation. The relative performance weights assigned to the treatment alternatives on the decision criteria are visible in appendix C. Regarding the long term complications it was believed that all future BAP scenarios are going to perform slightly better compared to conventional islet transplantation. For the necessary amount of donor material one or even less than one donor organ will suffice. Reducing the necessary amount of donor organs to less than one donor organ shall also eventually positively influence the period on the waiting list, resulting in a large increase in performance score.
Based on the transplantation site an intervention was chosen for BAP placement. The minimal incision for subcutaneous BAP placement is less invasive and performs better on the impact of the treatment for the patient than the percutaneous trans-hepatic catheterization of the portal vein necessary in conventional islet transplantation.

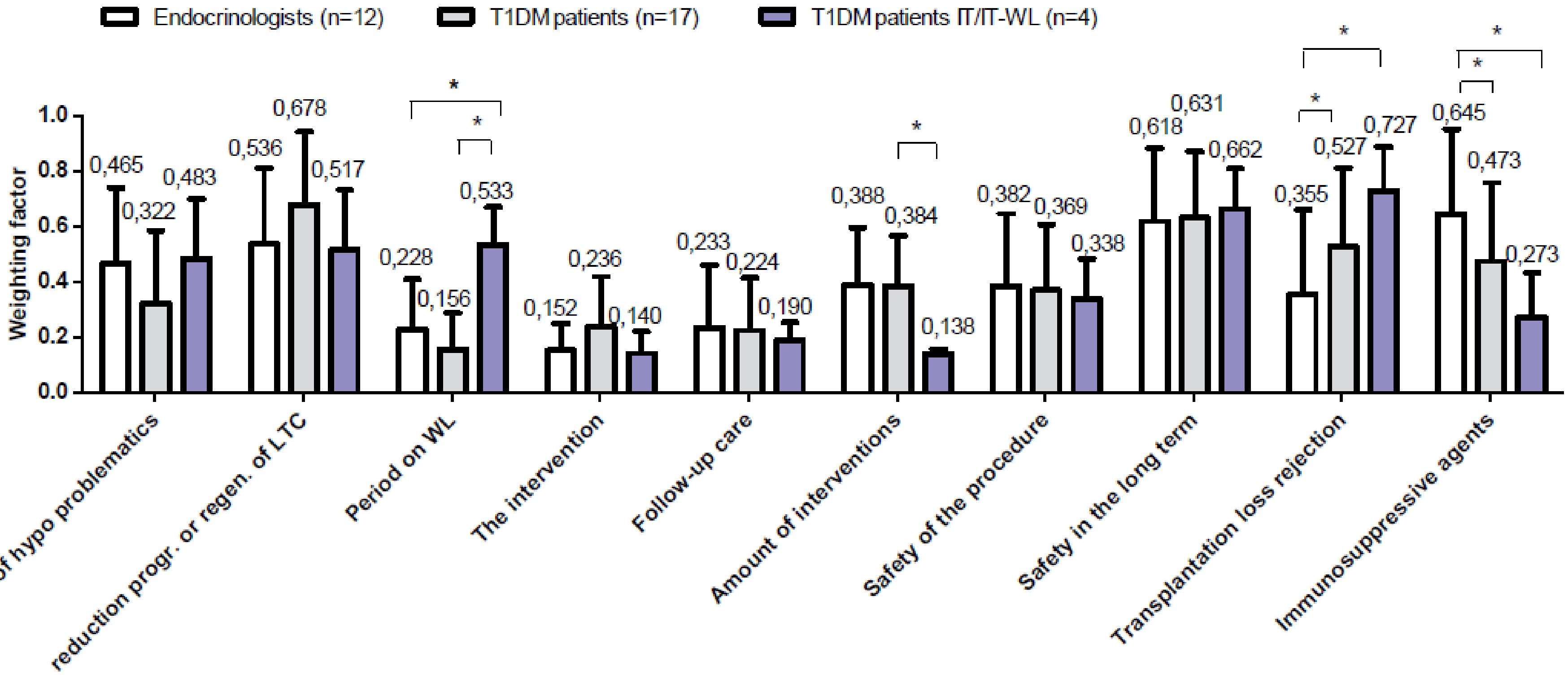


Figure 7 *The average weights assigned by the participant groups to the subcriteria that determine the effectiveness of the transplant, the impact of the treatment for the patient and patient safety. Between groups significant differences were found for the transplant loss due to rejection (p<0,05) and the immunosuppressive agents (p<0,05) for the T1DM patient or T1DM IT/IT-WL patient and the endocrinologist, for the period on the waiting list (p<0,05) between the T1DM IT/IT-WL patient and the endocrinologist and for the period on the waiting list (p<0,05) and the number of interventions (p<0,05) between the T1DM IT/IT-WL patient and the T1DM patient. Standard deviation (σ) is indicated by the black bars. Abbreviations: hypo= hypoglycaemic, progr. or regen. of LTC= progression or regeneration of long term complications, WL= waiting list. For an extensive description of the criteria see appendix A. The average inconsistency between the pairwise comparisons of the subcriteria of the impact of the treatment for the patient was 0.19 (T1DM patients), 0,09 (T1DM IT/IT-WL patients) and 0.12 (endocrinologists).*

The laparoscopic procedure, however, performs less, though, slightly better on impact of the treatment for the patient compared to the open surgery in whole organ pancreas transplantation. The follow up care and the safety of the procedure are both dependent on the chosen intervention for BAP placement. In both cases, the safest option is the minimal incision with less follow up care, followed by the percutaneous trans-hepatic catheterization of the portal vein, the laparoscopic procedure and the open surgery. Regarding the number of interventions it was expected that for all future BAP scenarios one intervention will be sufficient and therefore conventional pancreas transplantation and all future BAP scenarios score the same. For the safety in the long term, whole organ pancreas transplantation scored best on the criterion transplant loss due to rejection.

The future BAP scenarios and conventional islet transplantation had a greater risk to be rejected and therefore received a lesser performance weight. Because of the design focus on islet revascularization improvement a normal dose of immunosuppressive agents is required. Reducing this dose by half, as done in the positive future BAP scenario, is definitely preferred, receiving a much higher performance weight than the conventional dose.

3.4 PREDICTED PREFERENCES FOR THE TRANSPLANTATION ALTERNATIVES

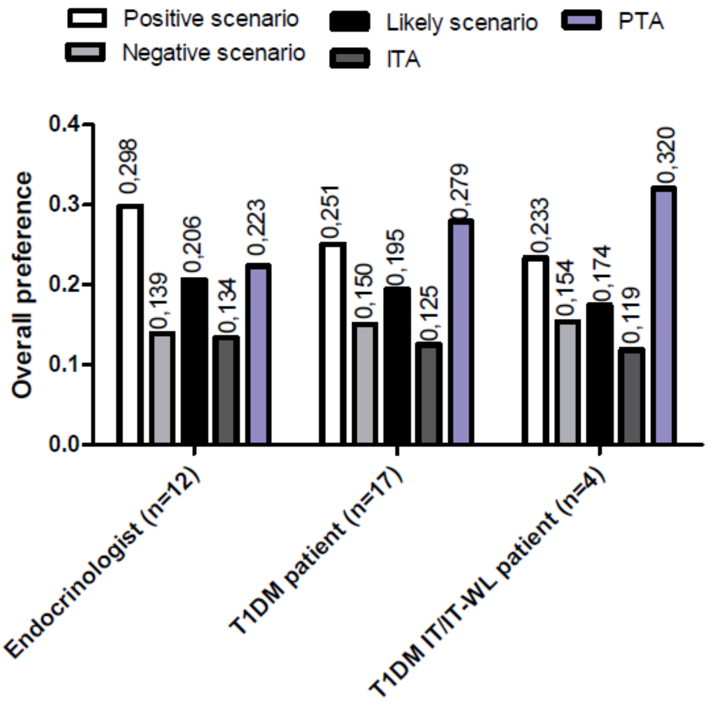
Based on the relative importance of the decision criteria and the relative performance of the transplant alternatives on every decision criterion, the overall preferences for current transplant alternatives and three future BAP scenarios were calculated.

From these results, shown in figure 9, it may be concluded that conventional islet transplantation is the least preferred transplant alternative for both the T1DM patient (0,125), the T1DM IT/IT-WL patient (0,119) and the endocrinologist (0,134). The negative future BAP scenario is performing slightly better receiving an overall preference of 0,150 from the T1DM patient, 0,154 of the T1DM IT/IT-WL patient and an overall preference of 0,139 from the endocrinologist. Placing the BAP subcutaneously requiring only one or less than one donor organ further improves overall preference toward 0,195 (T1DM patient), 0,174 (T1DM IT/IT-WL patient) and 0,206 (endocrinologist) for the most likely future BAP scenario and 0,251 (T1DM patient), 0,233 (T1DM IT/IT-WL patient) and 0,298 (endocrinologist) for the positive future BAP scenario. In comparison to conventional PTA, rewarded with an overall preference weight of 0,223 by the endocrinologist, the positive future BAP scenario is the most preferred transplant alternative (0,298). For both the T1DM patient and the T1DM IT/IT-WL patient PTA remains the most preferred transplant alternative with an overall preference weight of 0,279 of the T1DM patient and even 0,320 of the T1DM IT/IT-WL patient.

3.4.1 POSITION OF THE BAP

Of the three created future BAP scenarios, the positive future scenario is the most favoured by both the endocrinologist as the patient. The likely future scaffold scenario is the third preferred transplantation alternative in row, after conventional PTA and the positive future BAP scenario. The difference in the overall preference of the endocrinologist between the most likely future BAP scenario and conventional PTA is very small though. Choosing for a BAP transplantation site in the patient's greater omentum results in a weaker preference advantage above conventional ITA compared to a subcutaneous transplant site. This is attributable to the two donor organs necessary, the relatively invasive laparoscopic procedure, the additional risks of this procedure and the more intensive follow-up care.

Figure 9. *The overall preference weights for the five assessed transplant alternatives.*



3.5 RELATIVE IMPORTANCE OF TRANSPLANT CHARACTERISTICS

The relative importance of the transplant characteristics (or decision criteria) and the relative importance of the different performance levels of the transplant alternatives on these transplant characteristics can be observed in figure 10. The relative importance for the endocrinologist and both T1DM patients are plotted on a scale of 0, representing the least desirable characteristic level, to 10, representing the most desirable characteristic level.

The most important transplant characteristic in BAP uptake, defined as the largest difference between the highest and lowest score per criterion for the endocrinologist, the T1DM IT/IT-WL patient and the T1DM patient together ((MAX-MIN) endocrinologist + (MAX-MIN) T1DM IT/IT-WL patient + (MAX-MIN) T1DM patient), was the reduction in progression and potential regeneration of long term complications (16,39), followed by the reduction in hypoglycaemic problems (15,64), transplant loss due to rejection (12,00), the safety of the procedure (10,95), the amount of donor material necessary for a successful transplantation (9,44), the use of immunosuppressive agents (8,61), the period on the waiting list (4,71), the follow up care (3,04),the number of interventions (2,99) and the intervention (2,32).

The most preferred transplant characteristic mix is a treatment in which the transplant shall be placed subcutaneously, with a minimal incision, requiring only half a donor organ, half the period on the waiting list before treatment, half the immunosuppressive agent dose, equating the effectiveness of the transplant and the risk of transplant loss due to rejection of conventional PTA. In the less preferred transplant characteristic mix, the transplant shall be placed intraperitoneally with an open procedure, requiring 2/3 donor organs, a normal period on the waiting list, a normal immunosuppressive agent dose, equating only the effectiveness of the transplant and the risk of transplant loss due to rejection of conventional ITA.

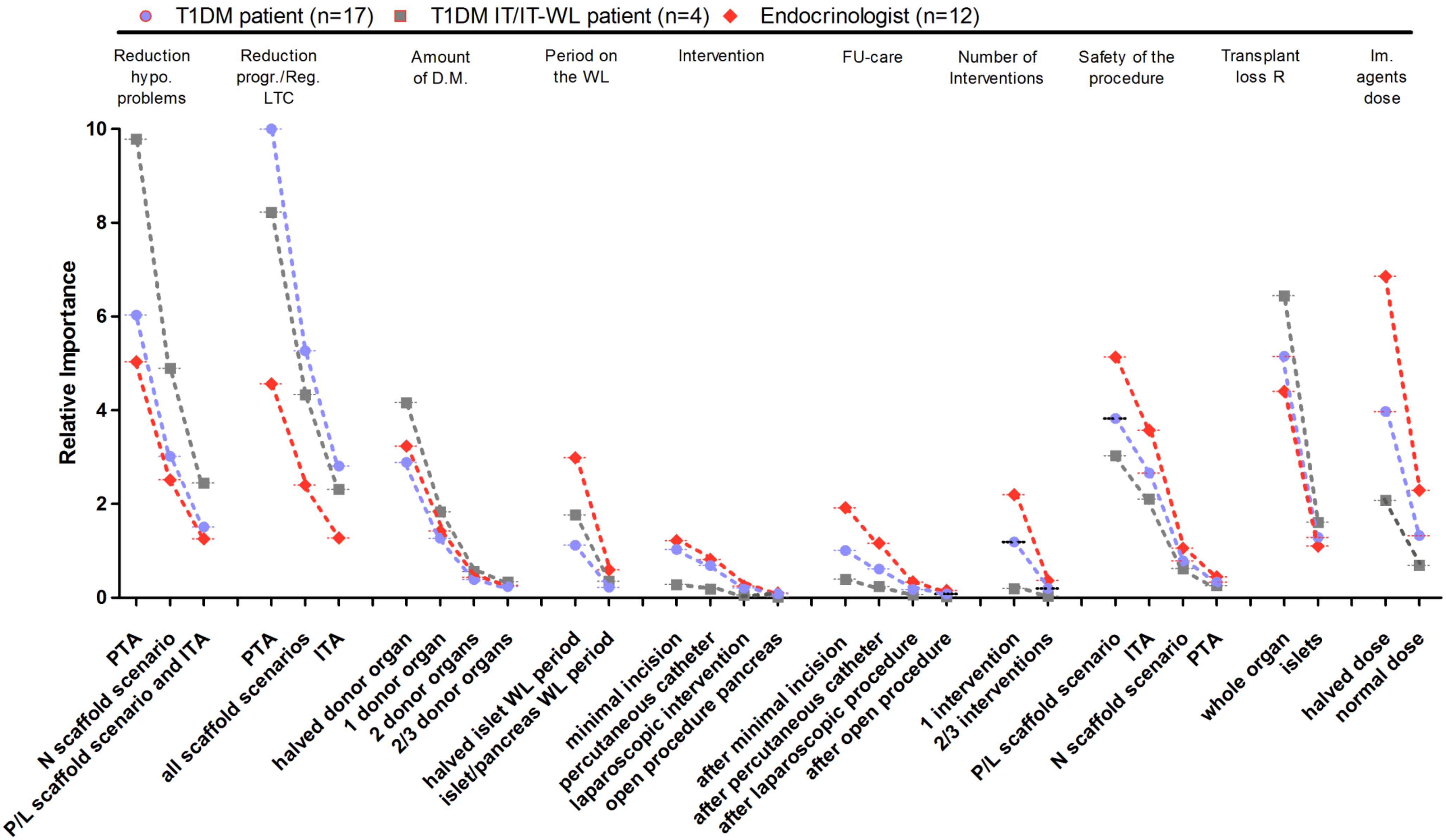


Figure 10. *The relative importance of the different decision criteria (transplant characteristics) and the relative preferences for the levels of each decision criterion rescaled from 0 to 10. The more critical a decision criterion is in the decision for a transplantation method the farther apart are the parameter values. A higher value furthermore indicates that that specific criteria level is preferred. Abbreviations: hypo. = hypoglycaemic, progr./Reg. LTC= progression/regeneration long term complications, D.M.= donor material, WL= waiting list, FU= follow-up, loss R= loss due to rejection, Im. =immunosuppressive, P/L=positive/likely, N=negative.*

6.0 DISCUSSION AND CONCLUSION

In this study an early medical technology assessment was performed to prospectively evaluate if, and when the new BAP becomes an alternative for patients and endocrinologists in the treatment of the diabetes type 1 patients eligible for conventional islet and pancreas transplantation. Evaluating the overall preferences (figure 9) - based on the expected performance in terms of effectiveness of the transplant, the amount of donor material, the impact of the treatment for the patient and patient safety - it becomes clear that the BAP is the preferred transplant alternative compared to conventional islet transplantation, even for the negative future BAP scenario. This preference for BAP is due to an assumed better islet viability and functionality which results in better effectiveness of the transplant, a lesser amount of donor organs and only one intervention necessary for a successful transplantation. In combination with also a relatively less invasive way of BAP placement compared to conventional whole organ pancreas placement, the BAP will result in a transplantation method that may be seen as a substitute for conventional ITA or an alternative to both conventional ITA and PTA.

EXPECTED VALUE OF THE BAP

The BAP can most likely be seen as a treatment method in future diabetes care when the new technology performs equally or better than the defined negative future BAP scenario. According to this study, the negative future BAP scenario is slightly preferred by the endocrinologist in comparison to conventional ITA. Another point of interest is the larger overall preference of the endocrinologist for the positive future BAP scenario in comparison to conventional PTA. This larger preference for the BAP is attributable to a less invasive procedure and a reduction in donor tissue and immunosuppressive agents necessary. Limiting BAP performance to only a less invasive procedure isn't enough to exceed the overall preference for PTA. Surprisingly, the observed difference in overall preference between PTA and the likely future BAP scenario is very small. Hence the possibility remains that by the new BAP, conventional PTA may be replaced.

For both the T1DM patient and the T1DM IT/IT-WL patient, conventional ITA again may be replaced by the BAP. Every defined scenario obtained a larger overall preference from the average T1DM (IT/IT-WL) patient than conventional ITA. For now, BAP performance isn't enough to exceed PTA preference though. Especially because of the importance of the effectiveness of the transplant for the patient, PTA remains the preferred transplant alternative.

Based on these outcomes it may be concluded that if the overall preference for the BAP exceeds conventional ITA performance, the BAP may be used by both the endocrinologist and the patient as an alternative to, or substitute of ITA. However, also for IAK and the less performed SIK it is likely that the BAP, when accepted for type 1 diabetes treatment, will be a serious competitor. Unfortunately, this clinical market for BAP use is limited. The Collaborative Islet Transplant Registry (CITR) reported 412 recipients of allograft islet infusions between 1999 and 2008 [27] and at a national level only 7 islet transplantations were performed with 14 organs in 2011 [28]. Because of a donor shortage, the possible procedure related risks, and the use of immunosuppressive agents only the most severe T1DM patients become eligible for transplantation. In addition, islet transplantation must compete with pancreas transplantation in the allocation of donor organs. Today, only those organs deemed unsuitable or declined for use in whole organ pancreas transplantation are used in islet transplantation [29].

Obtained results so far with human pancreatic donor islet transplants, and the donor organ shortage problem both encourage efforts to generate new sources of insulin producing cells [8]. Combining the BAP with these new beta cell sources excludes the donor shortage problem and may further enlarge the clinical market for BAP use.

If the overall preference for BAP is going to exceed even PTA, the BAP may be used as a pancreas transplant replacement in SPK, PAK and PTA which again could broaden BAP's horizon. Unfortunately, exclusion of the procedure related risks and elimination of the donor shortage problem isn't enough to really change diabetes care. Chronic immunosuppressive agent-use makes the choice for any transplantation, including the BAP, less attractive especially for the younger population. Changing design focus from the promotion of revascularisation towards the creation of a BAP which provides immunological protection by immunoisolation could reduce or exclude immunosuppressive agent-use though.

In an article of Giraldo, Weaver and Stabler a review is given of emerging methods for engineering an optimal islet transplantation site. This review provides a state of the art of attempts to optimize the transplant site, including methods to accelerate angiogenesis and islet engraftment and methods which focus on immunoisolation of transplanted islets.[2] The development of the BAP isn't the only strategy which evolves in the research pipeline; many known and unknown competitors may preclude future use of the BAP. To really make a difference the BAP needs to distinguish itself by making the best fit with consumer needs.

EXPECTED VALUE TO PATIENTS AND ENDOCRINOLOGISTS

Of all transplant characteristics defined and weighted in this study both effectiveness of the transplant and patient safety were rated as the two most important aspects of a transplantation method by the endocrinologist, the T1DM patient and the T1DM IT/IT-WL patient. For the endocrinologist and the T1DM IT/IT-WL patient both the reduction of the hypoglycaemic problems as the reduction in progression and the potential regeneration of long term complications determine the effectiveness of the transplant. The T1DM patient, however, significantly prefers a reduced progression and potential regeneration of long term complications.

Patient safety in the long term is the subcriterion that seems to be more important than the safety of the procedure for both the endocrinologist and the T1DM patient, though, only a significant difference between these two criteria for the "conventional" T1DM patient could be found. Of the criteria that determine patient safety in the long term, transplant loss due to rejection seems to be more important especially for the T1DM IT/IT-WL patient while the immunosuppressive agents are selected to play a greater role for the endocrinologist. Another discrepancy between both types of T1DM patients and the endocrinologist could be found between the weights assigned to the effectiveness of the transplant and patient safety. Effectiveness of the transplant is significantly preferred by the patient in comparison to the endocrinologist, were patient safety is significant more important for the endocrinologist in comparison to the effectiveness of the transplant. This could indicate that the potentially "desperate" patient is willing to take a risk in order to receive a decent long-term solution for their type 1 diabetes problems were endocrinologists may be more conservative and protective regarding the new technology and the risks bound to transplantation, with an emphasis on the potential detrimental effects bound to immunosuppressive agent use. This is also in accordance with the even larger importance weight of effectiveness of the transplant assigned by the T1DM patient on the waiting list or those T1DM patients that already received an islet transplant. This sub population of the T1DM patients is known with the health condition and the problems of the hypothetical patient and is aware of the importance of a well functioning transplant. On the contrary, the ability exists that the average T1DM patients consider themselves to be in good hands and that those familiar with the islet transplantation assign weights from their own experience with islet transplantation.

The impact of the treatment is the third most important criterion for both the T1DM patient and the endocrinologist. The difference for the endocrinologist between the effectiveness of the transplant (2nd place) and the impact of the treatment for the patient is very small. A higher weight may be assigned by the endocrinologist because of the interdependence between the impact of the treatment and patient safety. A longer period on the waiting list and repetitive interventions may affect patient safety. For the T1DM IT/IT-WL patient the impact of the treatment is the least important transplant characteristic. This weight may be that low because of their experience with islet transplantation. Comparing the subcriteria that determine the impact of the treatment, only the number of interventions seems to be slightly more important for both the T1DM patient and the endocrinologist. This is in accordance with an article of Lloyd in which researchers tried to capture the preference weights for the process of undergoing islet transplantation. It was concluded that people with diabetes recognize the disutility of undergoing infusion cycles. [16] The T1DM IT/IT-WL patient questioned in this study especially recognizes the importance of the period on the waiting list. This assigned weight may again be influenced by their experience with the waiting list for an islet transplant.

The final top level criterion assessed was the amount of donor material necessary for transplantation. Because of the chronic donor shortage and the potential compassion with other T1DM patients it was assumed that this criterion would strongly interfere with the decision for a transplant alternative. Nevertheless, this idea was not an entirely true reflection of reality. Only a relative low compassionate weight was assigned by both groups to the amount of donor material necessary per transplantation in comparison to the other top level criteria. In the choice between transplantation methods for a single patient the criterion may be less important, and yet, it needs to be considered that this characteristic may be all determining in the actual implementation of the scaffold.

In order to improve BAP performance, design enhancement should be carried out that is focused on the most important transplant characteristics. However, a debate can be held on the importance of the opinion of the T1DM patient versus the opinion of the endocrinologist in the choice for a transplantation method.

Patient preference becomes increasing important in the allocation of scarce health care resources and also plays an all determining role in medical decision making [30]. The opinion of the patient is influenced amongst others by demographic variables, the patient's experience of illness and medical care, diagnosis and health status, the amount of knowledge the patient has acquired on his or her condition and the interactions and relationships the patient experiences with health professionals [31,32]. It is important to realize that there are different relationships in shared decision making [33] which makes it difficult to make the right design choices. Combining the overall preferences of the "conventional" T1DM patient and the endocrinologist found in this study -in which both opinions count equally- results in an overall preference of 0,274 for the positive future BAP scenario, 0,251 for PTA, 0,200 for the most likely future BAP scenario, 0,145 for the negative future BAP scenario and 0,130 for ITA. An combination of the opinion of the T1DM IT/IT-WL patient and the endocrinologist results in an overall preference of 0,272 for PTA, 0,266 for the positive future BAP scenario, 0,190 for the likely future BAP scenario, 0,146 for the negative future BAP scenario and 0,126 for ITA. According to these results BAP remains the preferred alternative above conventional ITA and may even defeats PTA.

Another point for debate, impeding the right design choices, is the interdependence between the transplant characteristics. Essential in BAP uptake is the choice for the transplantation site and the related intervention required for BAP placement. The intervention has a large influence on the overall preference for a transplant alternative because of the interdependence between the intervention, the follow-up care and the safety of the procedure. The relative importance weight of the intervention, follow up care and the safety of the procedure together is 0,188 for the T1DM patient, 0,126 for the T1DM IT/IT-WL patient and even 0,257 (equal to the weight assigned by the endocrinologist to the effectiveness of the transplant) for the endocrinologist. Based on the results of this study, subcutaneous BAP placement will be the best choice. Figure 11 provides insight in the interdependence between the transplant characteristics.

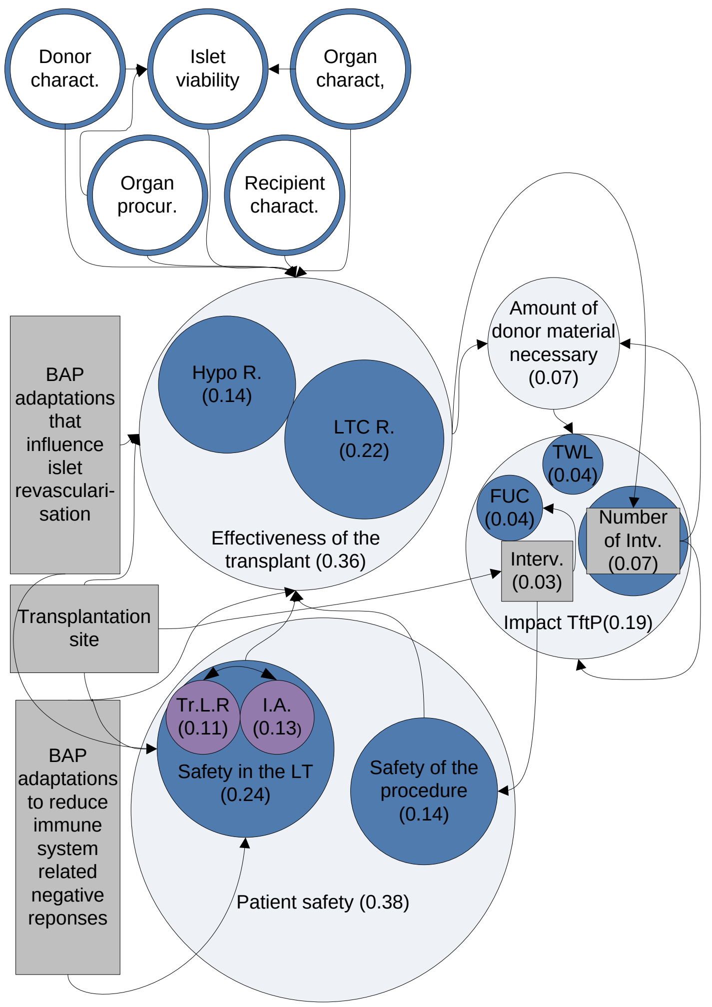


Figure 11. *Influence diagram representing a few vital decisions developers have to make (grey squares) and the influence of those decisions on treatment characteristics (circles) that determine transplantation decision making. The top-level criteria are shown in light blue. The subcriteria are dark blue and purple. The importance of a decision criterion is visualized by the size of the figures and the exact weight is shown between the brackets. For the weights shown in this figure the average is taken of both the weight assigned by the T1DM patient and the weight assigned by the endocrinologist. In the top of the figure the elements donor characteristics, islet viability, organ characteristics, organ procurement and recipient characteristics are named. These aspects also determine transplant effectiveness; however, they can't be influenced by the scaffold. Abbreviations: Hypo R. = reduction of the hypoglycaemia problems, LTC R.= reduction in progression and the potential regeneration of long term complications, TWL=period on the transplantation waiting list, Interv.=the intervention, FUC=follow-up care, Number of Intv.=number of interventions, Tr.L.R.=transplant loss due to rejection, I.A.=immunosuppressive agents.*

Finally, it is important to recognize the opportunities for improvement. Currently, BAP development of the University of Twente focuses on islet revascularisation improving islet viability and functionality which in turn increases the effectiveness of the transplant. Unfortunately, a lot of further progress still has to be made comparing expected BAP performance to the performance of conventional pancreas transplantation at this point (figure 10). Extra performance benefit can still be obtained on the criteria effectiveness of transplant and patient safety in the long term (figure 10). To reduce both the risk of transplant loss due to rejection as well as the risk of immunosuppressive agents effectively, it is necessary to change design focus from islet revascularisation towards immunological protection, though. Reducing the dose of immunosuppressive agents and the risk of transplant loss due to rejection by providing immunological protection in turn may also positively influences the effectiveness of the transplant (figure 11).

LIMITATIONS RESEARCH DESIGN

The AHP proved to be suitable for the early health technology assessment of the BAP. A future prospect is given whether and when the BAP is going to be considered an alternative in the treatment of T1DM patients with uncontrollable type 1 diabetes and important design criteria were identified. However, when applying these results for future design guidance the following considerations should be kept in mind.

At first the set of criteria included in this study may not provide a complete view of the situation. As an example; the costs bound to a transplant alternative were excluded from this study but were named during the interviews and focus groups as criterion that may play a role in the choice between transplant alternatives. In addition, the hierarchic structure, including all decision criteria, is to a large extent established based on the opinion of only patients and caregivers.

Second, the time necessary for questionnaire fulfilment and questionnaire complexity may have interfered with the research outcomes, leading to a larger variance and inconsistency in the weights assigned. For an overall correct interpretation of the results found in this study it is important to remain critical on the accepted inconsistency for inclusion and the found intergroup variance in weights assigned.

Third, no direct face to face contact between the different participants has taken place which excludes the ability to exchange knowledge, discuss and gain consensus on the criteria important in the choice between transplantation methods and the exact interpretation of every decision criterion included. Every questionnaire included an information sheet to pursue a correct and equal interpretation of the definitions of the decision criteria. Whether everybody that participated actually used the information sheet cannot be verified. Moreover, it was tried to register those demographic characteristics of the participants that could have coloured the participant's opinion. Nevertheless, little relevant correlation was evident between the participant's characteristics and the weights assigned.

For the generalizability of the results it is essential that all groups of participants form a representative group of their population. Although, the participants included in this study come from different regions across the Netherlands and there is certainly a variation in age, no one received compensation for their participation and a large proportion of the included population was highly educated. In addition, the opinion of the T1DM IT/IT-WL population may be coloured because of the information previously received on and/or experience with islet transplantation. Their opinion may provide explicitly a view on those aspects where islet transplantation still can improve.

Finally, some last comments need to be made on the performance assessment done in this study and the included transplant alternatives. Assumptions on the performances of the transplant alternatives are made based on the opinion of one expert. This opinion may be subjective, in time these performances may change and only a limited amount of BAP competitors was included.

RESEARCH RECOMMONDATIONS

For the future, it may be useful to apply AHP in a group session or to discuss the found results of this study in a group session with representatives of all stakeholders crucial in BAP acceptance and distribution. The assessment conducted in this study, according to the AHP analysis method, is primary a method to overcome unsatisfactory value of the outcomes; one of the basic problems in traditional and conventional technology assessment [23]. By directly involving the actors concerned with development and diffusion, face to face, an AHP session focuses on consensus formation on the created hierarchic structure; broadening the perspectives of those involved and excluding sources of misunderstanding by the sharing of knowledge[23]. If a group session can't be realized, a greater distinctiveness between the importance weights obtained could be achieved by the inclusion of both more endocrinologists and T1DM patients. It is especially beneficial to focus on those T1DM patients unknown with the transplantation alternatives and known with the problems experienced by the hypothetical patient. Individual inconsistency in the future may be reduced by keeping the hierarchic structure as simple as possible and returning weights and inconsistent comparisons to the participant after a period of considered thought. The variety in weights assigned by the same sort of participants can be clarified by collecting feedback of those that exhibit dominant preferences.

During future use of the analytic hierarchy process to elucidate the opinion of product consumers some criticism is required on the included decision criteria and the applicability of AHP to weight these decision criteria. Other multi criteria decision methods may be more applicable to weight certain criteria. (Conjoint analysis may be a suitable method to determine the importance of amongst others insulin independence in the choice between transplant alternatives[34]. In addition, it may also reduce the problem of the participant in need for more specific information. Nevertheless, ANP could also be preferred and used as an alternative method because it allows consideration of the interdependence between decision criteria**.)**

For the performance assessment it is recommended to take notice of the current advances in procurement techniques from cadaveric donors and the improvements concerning less toxic and more potent immunosuppressive agents [8]. It is essential that the performance assessment should be adjusted when new data on the transplant alternatives becomes available and above all it is recommended to include more expert opinions to reduce the impact of subjectivity. A methodological challenge could be the use of expert elicitation to quantify the uncertainty about future performance of a new technology, like the BAP, based on expert opinion[35]. Moreover, it needs to be noted that other treatments opportunities -already used on a limited scale like continuous intraperitoneal insulin infusion pump[36] or emerging in the research pipeline like recent advances in the development of other bioartificial pancreata[37] - may be serious competitors for the BAP being developed.

Two last points for future research; the potential applicability of the obtained results towards these other clinical situations -e.g. a patient eligible for either IAK or SIK- remains to be demonstrated. Furthermore, when the choice is made for immunological protection of the islets focus groups with diverse disciplines should be kept to search for opportunities to protect the islets from the immune system thereby improving the effectiveness of the transplant, reducing immunosuppressive agent use and decreasing the risk of transplant loss due to rejection.

Taking into account all named considerations, it can be concluded that with this study a contribution is given to future BAP development by clarifying the potential profitability of the intended BAP application and the potential areas for further BAP improvement. The weights retrieved provide new insights between the differences in opinions of the endocrinologist and the T1DM patient and also the main uncertainties of BAP development are visualized. Based on the results of this study it may be confirmed that the BAP has a realistic chance of success, especially when the donor shortage problem and the procedure related risks can be reduced. With the creation of the BAP in combination with allogeneic or autogenic islets the carrier could make its entrance in health care. However, in order to enlarge this relatively small clinical market and to actually make a difference for all affected patients with type 1 diabetes it is wise to focus on immunological protection of the transplanted islets. Early health technology assessment proved to be a valuable methodology to inform and guide decision makers in the product development phase, which eventually may enhance new medical technology acceptability.

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APPENDIX A

BIJLAGE:
OMSCHRIJVING CRITERIA

Houd deze beschrijving bij de hand wanneer u gewichten aan de criteria gaat toekennen.

1. **Effectiviteit van het transplantaat** ~ Definitie: De mate waarin je met het transplantaat een normale glucose regulatie kan realiseren.

1.1 ***Vermindering van de hypoglycemie problematiek*** ~ Definitie: Hieronder valt het verminderen van de ernst (hoe laag) en de frequentie (het aantal keer) waarmee te lage bloedsuikerspiegels zich voordoen. Onder deze definitie valt ook de terugkomst en het behoud van de herkenning van de symptomen van een te lage bloedsuikerspiegel door de patiënt. Hierdoor zal de patiënt zijn te lage bloedsuikerspiegels weer tijdig kunnen herkennen.

1.2 ***Het verminderen van de progressie en het herstel van lange termijn complicaties*** ~Definitie: Het transplantaat is in staat om, mede door verlaging van de gemiddelde bloedsuikerspiegel, de progressie van diabetes gerelateerde micro- en eventueel ook de macro vasculaire complicaties te verminderen/voorkomen en de geleden schade mogelijk te herstellen. (microvasculaire complicaties: nefropathie, retinopathie, neuropathie en macrovasculaire complicaties: cardiovasculaire aandoeningen).

1.1.1/1.2.1 ***10 jaar partiële transplantaat functie*** ~Definitie: Het transplantaat zorgt 10 jaar lang voor een stabiele partiële functie waardoor het gebruik van exogene insuline kan worden gereduceerd in vergelijking tot voor de transplantatie.

1.1.2/1.2.2 ***Voor 1 jaar volledige transplantaatfunctie met normale glucose regulatie*** ~Definitie: Het transplantaat zorgt voor een normale glucose regulatie in het eerste jaar na transplantatie. ** In deze periode is de patiënt vrij van insuline toedieningen en strikte dieet beperkingen. In de jaren die volgen vermindert de functie van het transplantaat. Dit kan per patiënt verschillend zijn.**

1.1.3/1.2.3 ***Voor 5 jaar volledige transplantaat functie met normale glucose regulatie*** ~Definitie: Het transplantaat zorgt voor een normale glucose regulatie gedurende de eerste vijf jaar na transplantatie. **zie hierboven**

1.1.4/1.2.4 ***Voor 10 jaar volledige transplantaat functie met normale glucose regulatie*** ~Definitie: Het transplantaat zorgt voor een normale glucose regulatie tot 10 jaar na transplantatie. ** zie hierboven**

2. **De hoeveelheid donormateriaal voor een succesvolle transplantatie** ~Definitie: Het aantal donororganen dat nodig is om één patiënt te helpen. Dit heeft invloed op het aantal patiënten dat geholpen kan worden.

3. **Impact van de behandeling voor de patiënt** ~Definitie: Wat moet de patiënt doorstaan bij het ondergaan van een behandeling. Welke medewerking wordt er van de patiënt verwacht vanaf het moment dat de patiënt op de wachtlijst voor een donororgaan wordt geplaatst tot en met de controle na transplantatie.

3.1 ***De periode op de wachtlijst*** ~Definitie: Hiermee wordt de periode bedoeld die de patiënt moet wachten totdat hij transplantaatweefsel toegewezen krijgt en een transplantatie kan ondergaan.

3.2 ***De interventie***~Definitie: Wat betekent het voor een patiënt om transplantatie te ondergaan? Hier wordt gerefereerd naar de voorbereiding, de duur van de medische ingreep, de lengte van het ziekenhuis verblijf, de duur en intensiviteit van het herstelproces en de littekens die de patiënt er mogelijk aan overhoudt.

3.3 ***Follow-up zorg***~Definitie: Onder deze term valt de educatie die de patiënt krijgt om op een verantwoorde manier met medicatie en transplantaat om te gaan. De patiënt moet zichzelf monitoren om de functie van het transplantaat in de gaten te houden en daarnaast heeft de patiënt frequente consulten en onderzoeken in het ziekenhuis ter controle.

3.4 ***Het aantal interventies***~ Definitie: Het aantal procedures dat de patiënt moet ondergaan om het gewenste doel van een transplantatie te behalen. Het betreft hier dus het aantal keer dat de patiënt dezelfde transplantatie procedure moet ondergaan.

4.**Patiënt veiligheid** ~Definitie: De mate waarin een behandeling, zowel tijdens als na de interventie, de patiënt veiligheid beinvloedt. (Complicaties die optreden kunnen leiden tot verminderd comfort (pijn), extra ziekenhuisopnames, onderzoeken, medische ingrepen en medicatie.)

4.1 ***Veiligheid van de procedure***~Definitie: Dit is de mate waarin mogelijke adverse events van de procedure/interventie patiënt veiligheid kunnen beinvloeden.

4.2 ***Veiligheid op lange termijn***~Definitie: Dit is de mate waarin patiënt veiligheid op lange termijn wordt beinvloed door bijvoorbeeld afstoting van het orgaan en het langdurige gebruik van immunosuppressiva.

4.2.1***Transplantaat verlies door afstoting***~Definitie:(Hyper)acute of chronische afstoting zorgt voor gedeeltelijk/geheel verlies van het transplantaat.

4.2.2**Immunosuppressiva**~Definitie: Het gebruik van immunosuppressiva zorgt voor een vergrote kans op kanker, infecties, beta cel destructie en hart- en vaatziekten. Daarnaast zijn er meer ernstige bijwerkingen verbonden aan het gebruik van immunossuppressiva.

APPENDIX B

Characteristic	n (%)	Characteristic	n(%)
Age		**Quality of Life (QoL)**	
Mean (years)	39,95	*5.0-6.0*	1(5)
SD(years)	18,08	*6.1-7.0*	4(19)
Gender		*7.1-8.0*	5(24)
Male	10(48)	*≥8.1*	10(48)
Female	11(52)	*missing*	1(5)
Highest completed level of education		**Satisfaction current treatment**	
primary school	1(5)	*Very satisfied*	15(71)
secondary school	7(33)	*Moderately satisfied*	3(14)
college or university	13(62)	*Neutral*	2(10)
Missing	-	*Moderately dissatisfied*	1(5)
Cultural background		**Satisfaction diabetes knowledge**	
Dutch	21(100)	*Very satisfied*	14(67)
Age T1DM diagnosis		*Moderately satisfied*	7(33)
0-10	4(19)	**Known with hyperglycemia**	
11-20	11(52)	*yes*	20(95)
21-30	2(10)	*no*	1(5)
31-45	4(19)	**Hypercholesterolemia**	
HbA1c		*yes*	4(19)
<42 (mmol/mol)	4(19)	*no*	17(81)
42 ≤ HbA1c ≤ 64 (mmol/mol)	13(62)	**Hypertension**	
HbA1c >64 (mmol/mol)	4(19)	*yes*	6(29)
missing	-	*no*	15(71)
Known with hypoglycemia		**Presence LTC**	
yes	20(95)	*yes*	7(33)
no	1(5)	*no*	14(67)
Recognision hypoglycemia		**(Used) insulin administration technique**	
no	1(5)	*Injections*	12(57)
sometimes	6(29)	*Pump*	7(33)
yes	13(62)	*Unclear*	2(10)
missing	1(5)		

APPENDIX C

Table 6. Relative performance of the alternatives at the decision criteria

Top-level decision criteria	*Effectiveness*		*Amount of donor material necessary*	*Impact of the treatment for the patient*				*Patient safety*		
Top-level and sub criteria numbers:	1.0		2.0	3.0				4.0		
	1.1	1.2		3.1	3.2	3.3	3.4	4.1	4.2.1	4.2.2
Performance weights for:										
(1) + future scaffold scenario	1.0		0.477	3.0				4.0		
	0.111	0,184		0.556	0.339	0.349	0.240	0.335	0.125	0.429
(2) – future scaffold scenario	1.0		0.064	3.0				4.0		
	0.222	0.184		0.111	0.068	0.061	0.240	0.069	0.125	0.143
(3) likely future scaffold scenario	1.0		0.210	3.0				4.0		
	0.111	0.184		0.111	0.339	0.349	0.240	0.335	0.125	0.143
(1) ITA	1.0		0.039	3.0				4.0		
	0.111	0.098		0.111	0.226	0.212	0.040	0.233	0.125	0.143
(2) PTA	1.0		0.210	3.0				4.0		
	0.444	0.349		0.111	0.028	0.029	0.240	0.029	0.500	0.143

APPENDIX D

ADDITIONAL INFORMATION CONVENTIONAL TRANSPLANTATION METHODS

Both pancreas and islet transplantation is only considered an option when all other usual treatment options already have been tried and the safety of the patient still can't be guaranteed because of acute and/or long-term complications due to type 1 diabetes. The choice for transplantation is not easily made due to the chronic donor shortage and the high costs, intensive procedures and the chronic use of immunosuppressive agents bound to transplantation [11]. In the year 2010 only 26 pancreas transplantations, including five islet transplantations were performed in the Netherlands [28].

Whole organ pancreas transplantation is especially considered an option in combination with a renal graft for type 1 diabetes patients with end-stage renal disease [38]. Only recently whole organ pancreas transplantation is also advocated for type 1 diabetes patients who have either an adequate functionality of their native kidneys or an already earlier received renal transplant. Very poor glucose control and dangerous episodes of hypoglycaemia due to hypoglycaemia unawareness are in these cases the usual indications for pancreas transplantation [27,29]. Pancreas transplantations significantly improved the last 25 years resulting in a 1 year graft functional survival of around 80% [39].

Yet, whole organ pancreas transplantation remains controversial because of the morbidity and mortality bound to the procedure of pancreas placement [40]. Patients receiving a pancreas transplant are frequently hospitalized for extended periods and readmitted because of serious complications [3], including early postoperative technical complications like allograft thrombosis, pancreatitis, bleeding, infections and abscesses [41,42].In the decision for transplantation, the benefits in the long term should be carefully considered and balanced with the potential morbidity and mortality of the surgical procedure and the chronic use of immunosuppressive agents [3,11,29,38,42–44].

In contrast to pancreas transplantation, the less invasive islet transplantation does not require significant surgery or general anaesthesia [38] and may therefore be a better alternative transplantation method. In addition, islet transplantation may also form a solution for those type 1 diabetics not eligible for the major surgical procedure necessary in whole pancreas transplantation [40,45,46].

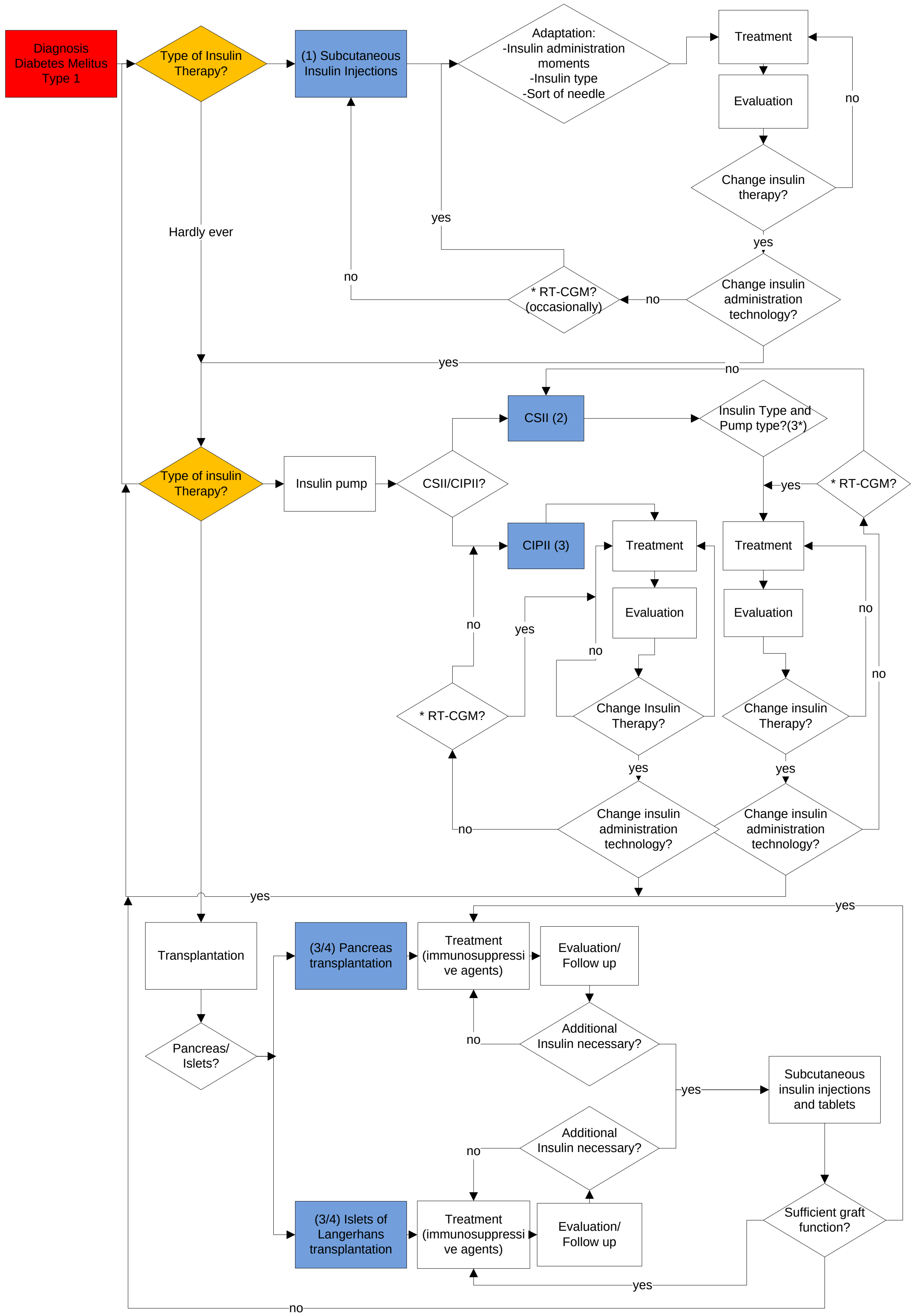
After the complicated process of islet isolation, the allogenic islets are infused intrahepatically using a percutaneous catheter inserted in the portal vein [11,47]. The morbidity and mortality related to this procedure has been very low and most patients only require a short hospital stay of around two days [38]. Short term procedure related complications bound to the process of islet transplantation include portal vein thrombosis, bleeding and portal vein hypertension [11,47]. Similar to other transplants, long term complications are mostly related to the use of systemic immunosuppressive agents, increasing the risk of infection and cancer [47,48]. After transplantation, the transplant is exposed to the risk of acute and chronic immunological rejection and the recurrence of autoimmunity for which these immunosuppressive agents are given [39,42]. Ironically, all commonly used immunosuppressive drugs have been reported to have adverse effects on pancreatic beta cells [47].

A major disadvantage of islet therapy today is the number of donor organs necessary to achieve insulin independence. Two or three islet infusions are usually needed to reach insulin independence and this independence is rarely sustained due to a significant reduction in islet number and quality [11].

This islet loss may be attributable to islet emboli occluding the hepatic vasculature, an immediate blood mediated inflammatory reaction (IBMIR) triggered by the direct contact of islets with blood components, non-native mechanical stress and exposure to toxins, including elevated glucose levels (glucotoxicity) [2,11].

It may be interesting to shift the transplantation site away from the liver to improve beta cell survival and functionality. Promoting revascularisation also positively influences beta cell viability and functionality and ultimately results in a reduction of the amount of necessary donor organs per recipient. Keeping the chronic shortage of donors and the worldwide growing diabetes population in mind, the BAP may therefore be the technique to potentially improve future diabetes care.

APPENDIX E



Extensive flow diagram representing the choices made for insulin therapy. Abbreviations: RT-CGM: real-time continuous glucose monitoring, CSII: continuous subcutaneous insulin infusion, CIPII: continuous intraperitoneal insulin infusion.

APPENDIX F

QUESTIONNAIRES