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Using the cost-effectiveness of allogeneic islet transplantation to inform iPSC derived beta cell therapy reimbursement

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Using the cost–effectiveness of allogeneic islet transplantation to inform induced pluripotent stem cell-derived β -cell therapy reimbursement

Aims: In the present study a cost–effectiveness analysis of allogeneic islet transplantation was performed and the financial feasibility of a human induced pluripotent stem cell-derived β -cell therapy was explored. **Methods:** Previously published cost and health benefit data for islet transplantation were utilized to perform the cost–effectiveness and sensitivity analyses. **Results & conclusion:** It was determined that, over a 9-year time horizon, islet transplantation would become cost saving and ‘dominate’ the comparator. Over a 20-year time horizon, islet transplantation would incur significant cost savings over the comparator (GB£59,000). Finally, assuming a similar cost of goods to islet transplantation and a lack of requirement for immunosuppression, a human induced pluripotent stem cell-derived β -cell therapy would dominate the comparator over an 8-year time horizon.

Keywords: β cell • allogeneic islet transplantation • cost–effectiveness • diabetes • incremental cost–effectiveness ratio • induced pluripotent stem cell • quality-adjusted life years • reimbursement

Aims

The present study will examine whether the efficacy of allogeneic islet transplantation over a 20-year period is sufficient to warrant its increased initial cost, in comparison to insulin therapy, by utilizing the current methods of cost–effectiveness analysis. Additionally, the feasibility of a human induced pluripotent stem cell (hiPSC)-derived β -cell therapy for the treatment of Type 1 diabetes will be explored by examining the cost–effectiveness of this technology, in comparison to allogeneic islet transplantation and insulin therapy. Sensitivity analyses will be performed, in which cost and efficacy data for allogeneic islet transplantation will be manipulated, in order to determine the impact of improvements in efficacy and increased cost upon the reimbursement potential of such a therapy in the UK. These analyses will also identify the gaps in the available data for a hiPSC-derived β -cell therapy that must be addressed in order to inform Health Technology Appraisals (HTA).

Reimbursement in the UK

At present, the analysis of new healthcare technologies in the UK, known as HTAs, is performed by the NICE and provides the basis for most reimbursement decisions in the UK healthcare system. Furthermore, the WHO has reported that these appraisals are frequently used as international benchmarks [1]. The main component of these HTAs is the cost–effectiveness analysis of new technologies, although a number of other factors are also considered during the appraisal process. In order to calculate how cost effective a new technology may be, the ‘incremental cost–effectiveness ratio’ (ICER), or ‘incremental cost per quality-adjusted life year (QALY)’ must be determined. This ICER value is then compared with the NICE threshold, currently set between GB£20,000 and GB£30,000 per QALY, to inform the decision making process and to therefore determine whether a recommendation for the reimbursement of the new technology will be considered. A favorable recommendation

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from NICE becomes increasingly unlikely, and the requirement for stronger supporting evidence outside of the cost–effectiveness analysis becomes increasingly necessary, the further above the GB£20,000 per QALY threshold the ICER for a new technology falls.

The current system, through which price setting of new medicines occurs, particularly pharmaceuticals, is known as the Pharmaceutical Price Regulation Scheme (PPRS). This scheme allows free pricing of new products by manufacturers, and therefore potentially the incorporation of significant profit margins, as well as price negotiations between manufacturers and the Department of Health. With regards the reimbursement of regenerative medicines and cell-based therapies, although it is unlikely that these technologies would be reimbursed through the PPRS, it may be that, if significant adoption were achieved, an alternative scheme to PPRS would be put in place to determine the pricing of these therapies, although this is speculative. For example, the NICE highly specialized technologies program, which is currently in development, will appraise new or existing technologies that target ‘ultra-orphan’ indications and that would not typically be considered cost effective [2]. Alternatively, the development of innovative business models involving risk-sharing schemes between manufacturers and the National Health Service (NHS) has been proposed [3]. However, the approach to reimbursement may differ between allogeneic and autologous cell therapies, each of which are likely to utilize varying manufacturing and delivery processes. This disparity between allogeneic and autologous approaches has been identified as one of the key barriers to the adoption of regenerative medicines by the NHS [3].

Diabetes & islet transplantation

Diabetes has been reported to affect approximately one in 17 people in the UK, with 3.2 million individuals diagnosed, and approximately 630,000 remaining undiagnosed, in 2013 [4]. Furthermore, this report approximated that 10% of diabetic patients in the UK have Type 1 diabetes and 90% have Type 2 diabetes.

Importantly, diabetes has also been linked to a number of chronic complications and comorbidities. Diabetic patients have been found to have twice the risk of developing a range of cardiovascular diseases compared with healthy individuals [5]. Furthermore, treatment of diabetes with exogenous insulin is not associated with a reduction in the risk of long-term cardiovascular complications [6,7]. Additionally, it has been estimated that one in four diabetes patients will develop kidney disease during their lifetime [8]. Therefore, a curative treatment for diabetic patients at risk of renal failure may reduce their mortality risk.

Type 1 diabetes, caused by insufficient physiological insulin production, is usually treated with the utilization of regular exogenous insulin injection. However, in 2000, Shapiro and colleagues [9] demonstrated that the transplantation of islets from the pancreata of brain-dead donors was capable of restoring insulin independence in Type 1 diabetes patients. Although this represents a promising cell-based therapy, long-term immunosuppressive therapy is required in conjunction with allogeneic islet transplantation and graft failure within a year of transplantation may occur, with a 28% complete graft loss after 1 year previously demonstrated [10]. However, although insulin independence may not be sustainable in the long term, the transplanted islets may still provide protection from severe hypoglycemia and hypoglycemia unawareness, as well as maintaining a normal level of glycated hemoglobin. Furthermore, recent developments in allogeneic islet transplantation protocols have yielded significant improvements in insulin independence rates, with increases in 3-year insulin independence rates from 27% in 1999–2002 to 44% in 2007–2010 [11]. Although insulin independence after islet transplantation may not be maintained in the long term, 50% graft survival over 5 years has been reported in a previous study when combined with T-cell depleting antibody treatment and TNF- α inhibition, and this was found to be comparable to that of whole pancreas transplantation [12].

However, the availability of pancreatic tissue for transplantation is limited, with only 456 pancreas donors, from either brain-dead individuals or those who have suffered circulatory death, in the UK in 2013/2014 [13]. During that time, 270 patients were placed on the transplant list and 246 pancreas or islet transplantations were performed. These pancreatic transplantations are often combined with kidney transplantation [13], and therefore, the availability of a curative diabetes treatment would significantly reduce the incidence of renal failure and the mortality risk in diabetic patients.

Since the development of the Edmonton Protocol [9], in which islets from brain-dead donors are transplanted into diabetic patients, there has been an increasing emphasis on identifying alternative sources of islets, due to the issue of donor and tissue availability associated with Autologous and allogeneic islet transplantation [14]. Within the last decade, the possibility of deriving functional β cells, the insulin secreting cells of pancreatic islets, from pluripotent stem cells has been much explored.

A significant body of research has been published regarding the generation of functional human embryonic stem cell (hESC)-derived β cells [15–17]. In recent

years, Douglas Melton and his colleagues at Harvard University have successfully derived mature, human pancreatic β cells *in vitro* and these cells are currently under examination in primate models of diabetes [18]. An alternative strategy for the manufacture of insulin producing cells from hESCs has been developed by a company known as ViaCyte (CA, USA), involving the differentiation of these cells into pancreatic endodermal cells, which, after encapsulation and transplantation, mature into insulin producing β cells [19,20]. Animal trials of this combination product have been completed and a Phase I/II trial in humans is underway [21].

Considerations for the development of an induced pluripotent stem cell-based product by differentiation to β cells

With the recent discovery of hiPSCs by Yamanaka and colleagues [22], significant advances have been made in differentiating these cells into functional β cells. The transplantation of these differentiated cells into animal models of Type 1 diabetes has also been explored and it has been determined that blood glucose is normalized after the production of insulin by β cells in response to glucose [23–25]. One potentially significant advantage of the derivation of β cells from hiPSCs, rather than hESCs, is that these hiPSC-derived cells could be used as an autologous therapy. Human leukocyte antigen matching, or the derivation of source material from the patient, may mitigate alloimmune reactions to transplanted cells. Differentiated cells derived from pluripotent stem cells, including iPSCs, have been found not to induce an immune reaction in mice [26–29], which may suggest that iPSCs represent a valuable source of a variety of cell types for cell-based therapies.

However, the autoimmune destruction of native pancreatic β cells that occurs in Type 1 diabetes may represent an additional challenge, with graft failure after allogeneic islet transplantation often associated with the immune clearance of transplanted cells [30]. It is conceivable that autoimmune reactions in Type 1 diabetes patients against transplanted autologous pluripotent derived β cells may lead to recurrence of the condition [31]. Such autoimmune rejection would be likely to limit the efficacy and safety of a hiPSC-derived β -cell therapy in the absence of immunosuppression, and therefore such a therapy would be unlikely to achieve adoption into healthcare. Additionally, long-term teratoma formation after the transplantation of hiPSC-derived cells may represent an additional safety risk, and this has recently been identified in a mouse spinal cord model after hiPSC-derived neural cell transplantation [32]. However, this was not observed after hiPSC-derived β -cell transplantation in mice [23].

Nevertheless, it is yet unknown whether the transplantation of β cells derived from autologous hiPSCs would induce an autoimmune reaction, and further investigation is required. A recent investigation into the immunogenicity of iPSC-derived organs determined that transplanted iPSC-derived islets were not rejected by the recipient immune system in mice [33], however further research is required. An approach to avoiding the autoimmune clearance of pluripotent stem cell-derived β cells, or insulin-producing cells, that is currently under investigation in early clinical trials and animal studies [18,21], is the encapsulation of these cells in order to provide protection from the immune system while allowing the secretion of the appropriate molecules. Besides immunosuppressive therapy, cell encapsulation currently represents the most promising method of avoiding autoimmune rejection of transplanted pluripotent stem cell-derived β cells that may occur in Type 1 diabetes patients. However, there is currently a lack of clinical data regarding the efficacy of encapsulated pluripotent stem cell derived β cells for the treatment of Type 1 diabetes.

Provided that adequate clinical evidence supporting the avoidance of immune rejection after hiPSC-derived β -cell therapy can be generated, and given that the cost of immunosuppression is one of the most significant contributors to the estimated US\$19,000 yearly costs associated with allogeneic islet transplantation [34], the derivation of functional β cells from hiPSCs may significantly reduce the annual costs after transplantation. Although the manufacturer of a hiPSC-derived β -cell technology may not offer immunosuppressive therapy along with their product, it is likely that, if immunosuppressive therapy is required, the cost would be accounted for in a HTA of their technology as part of the care pathway. However, if it can be demonstrated that treatment with a hiPSC-derived β -cell therapy does not require immunosuppression, the annual cost of treatment may be reduced and patient quality of life (QoL) may improve, which may lead to a lower ICER and therefore a more cost-effective therapy.

An additional advantage of a hiPSC-derived β -cell therapy is that this approach would not be limited by the availability of organ donors, unlike an allogeneic islet transplantation approach which often requires multiple donors [9]. The utilization of a hiPSC-derived β -cell therapy would not reduce the number of pancreas donors, and would not diminish the number of organs available for whole pancreas transplants.

However, the initial costs associated with generating β cells from hiPSCs would likely be far greater than the derivation of source material for allogeneic islet transplantation, which is already considered to have high upfront costs. The development of hiPSC-derived

β cells would be likely to face a number of costly challenges, including the creation of a hiPSC bank, the optimization of the hiPSC differentiation process and the development of a scalable manufacturing process. Furthermore, for an encapsulated hiPSC-derived β -cell therapy product, the development, testing, optimization and manufacture of an appropriate cell encapsulation device will add additional cost, although this is unlikely to be as significant as the cell banking, differentiation and manufacturing costs.

It has been noted that the cost of generating, testing and expanding research-grade hiPSC lines is approximately US\$10,000–20,000 each, however, when creating a hiPSC line for clinical use, this cost would be likely to rise to approximately US\$800,000 [35]. Therefore, in order to create one or more Master Cell Banks, and to perform the necessary comparability work to demonstrate the equivalence of each hiPSC line, the cost is likely to escalate above US\$1,000,000 [35].

Developing a scalable differentiation process is likely to represent the most challenging process step in the manufacture of functional β cells from hiPSCs. The efficiency of the differentiation process raises a number of concerns including, not only the presence of undifferentiated hiPSCs in the final product [36], but also the number of hiPSCs required to generate a sufficient dose of β cells for transplantation. In the published literature, the expression of insulin in response to glucose is a commonly used potency marker for functional differentiated β cells. The majority of these studies has reported the percentage of differentiated cells expressing insulin to be between 0.7 and 17% [37–40], although Alipio and colleagues [24] discovered that this percentage increased to 50% after 20 days of culture. Therefore, due to the relatively low yield of insulin producing cells derived from hiPSC cultures, a large number of these cells would be required to create a sufficient dose of pancreatic β cells. Thus, significant expense will be required to generate large numbers of hiPSCs in order to derive sufficient β cells using a low differentiation efficiency, or in order to optimize the differentiation process and improve the β cell yield.

Additionally, the scalability of both the differentiation and manufacturing processes would be likely to incur substantial cost to the manufacturer, with consumables utilization increasing significantly. For example, it has previously been estimated that the cost of cell culture medium will comprise approximately 24% of the cost of goods in a manufacturing process that provides 1000 doses of cells per year, whereas this percentage of cost of goods will increase to approximately 58% when the number of doses is increased to 100,000 per year [41]. If the generation of

β cells from hiPSCs were based upon the creation of a number of hiPSC ‘haplobanks’ and the generation of HLA-matched hiPSC-derived β cells, it is likely that the initial cost of generating a scalable manufacturing process would be large. However, this approach may allow for a large patient throughput. On the other hand, if an autologous approach were to be utilized, in which hiPSCs and differentiated β -cells were created from donated patient tissue, a similar scale of manufacturing process to that of a ‘haplobank’ approach may not be required. However, an autologous approach may not be feasible to treat a large number of patients at a reasonable cost [42].

Methods

Cost-effectiveness analysis of allogeneic islet transplantation

To calculate the ICER, the QALYs gained for both the ‘Gold Standard’ and ‘new’ treatments must be determined. In the present study, the cumulative QALYs gained, at each year over the 20-year time horizon, for both allogeneic islet transplantation (‘new’ treatment) and insulin therapy (‘Gold Standard’ treatment) were based upon data kindly provided by Beckwith and colleagues, which was published in their 2012 publication as part of the Markov simulations [34].

Next, the change in QALYs (Δ QALYs) is calculated, by subtracting the ‘Gold Standard’ treatment QALY from that of the ‘new’ treatment, in order to determine the difference in efficacy between the two treatments. The cost difference (Δ Cost) between the two treatments must then be identified by subtracting the cost of the ‘Gold Standard’ treatment from the cost of the ‘new’ treatment. The cumulative cost, at each year of the 20-year time horizon, for both allogeneic islet transplantation (‘new’ treatment) and insulin therapy (‘Gold Standard’ treatment) was kindly provided by Beckwith and colleagues and is presented in the Markov simulations of their 2012 publication [34]. Finally, the Δ Cost is divided by the Δ QALYs in order to generate the ICER, which can be compared with the NICE threshold (GB£20,000 per QALY). The formulae used to calculate the ICER of allogeneic islet transplantation compared with insulin therapy are presented below:

- Δ QALY = New Treatment QALYs - ‘Gold Standard’ QALYs
- Δ Cost = Cost of new treatment - Cost of ‘Gold Standard’ Treatment
- $ICER = \Delta Cost / \Delta QALY$

The ICER for allogeneic islet transplantation, in comparison to insulin therapy, is presented over

both a 20-year time horizon (Figure 1) and a 5-year time horizon (Figure 2), in order to demonstrate to cost–effectiveness of allogeneic islet transplantation over both a long, optimistic time horizon and a short, conservative time horizon.

The maximum cumulative cost for allogeneic islet transplantation (Figure 3) was calculated by first determining the maximum Δ Cost, performed by multiplying the NICE threshold (GB£20,000 per QALY) by the Δ QALYs. This maximum Δ Cost was then added to the total cumulative cost of insulin therapy, in order to determine the maximum cumulative cost of allogeneic islet transplantation that would still be considered cost effective. The actual cumulative cost of allogeneic islet transplantation was based upon the annual cumulative cost data provided by Beckwith and colleagues [34]. Both the maximum cumulative cost and the actual cumulative cost assume the same efficacy of transplantation.

In order to perform the cost–effectiveness analysis for allogeneic islet transplantation, a number of assumptions were made due to data availability, and in order to avoid unnecessary complexity. These included:

- A maximum time horizon of 20 years was utilized:
- This was based upon the time horizon of the annual cost data for allogeneic islet transplantation and insulin therapy provided by Beckwith and colleagues [34];
- A conservative assumption was made to not incorporate the clinical and cost benefits from avoiding long-term complications after allogeneic islet transplantation into this analysis;
- Allogeneic islet transplantation full graft function and complete graft failure rates per year were based upon those utilized within the Beckwith *et al.* study [34]. Complete graft failure rates were reported to be 0% over 1 year, 17% over 5 years, 24% over 10 years and 30% over 20 years. The proportion of patients with full graft function was reported to be 93% over 1 year, 47% over 5 years, 27% over 10 years and 7.5% over 20 years. The graft survival rates utilized in the present study are comparable to those described in recent longitudinal studies [11,12];
- Patients with full graft function are defined as being completely insulin independent, whereas patients with complete graft failure are defined

Figure 1. Incremental cost–effectiveness ratio of allogeneic islet transplantation over a 20-year time horizon, compared with the NICE threshold (GB£20,000 per quality-adjusted life year). The annual cost and QALY data utilized in the present sensitivity analysis were obtained from the corresponding author of the following publication [34].

ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life year.

Figure 2. Sensitivity analysis illustrating the incremental cost-effectiveness ratio of allogeneic islet transplantation with the time horizon limited to 5 years, compared with the NICE threshold (GB£20,000 per quality-adjusted life year).

- as no longer presenting detectable levels of C-peptide [34];
- The NICE 'reference case' methods were not utilized to derive the health utility and cost values, or the time horizon, utilized in the present analysis.

Cost-effectiveness sensitivity analyses for a hiPSC-derived β -cell therapy

In order to perform sensitivity analyses for an estimated hiPSC-derived β -cell therapy ICER, a number of optimistic assumptions were made due to long term clinical and cost data, for the treatment of diabetes patients with a hiPSC-derived β -cell product, not yet being available. For both the cost (Figure 4) and efficacy (Figure 5) sensitivity analyses, insulin therapy remained as the 'Gold Standard' comparator to which a prospective hiPSC-derived β -cell therapy was compared. The results of these analyses were then compared with the cost-effectiveness analysis of allogeneic islet transplantation, in which insulin therapy was also the 'Gold Standard' comparator.

For the first hiPSC-derived β -cell therapy sensitivity analysis, it was assumed that the efficacy of such a product for the treatment of Type 1 diabetes was equal to that of allogeneic islet transplantation, and

therefore the QALY gains and incremental effectiveness utilized were identical. The initial cost of goods for a hiPSC-derived β cells product was also assumed to be equal to that of allogeneic islet transplantation (US\$99,629/GB£61,770), as there are little available data on the likely cost or price of such a product, and this value would not be considered highly unrealistic. The cumulative cost data were then manipulated in order to examine the effect of an increased cumulative cost, in comparison to allogeneic islet transplantation, or the avoidance of immunosuppressive treatment costs, upon the ICER over a 20-year time horizon (Figure 4).

In order to account for the lack of immunosuppressive therapy, the annual cost of immunosuppressive therapy, assumed to be US\$19,000 [34], was subtracted from the annual cumulative cost of allogeneic islet transplantation. However, this cost also includes the cost of consultations and associated procedures, and therefore may not be completely accurate.

To generate ICERs in which 30, 50 and 70% profit margins were incorporated, the cost of goods remained the same (US\$99,629/GB£61,770), however the price of the product was increased (30, 50 or 70%) and this was discounted based upon inflation rates. The final ICER within the first sensi-

tivity analysis (Figure 4) assumes an initial cost of goods of US\$200,000 (GB£124,000), rather than US\$99,629 (GB£61,770), and includes the annual immunosuppressive therapy costs.

For the 30, 50 and 70% profit margin ICERs, as well as the US\$200,000 initial cost ICER, a 1.3% annual discount rate, based upon the current UK inflation rates (October 2014) [43], was applied to the initial cost when included in the cost calculations for each year of the analysis.

The second hiPSC-derived β -cell therapy sensitivity analysis (Figure 5) assumed that the cost of this new therapy would be the same as allogeneic islet transplantation, and therefore the Δ Cost compared with insulin therapy would be the same. Furthermore, it was assumed that immunosuppression would not be required and this annual cost (US\$19,000) was subtracted from the cumulative cost. However, in order to estimate the effect of an improved efficacy upon the ICER, the Δ QALYs was increased proportionally in order to produce a 2 or 2.5 QALY gain over the 20-year time horizon. The resultant ICERs were then compared with the ICER in which a 1.5 QALY gain is observed, as with allogeneic islet transplantation.

Results & discussion

Cost–effectiveness analysis of allogeneic islet transplantation

In order to perform the ICER calculations for allogeneic islet transplantation, the QALYs gained from both the new (allogeneic islet transplantation) and ‘Gold Standard’ (insulin therapy) must first be identified. Typically, QALYs gained are calculated based upon the patients’ health state after treatment, on a scale of 0–1, and the duration for which they are in that health state. Generally, the duration values are equal for both the new and ‘Gold Standard’ treatments, unless the new treatment extends patient life expectancy.

- $\text{QALYs gained} = \text{Health utility (0–1 scale)} \times \text{duration (years) of that state}$

However, the QALYs utilized in the present study are based upon the results of the Markov simulations performed by Beckwith *et al.* [34]:

- Allogeneic islet transplantation QALYs gained = 10.7 QALYs over 20 years [34]
- Insulin therapy QALYs gained = 9.2 QALYs over 20 years [34]

Figure 3. Comparison of the maximum cumulative cost to fall below the NICE threshold (GB£20,000 per quality-adjusted life year) and the actual cumulative cost of allogeneic islet transplantation. The efficacy of treatment was assumed to be the same for both the maximum and actual cumulative costs. ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life year.

Figure 4. Sensitivity analysis illustrating an estimate of a prospective incremental cost–effectiveness ratio for a human induced pluripotent stem cell derived β -cell therapy compared with the NICE threshold (GB£20,000 per quality-adjusted life year), over a 20-year time horizon. The impact of the incorporation of profit margins (30, 50 and 70%), the avoidance of the requirement for immunosuppressive therapy and an increase in manufacturing costs (US\$200,000) is demonstrated.

hiPSC: Human induced pluripotent stem cell; ICER: Incremental cost–effectiveness ratio; QALY: Quality-adjusted life year.

Next, the change in QALYs must be determined by subtracting the QALYs gained from the ‘Gold Standard’ treatment from the QALYs gained for the new treatment, as shown in the formula below:

- $\Delta\text{QALY} = \text{New treatment QALYs} - \text{‘Gold Standard’ QALYs}$
- $\Delta\text{QALY} = 10.7 - 9.2 \text{ QALYs} = 1.5 \text{ QALYs}$

The change in cost, due to the introduction of the new treatment, is calculated by subtracting the cost of the ‘Gold Standard’ treatment from the cost of the new treatment, as shown in the formula below. In the current reimbursement system, the price proposed by the manufacturer is used as the cost values for the new treatment during ICER calculations. For the change in cost calculations within the present study, allogeneic islet transplantation is viewed as an interventional procedure, for which the cost of the treatment is utilized, rather than as a new product from a manufacturer, in which the price with an incorporated profit margin would be incorporated. However, although cost–effectiveness

analyses are not routinely incorporated into NICE interventional procedures guidance [44] and given the high costs associated with allogeneic islet transplantation, it is likely that an economic evaluation would be incorporated into an appraisal of this procedure.

- $\Delta\text{Cost} = \text{Cost of new treatment} - \text{cost of ‘Gold Standard’ treatment}$
- $\Delta\text{Cost} = \text{GB£}321,704.20 - \text{GB£}410,870.63 = \text{GB-£}89,166.44 \text{ over 20 years [34]}$

The results of this analysis indicate that adopting allogeneic islet transplantation to treat Type 1 diabetes would generate a 1.5 QALY gain compared with using insulin treatment, while saving the payer approximately GB£89,000, over a 20-year period. However, the initial, one-off costs of approximately GB£60,000 for islet transplantation, attributed to organ donation, islet manufacture, screening and the performance of the medical procedure, may be prohibitively expensive. Although, provided sufficient certainty in the long term cost-saving nature of the new technology exists,

high initial costs may not be considered unreasonable. With regards patient QoL, it must also be noted that, in addition to the 1.5 QALY gain observed over a 20-year period, islet transplantation has been previously reported to reduce pain scores by up to 70% and to result in over 90% patient satisfaction [45].

The 20-year QALY and cost data for both insulin therapy and allogeneic islet transplantation utilized in the present analysis, were generated, using Markov modeling, and published by Beckwith and colleagues [34]. The cost data were originally published in US\$, and these values were converted into GB£ using a conversion rate of GB£0.62 per dollar (October 2014) [46]. Although the 20-year costs of allogeneic islet transplantation and insulin therapy, generated by Beckwith and colleagues [34], are likely to be specific to the healthcare system from which the initial cost estimates were taken, these data were applied to the UK healthcare system and utilized in the present study as it represents the most comprehensive long-term analysis of the costs of allogeneic islet transplantation.

The formula for the calculation of the ICER for allogeneic islet transplantation, as shown below, incorporates

the results of the two previous calculations, dividing the change in QALYs gained by the change in cost:

- $ICER = \Delta Cost / \Delta QALY$

After calculating the ICER for allogeneic islet transplantation using a 20-year time horizon, it is apparent that this intervention is associated with both cost savings and QALY gains, and therefore ‘dominates’ the comparator. Although negative ICERs lack meaning, the 20-year ICER calculation, which induces a negative ICER, is shown below:

- 20 year ICER = GB-£89,166.44/1.5 QALYs = GB-£59,087.70 per QALY

From the results of the ICER calculations, it is clear that the introduction of allogeneic islet transplantation for the treatment of Type 1 diabetes would be considered to be cost saving and would ‘dominate’ the comparator (insulin therapy) over an approximate time horizon of 9 years. However, as shown in the sensitivity analyses (Figures 1 & Figure 2), in the short term (9 years) this treatment would be unlikely to be cost saving. Additionally, if the costs of this procedure

Figure 5. Sensitivity analysis illustrating an estimate of a prospective incremental cost-effectiveness ratio for a human induced pluripotent stem cell-derived β -cell therapy compared with the NICE threshold (GB£20,000 per quality-adjusted life year), over a 20-year time horizon. The impact of an improved efficacy and the avoidance of the requirement for immunosuppressive therapy are demonstrated.
hiPSC: Human induced pluripotent stem cell; ICER: Incremental cost-effectiveness ratio; QALY: Quality-adjusted life year.

increase above those utilized in the present analysis, a longer period would be required in order to realize the cost savings and before the intervention dominated the comparator. However, if the treatment of diabetic patients with allogeneic islet transplantation successfully induced significant clinical benefit for approximately a decade, the likelihood of long-term cardiovascular complications may be significantly reduced [47,48].

By utilizing the data regarding the Δ QALY between insulin therapy and allogeneic islet transplantation, and the NICE threshold of GB£20,000 per QALY, the maximum cumulative cost of allogeneic islet transplantation required to achieve cost-effectiveness can be determined and is illustrated in Figure 3. It is apparent from the cumulative cost data that, given the efficacy of the treatment, allogeneic islet transplantation is too expensive to be considered cost effective in the short term. However, after 9 years, the cumulative cost falls below the maximum cumulative cost and could therefore be considered cost effective, as is also demonstrated in the ICER sensitivity analysis (Figure 1). In the long term, with a time horizon of 20 years, a cumulative cost of GB£441,051.63 could be incurred with the treatment remaining cost effective.

Within the published study by Beckwith and colleagues [34], rates of full graft function of 93% over 1 year, 47% over 5 years, 27% over 10 years and 7.5% over 20 years were assumed. This data, used within the Markov models [34], regarding the probability of graft function were obtained from the Diabetes Control and Complications Trial conducted between 1990 and 1993 [49], as this was considered to represent the most accurate estimates at the time. At the time of the publication of Beckwith *et al.* study [34], these graft survival rates were considered to be optimistic. However, given the recent improvements in allogeneic islet transplantation protocols and graft survival, with up to 50% graft survival reported after 5 years [12], these values can be considered more representative. If graft survival rates were to improve further, and the cost-effectiveness analyses performed in the present study were based upon these improved graft survival rates, the time point at which the intervention would become cost saving and would dominate the comparator would extend.

Due to the uncertainty of allogeneic islet transplantation graft survival over time, it may be appropriate to consider the consequences of a short time horizon. Therefore, in addition to the 20-year time horizon utilized in the present analysis, the cost-effectiveness of allogeneic islet transplantation was also examined over a conservative 5-year time horizon, based upon the duration of follow-up in a previous international

trial [10]. If the time horizon is limited to 5 years, it is unlikely that allogeneic islet transplantation would be considered cost effective with an ICER of GB£128,000 per QALY, as demonstrated in Figure 2. Furthermore, the maximum 5-year cumulative cost for allogeneic islet transplantation to be considered cost effective would be GB£73,141.37, whereas the actual cost is GB£119,224.06, as demonstrated in Figure 3. Therefore, greater evidence of long-term graft survival is required before the 9-year time horizon and the corresponding ICER would be considered to have sufficient certainty and thus for allogeneic islet transplantation to be considered cost effective.

After the determination of the ICER of the new treatment, a decision on the adequacy of the evidence provided and the certainty of the ICER is required for a HTA. Although the data provided in the Beckwith *et al.* [34] study were modeled over a 20-year period and give an indication of long-term costs, the significant rate of graft failure after transplantation creates uncertainty in the accuracy of the ICER and may therefore impact the likelihood of a positive reimbursement decision from the appraisal committee. Therefore, it is apparent that the duration of graft survival is a major determinant of cost-effectiveness, and that resolving uncertainty in this parameter, through longer term data collection in a larger group of patients, would increase the plausibility of estimates of cost-effectiveness.

Cost-effectiveness sensitivity analyses for a hiPSC-derived β -cell therapy

The generation of a sensitivity analysis to examine a prospective ICER for a hiPSC-derived β -cell therapy, based upon the allogeneic islet transplantation cost and efficacy data, allows the effect of an increased initial cost and a reduced annual cost, as a consequence of the need for immunosuppression being avoided, upon the required duration of graft function, in order to achieve cost-effectiveness, to be illustrated and explored. The comparator, or 'Gold Standard', for the hiPSC-derived β -cell therapy ICER sensitivity analysis was insulin therapy, as with the analysis of the allogeneic islet transplantation ICER.

Although the cost of developing the cell banking, differentiation and manufacturing processes would not be directly incorporated into the price of the hiPSC-derived β -cell product, the manufacturers of this technology are likely to incorporate a profit margin on top of the initial cost of manufacture. Therefore, although the total process development and manufacturing costs would not be directly incorporated into ICER calculations, the value utilized in ICER calculations would likely represent the cost of manufacture for one unit,

amortization of R&D costs and the incorporated profit margin. This would differ from the value for allogeneic islet transplantation which, as it is generally administered as an interventional procedure, would not incorporate a profit margin. Thus, in the short term, the ICER for a hiPSC-derived β -cell product would be likely to be significantly greater than that of an allogeneic islet transplantation procedure, assuming that the efficacy of the two technologies was similar. However, if the cost of immunosuppression can be avoided, the ICER for the hiPSC-derived therapy may be lower in the longer term. The effect of the incorporation of a 30, 50 or 70% profit margin upon the ICER of a hiPSC-derived β -cell therapy is demonstrated in **Figure 4**. **Figure 4** also demonstrates the effect of increasing the manufacturing costs (US\$200,000) and removing the cost of immunosuppression may have upon an estimated, prospective ICER for a hiPSC-derived β -cell therapy.

As expected, the results of the cost sensitivity analysis (**Figure 4**) would suggest that, when similar cost and efficacy data to allogeneic islet transplantation are assumed, a time horizon of 9 years would be required for a hiPSC-derived β -cell product to become cost saving. Additionally, a sufficiently low graft failure rate would be required in order to provide adequate certainty in the ICER and clinical efficacy after extrapolation of the clinical trial data to a 9-year time horizon. In the present study, the assumed graft failure rates for allogeneic islet transplantation were 0% over 1 year, 17% over 5 years, 24% over 10 years and 30% over 20 years, based upon Beckwith and colleagues simulations [34]. It is likely that significantly lower graft failure rates than is assumed for allogeneic islet transplantation would be required in order to create sufficient certainty in a ≤ 9 -year time horizon.

Depending upon the value proposition of the new technology, the clinical trial data are also likely to be required to demonstrate a lack of need for immunosuppressive therapy. If a hiPSC-derived β -cell product could be manufactured and delivered at a similar cost to an allogeneic islet transplantation procedure (US\$99,629/GB£61,770) while avoiding the requirement for immunosuppressive therapy, then, in order to achieve an ICER that falls below the NICE threshold, a time horizon of 8 years would be sufficient to incur cost savings. Therefore the long term clinical data, and estimated duration of full graft function, required to achieve a positive reimbursement decision is likely to be reduced. However, if profit margins of 30, 50 or 70% of the cost of goods are incorporated, with a 1.3% per annum discount rate, then the required time horizon increases to 9, 10 or 11 years, respectively. Finally, if an initial cost of goods

of US\$200,000 was required to manufacture a single therapeutic dose, and if the requirement for immunosuppressive therapy remained, a time horizon of approximately 14 years must be demonstrated in order to reach the 'breakeven point' for cost savings. However, if the cumulative cost of therapy is discounted at a rate of 1.3% per annum, the realistic time horizon to achieve cost savings with an initial cost of goods of US\$200,000 would remain at approximately 11 years.

It must be acknowledged that the results of the above sensitivity analysis (**Figure 4**) are based upon the assumption that a hiPSC-derived β -cell product would achieve a similar efficacy, and therefore QALY gain, to that of allogeneic islet transplantation. Due to the lack of available clinical data regarding a hiPSC-derived β -cell product, greater improvements in patient QoL compared with allogeneic islet transplantation cannot be accurately incorporated into these analyses. However, a hiPSC-derived β -cell therapy may yield an improved health state compared with allogeneic islet transplantation, provided that the requirement for immunosuppressive therapy can be avoided and, consequently, a greater duration of graft function can be achieved. Therefore, the incremental effectiveness, when compared with standard insulin therapy, may be greater than that of allogeneic islet transplantation. A sensitivity analysis (**Figure 5**) was performed in order to estimate the effect of greater QALY gains after hiPSC-derived β -cell therapy compared with allogeneic islet transplantation, using insulin therapy as the 'Gold Standard' comparator.

As illustrated in **Figure 5**, if the efficacy of a hiPSC-derived β -cell product, which avoided the requirement for immunosuppressive therapy and achieved a similar cost of goods to that of allogeneic islet transplantation (US\$99,629/GB£61,770), was greater than that of allogeneic islet transplantation, for example inducing a QALY gain of 2.5 QALYs over a 20-year time horizon, then the duration required to dominate the comparator would fall to 8 years. The costs of treatment are assumed to be the same as that of allogeneic islet transplantation, however the annual cost of immunosuppression was removed. The comparator, or 'Gold Standard', for the hiPSC-derived β -cell therapy ICER sensitivity analysis was insulin therapy, as with the analysis of the allogeneic islet transplantation ICER.

It is apparent from the sensitivity analyses in the present study that, due to the early stage of development of pluripotent-derived β -cell products, both the cost and efficacy of such a technology are currently unknown and that these may improve as scientific and manufacturing expertise advance. As observed with allogeneic islet transplantation, the duration of graft function is likely to be a key uncertainty

in hiPSC β -cell therapy efficacy and cost-effectiveness. Therefore, the cost and efficacy data utilized in Figures 4 & 5 represent major uncertainties. Furthermore, these findings reveal that the initial cost of goods, the requirement for immunosuppressive therapy and the demonstration of long term efficacy and graft survival will have a significant impact upon the likelihood of reimbursement for a hiPSC-derived β -cell therapy.

Conclusion

As a result of the allogeneic islet transplantation cost-effectiveness analysis, it was observed that, over a 20-year time horizon, this treatment would dominate the comparator (insulin therapy) and result in a cost saving of GB£59,000. Additionally, this treatment would become cost saving after a 9-year time horizon. However, if a shorter time horizon of 5 years is considered, it is unlikely that allogeneic islet transplantation would be considered to be cost effective with an ICER of GB£128,000 per QALY. From these analyses, it was identified that a sufficiently low graft failure rate would be required in order to create adequate certainty in a 9-year time horizon, after which allogeneic islet transplantation would be considered cost saving. Thus, it is clear that the duration of graft survival is a major determinant of cost-effectiveness, and that resolving uncertainty in this parameter would increase the plausibility of estimates of cost-effectiveness.

From the hiPSC-derived β -cell therapy sensitivity analyses, it was determined that, by avoiding the annual cost of immunosuppressive therapy, such a product would become cost saving after 8 years, assuming a similar initial cost to allogeneic islet transplantation. If the initial cost of a hiPSC-derived β -cell therapy reached US\$200,000, and the need for immunosuppressive therapy remained, the 'break-even point' to become cost saving would increase to 11 years. If the efficacy of a hiPSC-derived β -cell product increased to 2.5 QALYs over a 20-year time horizon, without the requirement for immunosuppressive therapy and at a similar cost to allogeneic islet transplantation, the duration required to dominate the comparator (insulin therapy) would fall to 8 years.

Limitations of the present study

- The present analysis was based primarily upon the Markov modeling performed and published by Beckwith and colleagues [34];
- The cost data generated by Beckwith and colleagues [34], were based upon the US healthcare

system and may not be directly applicable to the UK healthcare system;

- The time horizon of the analysis for both allogeneic islet transplantation and hiPSC β -cell therapy was limited to 20 years, due to the availability of accurate data, and this may not represent the lifetime of the treatment or the full duration of graft function;
- As is apparent from the results of the present study, allogeneic islet transplantation would be considered to be cost saving in the long term and therefore may not be appraised using the typical HTA parameters that were utilized in the present analysis;
- Currently, a lack of data regarding the cost and efficacy, including the avoidance of autoimmune rejection, of a hiPSC-derived β -cell therapy exists, and therefore the values utilized in the present study are speculative.

Future perspective

With regards future developments for the treatment of Type 1 diabetes patients, it is clear that a number of scientific and manufacturing challenges remain before the successful translation and adoption of hiPSC-derived β -cell therapies can be achieved. However, if a pluripotent-derived β -cell therapy product can be transplanted without the requirement for immunosuppressive therapy, this may lead to an increased efficacy and increased duration of graft function. Therefore, if the incursion of cost due to immunosuppressive treatment can be avoided and the duration of graft function can be increased, in comparison to allogeneic islet transplantation, the time to reach the 'breakeven point' may decrease. This may lead to such a technology being considered cost effective in the long term, and would therefore encourage a positive reimbursement decision. However, it is imperative that sufficient clinical trial data, demonstrating adequate certainty in the graft failure rate, the lack of requirement for immunosuppressive therapy and the time horizon considered, are collected. Although, in principle, public healthcare systems, such as the NHS, have a lifetime perspective on patients [50], the time horizon considered must reflect the realistic duration of benefit of a treatment, and therefore may represent a more conservative estimate.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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Executive summary

Allogeneic islet transplantation

- Allogeneic islet transplantation may be considered cost effective if graft function is maintained for over 9 years.
- However, given the available clinical evidence, a duration of graft function of 9 years could be considered unlikely. The assumed graft survival rates in the present study, specifically 93% over 1 year, 47% over 5 years, 27% over 10 years and 7.5% over 20 years, do not support the 9-year time horizon.
- The introduction of allogeneic islet transplantation may induce significant cost savings (GB£59,000) over insulin therapy if graft survival endures for 20 years.
- The duration of graft function after allogeneic islet transplantation represents the greatest uncertainty that influences cost–effectiveness.
- During appraisals, the time horizon considered must realistically reflect the duration of benefit of a treatment and consider graft failure rates. Therefore, the time horizon used by the reimburer is likely to represent a conservative estimate.

Human-induced pluripotent stem cell-derived β -cell therapy incremental cost–effectiveness ratio sensitivity analysis

- The cost of a human-induced pluripotent stem cell-derived β -cell therapy, the requirement for immunosuppression and the duration of graft survival represent the greatest unknowns that determine the cost–effectiveness of such a product.
- If immunosuppressive therapy is not required with treatment, the annual cost of therapy would be significantly reduced and the duration of graft function required to achieve cost–effectiveness would be reduced by 1 year to 8 years, assuming a similar initial cost to allogeneic islet transplantation.
- If the initial cost of a human-induced pluripotent stem cell derived β -cell therapy reached US\$200,000, and the need for immunosuppressive therapy after treatment remained, the duration of graft survival required to achieve cost–effectiveness would increase to 11 years.

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