Institution: University of Edinburgh		
Unit of Assessment: 1		
Title of case study: B: Assessment of islet transplantation with the BETA-2 score saves NHS resources and offers potential to reduce graft loss		
Period when the underpinning research was undertaken: 2012 – 2016		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	**Role(s) (e.g. job title):**	**Period(s) employed by submitting HEI:**
Shareen Forbes	Chair of Diabetic Medicine	2006 – present
Period when the claimed impact occurred: 2016 – 2020		
Is this case study continued from a case study submitted in 2014? N		

1. Summary of the impact

Underpinning Research: University of Edinburgh (UoE) research defined and validated the BETA-2 score, an easier and more accurate method than the previous standard (the beta score) to track the success of islet grafts following transplants in patients with Type 1 diabetes.

Significance and Reach of Impact: The BETA-2 score has been recommended by the international consensus groups International and European Pancreas and Islet Transplant Associations (2018), as well as the British Transplantation Society (2019). The BETA-2 score has been implemented into routine use in all 7 UK hospitals where islet transplants are performed (116 patients monitored since 2016), as well as in major islet transplant programmes in Edmonton (Canada; 200 patients since 2016) and Chicago (United States; 60 patients since 2016).

Use of the BETA-2 score allows a more frequent and accurate assessment of graft function than the beta score, therefore enabling intervention prior to the graft being lost. A successful graft enables control of blood glucose stability and maintenance of awareness of hypoglycaemia, without which patients risk sudden catastrophic loss of consciousness. The BETA-2 score is also faster and cheaper to calculate than the beta score, resulting in NHS cost savings of GBP906 per patient in the first 12 months, and GBP25,000 across all islet transplant recipients per year in the UK.

2. Underpinning research

The Challenge: Monitoring success of islet transplants to reduce dependence on insulin injections

More than 400,000 people in the UK live with Type 1 diabetes, a condition characterised by loss of insulin secretion, leading to fatigue, thirst and rapid weight loss. Type 1 diabetes can be managed with insulin injections to control blood glucose levels, but these are associated with complications of both hyperglycaemia and hypoglycaemia (where too little or too much insulin is administered, respectively). Repeated episodes of hypoglycaemia may result in a dangerous clinical situation in which the patient is unable to detect falling blood glucose levels, and are therefore unable to take appropriate action (such as ingesting carbohydrates) in time, leading to severe hypoglycaemia and potential unconsciousness without warning. This can be catastrophic if it occurs while the patient is busy, such as driving or looking after small children.

In order to manage impaired awareness of hypoglycaemia, some patients receive a transplant of islets (insulin-producing cells). When successful, the transplant restores a level of insulin secretion that can help to restore awareness of hypoglycaemia and reduce dependence on insulin injections. It is well documented that even small amounts of insulin secretion from the graft lead to much more stable blood glucose control and can retain this critical awareness of hypoglycaemia. However, in approximately 12% of cases, the graft fails completely, requiring reinstatement of full doses of insulin injections. To avoid this, UoE researchers have developed a novel, more sensitive method to track the success of islet transplants.

Current method for tracking islet transplant function has limited sensitivity
The previous standard tool to measure islet transplant success was the beta score. This had two main drawbacks: 1) the categorical nature of its measurements restricted its ability to detect subtle early changes in graft function and 2) it required a mixed-meal tolerance test to be administered 90 minutes before taking the blood sample. This was time-consuming, making the beta score unsuitable for frequent measurements, and therefore further limiting its ability to identify early signs of graft failure.

BETA-2 score allows sensitive accurate tracking of islet transplant function
To develop a more sensitive and practical tool to track islet transplant success, UoE researcher Forbes, together with colleagues at Edmonton (Alberta, Canada), used a database of over 300 islet transplant recipients to formulate a composite score, BETA-2, which requires only a single fasting blood sample, and is derived from fasting glucose and C-peptide concentrations, haemoglobin A1c and insulin dose [3.1]. This composite score utilises all the component variables continuously, allowing it to more accurately describe the spectrum of islet graft function. Forbes then validated the score in a further group of transplant recipients (n=114) and found that the BETA-2 score could detect glucose intolerance and insulin independence with 82% sensitivity and specificity; a significantly greater discrimination than that achieved by the beta score ($p < 0.05$) [3.1].

The BETA-2 score is also more practical than the beta score for frequent assessment of graft function over time: it is quicker to administer due to being derived from a fasting blood sample and not requiring a mixed meal tolerance test.

Thus, the BETA-2 score is both more sensitive than the beta score to small changes in graft function and more suitable for frequent tracking of islet graft function. This means that the BETA-2 score allows graft function to be followed with greater resolution.

3. References to the research

[3.1] Forbes, S., et al., Validation of the BETA-2 Score: An Improved Tool to Estimate Beta Cell Function After Clinical Islet Transplantation Using a Single Fasting Blood Sample. *Am J Transplant*, 2016. 16(9): p. 2704-13. doi: 10.1111/ajt.13807

Funding: Society for Endocrinology visiting fellowship grant 2014

4. Details of the impact

Following publication of the BETA-2, the score was independently validated by external groups, both against other measures of islet function, and in another transplant centre [5.1a, b].

Impact on clinical guidance
In 2018, the BETA-2 score was recommended by the International and European Pancreas and Islet Transplant Associations (IPITA and EPITA, respectively) [5.2], which are the main opinion leaders in the field of islet transplantation. As such, their endorsement both raises awareness of and legitimises the use of BETA-2.

The EPITA/IPITA recommendation has led to several clinical research groups (including in Edmonton, Chicago, Miami and Grenoble, France) adopting the BETA-2 score in their work [5.3; 5.7]. For example, the first multicentre randomised controlled trial in islet transplantation calculated both the beta and the BETA-2 scores, and a recent experiment with transplanting islets into the omentum similarly used both scores to determine the success of the graft [5.3a, b]. The use of BETA-2 in these new clinical studies demonstrates that the transplant community is adopting the score as the new standard.

In addition, BETA-2 was recommended in the British Transplantation Society guidelines for best practice in pancreas and islet transplants (2019), which state: "*In addition to the minimum data set required by NHSBT* [NHS Blood and Transplant]*, additional data must be collected to allow islet graft function to be categorised according to Igls criteria and BETA-2 score calculation*." [5.4].

Impact on clinical practice

United Kingdom
The BETA-2 score is now in routine use in 100% of hospitals in the UK where islet transplants are performed (Edinburgh, Newcastle, Oxford, King's College London, Royal Free Hospital, Manchester and Bristol; comprising the UK Islet Transplant Consortium (UKITC)) [5.5]. Since its implementation in 2016, 34 islet transplants were performed in 2016/17, 26 in 2017/18, 28 in 2018/19 and 28 in 2019/20, giving a total of 116 patients, all of whom had their graft function monitored using the BETA-2 score [5.5].

The Chair of the UKITC stated the reason for adopting the BETA-2: *"[The beta score] has major cost implications and is inconvenient in terms of the time required for the patient to spend in the hospital along with the need for further nursing input. Furthermore the key paper by Forbes et al. 2016 showed that the BETA-2 score was more precise than the 'beta score' for characterising graft function and its meaningful clinical impact*. […] *We recognise the superiority of the BETA-2 score for the above reasons and its utility in enabling more frequent assessment of graft function each time the patient attends the clinic in a fasted state."* [5.6].

International
In 2016, the BETA-2 score replaced the beta score as the main method of outcome evaluation in the Edmonton Islet Transplant Programme, which has transplanted a greater number of patients than any other single centre, and by itself makes up over 60% of the worldwide islet transplant registry. Edmonton has now used the BETA-2 score to assess and monitor the islet transplant function of 180 recipients of allo-islet transplants and 20 auto-islet transplants [5.7a]. Similarly, the Chicago Pancreatic Islet Transplant Program adopted the BETA-2 score in 2016, and has since used it to assess transplant function in over 60 patients [5.7b].

To facilitate the usage of the BETA-2 score for clinicians, the UoE team collaborated with a software company to develop an application to track BETA-2 scores longitudinally, store the data and generate a graphical visualisation of the scores over time. The website hosting the app became live in October 2020; by the 17th of December, 11 university hospitals (in addition to the 7 hospitals in the UKITC) had registered for it, including 4 from the US (from Philadelphia, Chicago, San Francisco, Miami and Minneapolis), and one each from Canada, Australia, France, Italy, Switzerland and Sweden [5.8].

The Directors of the Edmonton and Chicago transplant programmes, both senior members of IPITA, have endorsed the BETA-2 app and envisage it being adopted across the international transplant community [5.7a, b]. Given their status as international thought leaders, their endorsement encourages and expedites this community-wide adoption.

Impact on health and welfare
The cause of islet graft loss is multifactorial, but in many cases it is related to inadequate immunosuppression. The BETA-2 score allows clinicians to note early signs of graft deterioration and take immediate action, such as adjusting the patient's immunosuppressant regime. Recent research from an independent group demonstrated that a BETA-2 score cut-off of 17.4 on post-transplant day 75 predicts future insulin independence; no patients with a BETA-2 score over 17.4 returned to insulin dependence, while all patients with a BETA-2 score below 17.4 did. Importantly, a score below 17.4 predicted islet graft decline 9 months in advance, thus extending the time frame for therapeutic intervention to prevent loss of the graft [5.9].

Graft failure would mean that the patient would return being dependent on full doses of insulin injections, and may resume their prior condition of impaired awareness of hypoglycaemia, with all its potentially dangerous consequences, such as falling unconscious without warning. Timely therapeutic intervention, enabled by the BETA-2 score, can help to prevent this from happening.

Based on 5-year follow-up data from NHS Blood and Transplant [5.5], islet grafts were successful in 54% of patients. Thus, of the 116 patients whose islet grafts were tracked using the BETA-2 score, 63 successfully retained their grafts. Based on clinical experience, it is conservatively estimated that approximately 10% (n=6) of these patients would have suffered a graft loss had they been monitored less frequently using the beta score. A graft loss typically results in an average of 16 episodes of severe hypoglycaemia per year per patient [p. 68; 5.5]; thus, the use of BETA-2 has averted 6 x 16 = 96 episodes since 2016 in the UK alone.

Economic impact

The BETA-2 score achieves cost savings for the NHS through 1) being quicker to calculate at each clinic appointment, as there is no need for the 90-minute wait between the mixed meal tolerance test and blood sampling, and 2) the potential avoidance of complications related to graft failure and the associated costs of hospital-based treatment.

These savings were formally quantified through a health economic assessment using NHS Reference Costs and actual patient follow-up data collected by the UKITC. This assessment found that using the BETA-2 score instead of the beta score to routinely assess changes in islet graft function leads to estimated NHS cost-savings of GBP906 per patient (95% confidence interval: GBP408 to GBP1,425) in the first 12 months. Across all recipients of islet transplants in the 2018/19 financial year (n=28), this translates to overall cost-savings of GBP25,368 (95% confidence interval GBP11,428 to GBP39,990) in that year [5.10]. Given the stable patient numbers since 2016 [5.5], this GBP25,000 saving is likely to be repeated each year.

Furthermore, the analysis calculated that avoidance of episodes of severe hypoglycaemia, through more frequent monitoring of graft function enabled by the BETA-2 score, can result in average additional cost-savings of GBP2,400 per patient per episode, through averted hospital admissions and procedures [5.10]. Based on the estimated 96 episodes of severe hypoglycaemia that have been averted through use of the BETA-2 score, this has saved a further GBP230,400 for the NHS since 2016.

5. Sources to corroborate the impact

[5.1] Independent validation of BETA-2 score
a. Gołębiewska JE et al. Comparative evaluation of simple indices using a single fasting blood sample to estimate beta cell function after islet transplantation. American Journal of Transplantation. 2018;18(4):990-997. doi: 10.1111/ajt.14620
b. Gołębiewska JE et al. External Validation of the Newly Developed BETA-2 Scoring System for Pancreatic Islet Graft Function Assessment. Transplantation Proceedings 2017; 49(10), 2340-2346. doi: 10.1016/j.transproceed.2017.10.011

[5.2] IPITA/EPITA recommendation 2018; p. 348
Rickels MR et al. Defining outcomes for β-cell replacement therapy in the treatment of diabetes: a consensus report on the Igls criteria from the IPITA/EPITA opinion leaders workshop. Transplant International. 2018;31(4):343-352. doi: 10.1111/tri.13138.

[5.3] Two independent clinical studies that adopted the BETA-2 score:
a. Lablanche, Sandrine, Malvezzi, Paolo et al. Islet transplantation versus insulin therapy in patients with type 1 diabetes with severe hypoglycaemia or poorly controlled glycaemia after kidney transplantation (TRIMECO): a multicentre, randomised controlled trial. Lancet Diabetes & Endocrinology, 2018; 6(7), 527 – 537 doi: 10.1016/S2213-8587(18)30078-0

b. Baidal DA, et al. Bioengineering of an Intraabdominal Endocrine Pancreas. N Engl J Med. 2017; 11;376(19):1887-1889 doi: 10.1056/NEJMc1613959

[5.4] British Transplantation Society guidelines for pancreas and islet transplants, September 2019

[5.5] NHS Blood and Transplant annual report 2019–20 (including data between 1st April 2010 and 31st March 2020) p. 59 and p. 66

[5.6] Testimonial from UKITC Chair

[5.7] Testimonials from key islet transplant programme Directors
a. Testimonial from Director of the Edmonton islet transplant programme
b. Testimonial from Director of the Chicago islet transplant programme

[5.8] University hospitals that have signed up to BETA-2 app; screenshot from website on 17th December 2020

[5.9] Bachul, PJ, Gołębiewska, JE, Basto, L, et al. BETA-2 score is an early predictor of graft decline and loss of insulin independence after pancreatic islet allotransplantation. American Journal of Transplantation. 2019; 00: 1– 8. doi: 10.1111/ajt.15645

[5.10] Health economic assessment report