Institution: Swansea University		
Unit of Assessment: 24		
Title of case study: Mitigating Risk of Exercise-induced Dysglycaemia in Type 1 Diabetes.		
Period when the underpinning research was undertaken: 2011-2016		
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:**
Richard Bracken Liam Kilduff	Associate Professor Professor	01/02/2005 – Present 01/10/2002 – Present
Period when the claimed impact occurred: 2014-2020		
Is this case study continued from a case study submitted in 2014? No		

1. Summary of the impact

Regular physical activity is recommended for people with type 1 diabetes (T1D), but the resulting blood glucose disruptions can make exercise potentially dangerous. Research at Swansea University has demonstrated how these disruptions can be mitigated by adjusting carbohydrate intake and the dose, type and timing of insulin analogues before, during and after exercise. Our research has (i) significantly improved international clinical guidelines, recommendations, and consensus statements for safe physical activity in people with T1D, (ii) underpinned a multi-million-dollar international educational initiative endorsed by a global diabetes charity that has educated over 5,000 diabetes clinicians and patients to date, (iii) empowered a Union Cycliste Internationale (UCI)-accredited professional cycling team with T1D to maximise their performance on the world's stage, and (iv) created global economic and commercial impact by providing evidence that allowed an international nutrition company to gain global market access for the inclusion of low-glycaemic carbohydrates in food and drink beverages for safe consumption by exercising individuals with T1D.

2. Underpinning research

Background and Context of Research: The incidence of T1D in Europe ranges between 7.9 and 32.8 cases per 100,000 people (EURODIAB Consortium), and is rising; furthermore, there is strong evidence of earlier mortality in those with than in those without T1D. Regular physical activity comprising muscle strength and cardiovascular endurance is recommended by international charities and governmental guidelines to promote good health in people with T1D and close this mortality gap. However, acute exercise increases the risk of blood glucose disturbances (i.e., hypo- and hyper-glycaemia) that are dangerous in the short-term and contribute to reduced motivation to exercise and quality and length of life in the long-term, when poorly managed. Thus, safe participation in physical activity is a significant barrier for people with T1D.

High-quality clinical trials conducted by Dr Bracken between 2011 and 2016 established effective strategies to maintain blood glucose concentrations in people with T1D through adjustments in insulin analogue use and carbohydrate intake, in the context of (i) resistance and (ii) aerobic exercise. These research findings provide robust evidence where previous data were weak or non-existent. Importantly, these strategies are relevant to diabetes healthcare professionals and individuals with T1D and allow safe participation in regular recreational (health benefit) and competitive (elite performance) exercises.

Detailed Overview of Research: Our research has detailed the gluco-regulatory responses to (i) resistance and (ii) aerobic exercise in those with T1D and created insulin analogue and carbohydrate interventions to minimise blood glucose disruption specific to each exercise type.

i) Resistance exercise: Chronic hyperglycaemia predisposes people with T1D to earlier onset and progression of cardiovascular disease and mortality than those without T1D, and physical activity that incorporates strengthening exercises is recommended by global diabetes charities and organisations to improve long-term glycaemic control. However, resistance exercise can acutely raise blood glucose, and this might seem counterintuitive for people with T1D. Our clinical research

thoroughly characterised the metabolic impacts of acute resistance exercise on blood glucose in T1D **[R1]** and provided a mechanistic explanation for the development of resistance exercise-induced hyperglycaemia. We sought to minimise strength exercise-induced hyperglycaemia by reducing exercise intensity to be achievable by patients with low exercise capacity while attaining international physical activity guideline exercise volume **[R2]**. As resistance exercise-induced hyperglycaemia was evident even with low exercise intensities, we created a clinically important individualized patient algorithm for immediate post-exercise administration with modern insulin analogues and demonstrated how this strategy countered the blood glucose rise following resistance exercise in patients with T1D **[R3]**.

ii) Aerobic exercise: Though regular endurance activities have been shown to improve long long-term glycaemic control in T1D, by contrast, acute aerobic exercise causes a reduction in blood glucose and increases the potential for hypoglycaemia. Indeed, exercise-induced hypoglycaemia can occur at night, when it can be life threatening. Our clinical trials demonstrated the importance of carefully manipulating the administration of short and long-lasting insulin analogue (and its timing) and the ingestion of low-glycaemic index carbohydrates, to improve glycaemia around aerobic exercise and crucially, to dramatically reduce overnight hypoglycaemia **[R4 & R5]**. Finally, we showed how large insulin analogue reductions around exercise do not exacerbate the development of clinically serious ketoacidosis **[R5 & R6].**

3. References to the research

All outputs listed below are from peer-reviewed journals, half are Q1 or Q2 (JCR). Nearly all have either UK academic or NHS collaboration with half acknowledging external funders (ERDF, ESF, and Welsh Office of Research Development). The body of work is underpinned by competitively won grant awards totalling GBP78,226. This research has made important contributions to the discipline internationally, powered subsequent grant income of GBP694,000 and contributes important knowledge to the field with lasting influence.

[R1] Turner, D., Luzio, S., Gray, B.J., Dunseath, G., Rees, E.D., **Kilduff, L.P.,** Campbell, M.D., West, D.J., Bain, S.C., & **Bracken, R.M.** (2015). Impact of single and multiple sets of resistance exercise in type 1 diabetes. *Scandinavian Journal of Medicine and Science in Sports*, 25 (1), e99-e109. doi.org/10.1111/sms.12202

[R2] Turner, D., Gray, B.J., Luzio, S., Dunseath, G., Bain, S.C., Hanley, S., Richards, A., Rhydderch, D.C., Ayles, M., **Kilduff, L.P.,** Campbell, M.D., West, D.J., & **Bracken, R.M.** (2016). Similar Magnitude of Post-Exercise Hyperglycemia Despite Manipulating Resistance Exercise Intensity in Type 1 Diabetes Individuals. *Scandinavian Journal of Medicine and Science in Sports*, 26 (4), 404-412. doi.org/10.1111/sms.12472

[R3] Turner, D., Luzio, S., Gray, B.J., Bain, S.C., Hanley, S., Richards, A., Rhydderch, D.C., Martin, R., Campbell, M.D., **Kilduff, L.P.**, West, D.J., & **Bracken, R.M.** (2016). Algorithm that delivers an individualized rapid-acting insulin dose after morning resistance exercise counters post-exercise hyperglycaemia in people with Type 1 diabetes. *Diabetic Medicine*, 33 (4), 506-510. doi.org/10.1111/dme.12870

[R4] Campbell, M.D., Walker, M., **Bracken, R.M.**, Turner, D., Stevenson, E.J., Gonzalez, J.T., Shaw, J.A., & West, D.J. (2015). Insulin therapy and dietary adjustments to normalize glycemia and prevent nocturnal hypoglycemia after evening exercise in type 1 diabetes: a randomized controlled trial. BMJ Open Diabetes Research & Care, 3, e000085. doi.org/10.1136/bmjdrc-2015-000085

[R5] Campbell, M.D., Walker, M., Trenell, M.I, Luzio, S., Dunseath, G., Turner, D., **Bracken, R.M.**, Bain, S.C., Russell, M., Stevenson, E.J., & West, D.J. (2014). Metabolic Implications when Employing Heavy Pre- and Post-Exercise Rapid-Acting Insulin Reductions to Prevent Hypoglycaemia in Type 1 Diabetes Patients: A Randomised Clinical Trial. *PLoS One,* 23;9 (5), e97143. doi.org/10.1371/journal.pone.0097143

[R6] Bracken, R.M., West, D.J., Stephens, J.W., **Kilduff, L.P.**, Luzio, S., & Bain, S.C. (2011). Impact of Pre-Exercise Rapid-Acting Insulin Reductions on Ketogenesis Following Running in Type 1 Diabetes. *Diabetic Medicine,* 28 (2), 218-222. doi.org/10.1111/j.1464-5491.2010.03162.x

Grants:

Underpinning the research
[G1] Bracken, R.M. [Principal Investigator]. (2011-2014). Nutrition, Physical Exercise and Diabetes. European Union's Convergence programme. Knowledge Economy Skills Scholarships. European Social Fund (ESF). Welsh Government. GBP65,000.
[G2] Bracken, R.M. [Co Investigator]. (2011). Metabolic and Glycaemic responses to reductions in rapid-acting insulin dose after running exercise in type 1 diabetes. Diabetes UK. GBP13,226.

Pathway to impact
[G3] Bracken, R. [Principal Investigator]. (2016). Exploration of alterations in insulin aspart on a background of degludec around exercise in people with type 1 diabetes. Novo Nordisk A/S. GBP156,000
[G4] Bracken, R. [Principal Investigator]. (2018). A comparative trial exploring impact on Fiasp or aspart on glycaemic responses to exercise in patients with type 1 diabetes. Novo Nordisk A/S. GBP360,000.
[G5] Bracken, R. [Principal Investigator]. (2017-2019). Exploring exogenous insulin alterations around physical exercise in type 1 diabetes. COFUND, EU post-doctoral fellowship. GBP178,000.

4. Details of the impact

The pathways to impact have arisen through Dr Bracken's esteem within the field of diabetes related research. Dr Bracken's sustained contribution of high-quality clinical trials that provide real world solutions for diabetes patients, resulted in a range of partnerships spanning healthcare, elite sport and industry which have subsequently created impacts with global reach.

Improved International Diabetes Clinical Practice Guidelines, Recommendations and Consensus Statements

Dr. Bracken's research has been used to support clinical practice guidelines, recommendations and consensus statements published by leading International diabetes organisations including Diabetes Canada, International Society for Paediatric and Adolescent Diabetes (ISPAD), American Diabetes Association, and Juvenile Diabetes Research Foundation (JDRF) **[Table 1]**. These guidelines and recommendations have global reach because they also appear in high-quality international journals (e.g., Diabetes Care and Lancet Diabetes and Endocrinology) and their impact is significant because they serve as a primary reference point and evidence base for diabetes clinicians and healthcare professionals working with and advising T1D patients. An illustration of these wider impacts on clinical practice and patient outcomes is highlighted by a quote from the head of one diabetes outpatient clinic in Europe **[C1]**:

"*Overall, we find outpatients are benefitting from the implementation of insulin alteration strategies for both strength and endurance exercises and are encouraged to see the improvement in motivation in patients in their continuation of regular physical activity. His* [Dr Bracken's] *principles, borne out of clinical research studies, improve our daily practice and contribute to better outcomes for patients*".

Table 1 Swansea University Research Impact on Diabetes Clinical Practice Guidelines and Recommendations
Document: Diabetes Canada Clinical Practice Guidelines 2018: Physical Activity and Diabetes. *Canadian Journal of Diabetes*, 42 (S1), S54-S63. doi.org/10.1016/j.jcjd.2017.10.008 **Impact: R4 and R5** provided key underpinning evidence to support the recommendations on how to reduce the risk of hypoglycaemia during and following exercise by "*reducing the bolus dose of the insulin that is most active at the time of exercise (85* ***[R4]****)"* or by *"reducing total daily basal insulin by 20% for days when they are physically active (89* ***[R5]****).* **R2 and R3** provided the evidence to support the recommendation to *"give a small bolus of rapid-acting insulin during*

exercise recovery (97 ***[R3]****)"* to address the rise in blood glucose that can occur *"with brief intense exercise, such as…resistance training (93* ***[R2]****)"*

Document: Physical Activity/Exercise and Diabetes: A Position Statement of the American Diabetes Association 2016. *Diabetes Care*, 39 (11), 2065-2079. doi.org/10.2337/dc16-1728

Impact: R1-R5 provided key underpinning evidence to support recommendations on how to minimise exercise-related adverse in events in people with diabetes. **R4** created the recommendation that "*Risk of nocturnal hypoglycaemia following physical activity may be mitigated with reductions in basal insulin doses, inclusion of bedtime snacks, and/or use of continuous glucose monitoring".* Specific recommendations on reductions in pre-exercise meal insulin doses for different intensities and durations of aerobic exercise were made based on **R5**. **R1 and R2** provided evidence to support statements that *"very intense exercise like powerlifting may promote hyperglycaemia"*, whilst **R3** was used to create the recommendation that *"Exercise induced hyperglycaemia…may be modulated with insulin administration".*

Document: International Society for Adolescent and Paediatric Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2018: Exercise in Children and Adolescents with Diabetes. *Pediatric Diabetes*, 19 (S27), 205-226. doi.org/10.1111/pedi.12755

Impact: R6 provided evidence to support the clinical safety of recommendations to reduce insulin dose post exercise because *"patients can be reassured that reducing insulin down to 25% of pre-exercise doses does not make later ketosis more likely (51* **[R6]***)".*

Document: Exercise Management in Type 1 Diabetes: A Consensus Statement 2017. *Lancet Diabetes Endocrinology*, 5 (5), 377-390. doi.org/10.1016/S2213 8587(17)30014-1

Impact: [R1-3] provide key supporting evidence for sections on how to correct hyperglycaemia during and following resistance exercise, whilst **[R4-6]** support recommendations on how to reduce hypoglycaemia during and following aerobic exercise. **[R6]** supports the clinical safety of the recommendations for insulin dosing strategies.

Juvenile Diabetes Research Foundation (JDRF) Peak Performance Programme:

Dr Bracken's research contributed to the development of the world's first T1D physical activity educational programme, 'JDRF Peak Performance', a USD5,000,000 funded project, that created and delivered a curriculum globally to address a significant knowledge gap in the T1D healthcare community (endorsed in the UK by the Association of British Clinical Diabetologists). Dr. Bracken was invited to contribute to the development and delivery of the programme across the US, Canada, Australia and Europe, and his research *"provided the key underpinning evidence for a large portion of the programme content"* **[C2]**. This programme aimed to provide research-based information to diabetes clinicians, T1D patients and carers about the principles of good glucose management around exercise. Since its launch in 2017, JDRF Peak has educated and improved the knowledge of over 5,000 such workshop participants [**C2-5**] and has reached many more since being made available online. In 243 responses from a survey of clinicians at one workshop site, 100% reported that the course had enhanced their knowledge, 96% said it would allow them to implement new information and skills in their practice, and approximately 50% reported that it would either directly enhance patient outcomes or allow the creation/revision of protocols, policies and procedures in their organisation **[C4-5]**. US and European patients reported that the course was useful and relevant (95% strongly agree/agree), helped them better understand the factors influencing glucose control (89% strongly agree/agree) and helped them to improve judgement around exercise (94% strongly agree/agree) **[C4-5]**.

Changing practice to maximise performance in professional cyclists with T1D:

Our research has also been used in elite cycling to inform and change sport science support and rider practices of Team Novo Nordisk, the world's first and only UCI-accredited professional cycling team comprised entirely of riders with T1D. Their mission statement is to '*inspire, educate and empower those affected by diabetes'*. Following an invite to form a global research group of international diabetes and exercise experts, Dr Bracken and his team worked with this cycling team to impart knowledge of effective strategies that mitigate risk of exercise-induced dysglycaemia, evidenced by Dr Bracken's research **[R1-6]**. Recent published observational studies reveal the excellent glycaemia during team training and competition day that improve and empower them to maximise their performance **[C6].** Excerpts from a letter by Team Novo Nordisk Head of Performance demonstrates the significance of this impact **[C7]**:

"*This research has resulted in a change in the practices of our team of Sport Science staff at Team Novo Nordisk…it has allowed us to apply clear and effective advice to each of our athletes about adjustments in insulin dose/timing to 1) ensure good glycaemic regulation, and 2) optimise performance during training and competition."*

"Dr Brackens research has had important significance and impact….it has improved daily practices behind glucose management and riders' performance, increasing awareness on the association between glucose control and performance, and detailing more the strategies that each of our athletes need to perform at their very best. 2019 has been the most successful year in UCI rankings for Team Novo Nordisk."

Supporting global market access for low glycaemic index carbohydrates:

Beneo, a global sugar company, manufactures Palatinose™, a carbohydrate with a low blood glycaemic response. In our research, feeding Palatinose™ before exercise improved glycaemia, protected against hypoglycaemia and maintained run performance in patients with T1D. In addition, a Palatinose™-containing meal and bedtime snack improved night-time glycaemic control and reduced the risk of hypoglycaemic episodes **[R4]**. These findings were used as *"key supporting evidence"* **[C8]** for a white paper on Palatinose™ published in 2017 [**[C9]:** page 9] that was commercially beneficial and

"allowed us [Beneo] *to achieve approval for the use of isomaltulose (Palatinose™) as a functional carbohydrate from various regulatory bodies worldwide, including major markets like the US the European Union and its 27 Member States, Australia/New Zealand, Canada, Brazil and Argentina, or the confirmation of its food status in over 20 further countries worldwide. The impact of this for our business has been significant because it has allowed us to target Palatinose™ into new products and markets"* **[C9]**.

5. Sources to corroborate the impact

Where organisations provide testimonials below, in what capacity they are involved with the impact follows in brackets:

[C1] Letter, Head of Outpatient Clinic for Diabetes, Physical Activity and Exercise, Medical University Graz, Austria (Reporter)
[C2] Letter: Chief of Staff, Juvenile Diabetes Research Foundation (JDRF) (Reporter)
[C3] JDRF PEAK Programme summary; research studies on p17-18, 25, 31
[C4] JDRF PEAK Programme Assessment Summary
[C5] Healthcare professional and patient feedback from JDRF Global events
[C6] Published Paper to support maximising elite cyclist performance: PDF
[C7] Letter: Head of Physiology, Team Novo Nordisk (Reporter)
[C8] Letter: Head of Nutrition Communication, Beneo (Reporter)
[C9] White paper on *Palatinose™ (isomaltulose).* Page 9 and references.