**University of Leicester**

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| **Project Reference** | BRC Studentships |

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**Section 2 – *Project Information***

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| **Project Title** | ​The weight loss independent effects of new obesity pharmacotherapies on glycaemia, cardiometabolic parameters and weight regulation mechanisms​ in people with obesity and type 2 diabetes. |
| **Project Highlights:** | 1. | Development of advanced experimental medicine skills (including appetite, glycaemia and body composition assessments) |
| 2. | Weight loss interventions through low calorie diets and new obesity pharmacotherapies |
| 3. | Fully funded NIHR BRC PhD Scholarship (NIHR Leicester BRC) with support and mentoring by leading experts at the field of obesity and type 2 diabetes.  |
| **Project Summary**  |
| **Background:** ​Obesity account for 44% of type 2 diabetes (T2D) cases worldwide.1 In people with obesity and recent onset T2D, 64% of those who achieved and maintained ≥10% weight loss (WL) with a low calorie diet could achieve T2D remission at 2 years.2 The latest ADA/EASD consensus guideline for T2D management recommends 5% to 15% WL as a key component of care to improve quality of life (QoL) and prevent complications.3 These WL targets are based mainly on data from intensive lifestyle interventions and bariatric surgery.4 However, recent developments in obesity pharmacotherapy have transformed the management of T2D through combination of effective glycaemia reduction together with “double digit” (≥10%) WL.5-9 Gut hormone-based pharmacotherapies have also pleiotropic effects which are independent of WL including improvement in B-cell function, appetite suppression and reduction in postprandial inflammation which may contribute to their cardio- and reno-protective effects.10,11  The understanding of the weight independent cardiometabolic and glycaemic benefits that occur by achieving the recommended WL targets with gut-hormone based therapies vs low calorie diets will provide evidence for personalised WL targets in people with obesity and recent onset T2D, based on their selected treatment. ​ **Aim:** ​To investigate the weight independent effects of gut hormone-based obesity pharmacotherapies on glycaemia, cardiometabolic health and weight regulatory mechanisms in people with obesity and recent onset T2D. ​ **Research Plan:** For people with obesity and recent onset T2D, a comparison of glycaemic, cardiometabolic and appetite parameters will be conducted before and after achieving equivalent WL targets (5%, 10% and 15%) through gut-hormone based obesity pharmacotherapy (as adjunct to a moderate intensity lifestyle modification) vs an intensive lifestyle intervention (low calorie diet). Outcomes studied will include continuous glucose monitoring [time in range (primary outcome), glycaemic variability], HbA1c, food intake, gut hormones, food preferences, resting metabolic rate, 24-h movement profiles via accelerometry, body composition, QoL, B-cell function and pulse wave velocity. **Expected outcomes and impact:** ​This work will provide important data on the WL independent effects of gut hormone-based obesity pharmacotherapies in people with obesity and recent onset T2D and will support the development of personalised interventions for WL. Study outcomes will be disseminated at international conferences and will be published in high impact, international peer-reviewed journals.​  |
| **References**1. Leitner DR, Frühbeck G, Yumuk V, et al. Obesity and Type 2 Diabetes: Two Diseases with a Need for Combined Treatment Strategies - EASO Can Lead the Way. *Obes Facts* 2017; **10**(5): 483-92. 2. Lean MEJ, Leslie WS, Barnes AC, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. *Lancet Diabetes Endocrinol* 2019; **7**(5): 344-55. 3. Davies MJ, Aroda VR, Collins BS, et al. Management of Hyperglycemia in Type 2 Diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2022; **45**(11): 2753-86. 4. Lingvay I, Sumithran P, Cohen RV, le Roux CW. Obesity management as a primary treatment goal for type 2 diabetes: time to reframe the conversation. *Lancet* 2022; **399**(10322): 394-405. 5. Papamargaritis D, le Roux CW, Holst JJ, Davies MJ. New therapies for obesity. *Cardiovasc Res* 2022. 6. Frías JP, Davies MJ, Rosenstock J, et al. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. *N Engl J Med* 2021; **385**(6): 503-15. 7. Jastreboff AM, Aronne LJ, Ahmad NN, et al. Tirzepatide Once Weekly for the Treatment of Obesity. *N Engl J Med* 2022; **387**(3): 205-16. 8. Wilding JPH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med* 2021; **384**(11): 989. 9. Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet* 2021; **397**(10278): 971-84. 10. Drucker DJ. Mechanisms of Action and Therapeutic Application of Glucagon-like Peptide-1. *Cell Metab* 2018; **27**(4): 740-56. 11. Thomas MC, Coughlan MT, Cooper ME. The postprandial actions of GLP-1 receptor agonists: The missing link for cardiovascular and kidney protection in type 2 diabetes. *Cell Metab* 2023; **35**(2): 253-73.  |