National Institute for Health and Care Excellence

IP1846 - Endoscopic duodenal mucosal resurfacing for insulin resistance in type 2 diabetes

IPAC date: 14 March 2024

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Com. no.	Consultee name and organisation	Sec. no.	Comments	Response Please respond to all comments
			Comments on the draft recommendations	
1.	Consultee 1 Clinician	1	No comments but I agree with the recommendations.	Thank you for your comment.
2.	Consultee 2 Fractyl Health	1.2	Based on currently available data, DMR provides an adequate benefit/risk profile for certain populations of individuals with type 2 diabetes. DMR provides a viable treatment alternative for type 2 diabetics whose blood glucose is poorly controlled despite insulin intensification. Furthermore, NICE Guidance (Obesity, identification assessment and management clinical guideline Published: 27 November 2014 Last updated: 26 July 2023) recommends bariatric surgery for certain populations of type 2 diabetics (""BMI of 30 kg/m2 to 34.9 kg/m2 who have recent-onset type 2 diabetes and who are also receiving, or will receive, assessment in a specialist weight management service""). DMR provides a less invasive treatment alternative to bariatric surgery for this population and should be considered for use. The current guidance fails to adequately consider these populations of individuals and the associated treatment alternatives for which DMR may provide a more favorable benefit/risk ratio.	Thank you for your comment. The guidance is for insulin resistance in type 2 diabetes and the committee makes recommendations based on its assessment of the available evidence on the efficacy and safety of the procedure for the specific indication. 'Why the committee made these recommendations' is detailed in the final guidance.
			Comments highlighting ongoing studies	
3.	Consultee 2 Fractyl Health	**1**	Fractyl Health is actively enrolling subjects in two formal research studies; a double-blind, randomized, control trial and a real-world evidence registry. The RCT is being conducted across sites in the US, EU, and multiple sites in the UK. Up to a total of 465 subjects will be enrolled across an open-label training phase followed by a double-blind, randomized phase. Study data is expected to be available in early 2025. The registry is being conducted among multiple sites in Germany. Approximately 100 subjects will be enrolled, treated, and followed-up with in a real-world evidence setting for up to 24 months. Interim study data is expected to be available in early 2025. Based upon the on-going formal research activities Fractyl recommends that publishing of the final guidance is delayed until these studies have been completed and provide the additional research requested. Fractyl can provide copies of both study protocols upon request.	Thank you for your comment. The RCT (NCT04419779) was already included in the overview. The registry of patients undergoing the procedure in Germany (NCT06256497) has been included in the overview. The committee makes recommendations based on its

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				assessment of the available evidence on the efficacy and safety of the procedure. The committee has considered the comment and decided not to delay publication. Section 3.7 has been added, noting that the guidance will be considered for review when new key evidence is published.
4.	Consultee 2 Fractyl Health	1.3	Fractyl Health is actively enrolling subjects in two formal research studies; a double-blind, randomized, control trial (RCT) and a real-world evidence registry (Registry). Each point below will be addressed by both the RCT and Registry, as detailed for each.	Thank you for your comment. Please refer to response 3.
5.	Consultee 2 Fractyl Health	1.3	The RCT will evaluate percent change from baseline in insulin total daily dose at week 24 and 48 as well as the proportion of subjects who discontinue insulin at week 24 and 48. The Registry will assess the change in pharmacologic burden up to 24 months post DMR procedure, including medication type, dose, and frequency.	Thank you for your comment. Please refer to response 3.
6.	Consultee 2 Fractyl Health	1.3	The on-going RCT includes subjects with type 2 diabetes whose blood glucose is inadequately controlled despite oral glucose lowering medications and insulin therapy. The real-world Registry enrolls subjects in alignment with the Revita System's approved indications for use; type 2 diabetics who have preserved pancreatic beta cell function and whose diabetes is poorly controlled despite oral and/or injectable glucose lowering medications and/or long-acting therapy. This population of type 2 diabetics is currently underserved as existing treatment options (pharmacotherapy) have proven ineffective at controlling their diabetes.	Thank you for your comment. Please refer to response 3.
7.	Consultee 2 Fractyl Health	1.3	Within the RCT the DMR procedure will be performed among all training phase subjects as well those randomized to DMR during the randomized phase. All subjects in the Registry will receive the DMR procedure according to its approved label. Fractyl Health provides training to all first-time users.	Thank you for your comment. Please refer to response 3.

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8.	Consultee 2 Fractyl Health	1.3	Within the RCT, quality of life will be assessed via the Diabetes Treatment Satisfaction Questionnaire, one of the most widely used questionnaires in the field of diabetes. The Registry will assess quality of life via several patient reported outcome (PRO) questions. As of writing, 16 subjects within the Registry have reached 1 month follow-up post DMR. Of these subjects, 14 (87.5%) indicated they would undergo the procedure again, 15 (93.75%) indicated that they would recommend the procedure to a friend or relative with type 2 diabetes. Furthermore, the median rating on a scale from 1 to 10 for perceived success of the procedure and quality of life improvement were both 10.	Thank you for your comment. Please refer to response 3.
9.	Consultee 2 Fractyl Health	1.3	The RCT will evaluate change from baseline in HbA1c (DMR vs Sham) at 24 and 48 weeks as well as proportion of subjects who achieve an HbA1c of less than or equal to 7% (DMR vs Sham) at 24 and 48 weeks. The Registry will seek to characterize the effects on glycemia up to 24 months post DMR procedure, including change from baseline HbA1c, FPG, among others.	Thank you for your comment. Please refer to response 3.
10.	Consultee 2 Fractyl Health	1.3	All adverse events during the course of enrollment will be captured within the RCT. Safety endpoints will further evaluate incidence and event rates of hypoglycemic events, device- or procedure-related serious adverse events, unexpected adverse device effects, and adverse events of special interest. Within the Registry, adverse events and serious adverse events definitely or probably related to the DMR procedure will be evaluated.	Thank you for your comment. Please refer to response 3.
11.	Consultee 2 Fractyl Health	1.3	The RCT will evaluate the outcomes discussed above out to 48 weeks post DMR procedure. The Registry will evaluate outcomes up to 24 months post DMR procedure.	Thank you for your comment. Please refer to response 3.
12.	Consultee 2 Fractyl Health	1.3	This RCT is supported by a First-In-Human (FIH) Study, as well as 2 other open-label prospective studies (INSPIRE Study and Revita-1 Study) and includes data follow-up up to 24 months. The studies corroborate the findings that DMR produces significant improvements in glycemic outcomes among type 2 diabetics with inadequately controlled blood glucose despite insulin therapy.	Thank you for your comment. Please refer to response 3.
13.	Consultee 2 Fractyl Health	Overview	Furthermore, a real-world evidence registry is being conducted in Germany to gather additional safety and efficacy data on the Revita System. Up to 100 patients will be followed for 24 months post DMR procedure. Interim Registry data will be available in early 2025.	Thank you for your comment. Please refer to response 3.

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			Comments relating to the procedure safety	
14.	Consultee 2 Fractyl Health	1.3	"Uncertainties about the safety" are mainly focused on events of stenosis and perforation which are based on early experience with the DMR procedure among a limited population. Since this early experience, the catheter design has changed (incorporating 2 catheters into the current single catheter and changing from a stiff stainless steel guidewire to a nitinol with floppy tip guidewire) and Fractyl provides more extensive training to endoscopy teams prior to use (to require the endoscopist to identify the Treitz flexure at the time of placing the guidewire so it can be avoided, and to advance the catheter and scope together rather than independently, instructing physicians to NOT advance the endoscope with excessive force). The overwhelming majority of adverse events observed are risks typically expected for an upper endoscopic procedure and anesthesia use (difficulty swallowing, sore throat, malaise, fatigue, etc.) or mild GI symptoms which are well documented with the DMR procedure (abdominal pain, diarrhea, nausea, etc.). Thus, conclusions regarding "uncertainties about the safety" are disproportionally weighted in favor of early limited use of the system (which have been since mitigated) as opposed to the more substantial safety data.	Thank you for your comment. The committee makes recommendations based on its assessment of the available evidence on the efficacy and safety of the procedure for the specific indication. Section 3.5 has been amended.
15.	Consultee 2 Fractyl Health	3.3	Perforation and duodenal stenosis reflect early limited use of the system (which have been since mitigated) and not the more substantial safety data.	Thank you for your comment. Section 3.3 describes the key safety outcomes identified from the published evidence and from professional experts.
16.	Consultee 2 Fractyl Health	Overview	Jejunal perforation occurred due to self-described operator error in excessive force used advancing an endoscope when the endoscopist did not recognize he had reached the Treitz flexure. Training has been changed to mitigate this in two ways: to require the endoscopist to identify the Treitz flexure at the time of placing the guidewire so it can be avoided, and to advance the catheter and scope together rather than independently, instructing physicians to NOT advance the endoscope with excessive force.	Thank you for your comment. Please refer to response 14.

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17.	Consultee 2 Fractyl Health	3.5	Bullet 3: Early clinical experience utilized a previous generation of the catheter system involving the use of 2 catheters. Since then, the functions of the 2 catheter system has been incorporated in the a single catheter which was used in the Revita-1, Revita-2, and INSPIRE Studies as will be continue to be used in the on-going RCT and Registry. As such, it can be concluded that this technology is not longer evolvingand the safety of the current product has been demonstrated.	Thank you for your comment. Please refer to response 14.
			Comments on the condition and current treatments	
18.	Consultee 2 Fractyl Health	2	This narrative fails to capture the progressive nature of type 2 diabetes. As blood sugar rises, complications increase. A greater disease burden allows for more risk tolerance in treatment modalities such as insulin intensification and bariatric surgery which are not detailed in the following section. Therefore DMR is an appropriate treatment alternative for this population of type 2 diabetics.	Thank you for your comment. This section of the guidance is intended to be a summary of the condition. 'Progressive' has been added to the condition description.
19.	Consultee 2 Fractyl Health	Overview (indications and current treatment)	This narrative fails to capture the progressive nature of type 2 diabetes. As blood sugar rises, complications increase. A greater disease burden allows for more risk tolerance in treatment modalities such as insulin intensification and bariatric surgery (see NICE Guidance on Obesity, identification assessment and management clinical guideline Published: 27 November 2014 Last updated: 26 July 2023) which are not detailed in the following section. Therefore DMR is an appropriate treatment alternative for this population of type 2 diabetics.	Thank you for your comment. Please refer to response 18. The list of current treatments and alternatives is not intended to be definitive. It does not include the procedure being assessed.
20.	Consultee 2 Fractyl Health	2.1	This narrative does not consider bariatric surgery which may be a viable treatment option for certain overweigh adults with type 2 diabetes. The DMR procedure is a less invasive treatment alternative to bariatric surgery and thus may be favorable for this population and thus the assessment of DMR against currently available treatment alternatives is incomplete.	Thank you for your comment. The list of current treatments and alternatives is not intended to be definitive. It does not include the procedure being assessed.
21.	Consultee 2 Fractyl Health	2.2	"Furthermore, these treatments rely on patient adherence to achieve their benefits, a significant shortcoming for long-term success and patient treatment satisfaction.* The DMR procedure does not rely on patient adherence to achieve its benefit and	Thank you for your comment. Please refer to response 19.

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			thus may provide an appropriate alternative to type 2 diabetics whose blood glucose is poorly controlled despite insulin intensification. *There is broad consensus throughout the literature indicating poor medication adherence among the type 2 diabetes population which in turn is associated with poorer health outcomes. 1. Polonsky WH, Henry RR. Poor medication adherence in type 2 diabetes: recognizing the scope of the problem and its key contributors. Patient Prefer Adherence. 2016;10:1299-1307. Published 2016 Jul 22. doi:10.2147/PPA.S106821 2. Iglay K, Cartier SE, Rosen VM, et al. Meta-analysis of studies examining medication adherence, persistence, and discontinuation of oral antihyperglycemic agents in type 2 diabetes. Curr Med Res Opin. 2015;31(7):1283-1296. doi:10.1185/03007995.2015.1053048 3. Evans M, Engberg S, Faurby M, Fernandes JDDR, Hudson P, Polonsky W. Adherence to and persistence with antidiabetic medications and associations with clinical and economic outcomes in people with type 2 diabetes mellitus: A systematic literature review. Diabetes Obes Metab. 2022;24(3):377-390. doi:10.1111/dom.14603 4. Ligthart S, van Herpt TT, Leening MJ et al (2016) Lifetime risk of developing impaired glucose metabolism and eventual progression from prediabetes to type 2 diabetes: a prospective cohort study. Lancet Diabetes Endocrinol 4(1):44–51. https://doi.org/10.1016/S2213-8587(15)00362-9"	This section of the guidance is intended to list the treatment options rather than detailing the factors that affect their benefits. None of the cited studies meet the inclusion criteria, because they do not describe the intervention that is being assessed.
			Comment on the key efficacy outcomes	
22.	Consultee 2 Fractyl Health	3.2	Weight reduction should additionally be considered a key efficacy outcome with DMR.	Thank you for your comment. 'Weight loss' has been added as a key efficacy outcome.

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			Comments on the committee comments	
23.	Consultee 2 Fractyl Health	3.5	Bullet 2: Revita System has shown to have several metabolic benefits in addition to blood glucose control including reduced liver fat and weight loss and maintenance.	Thank you for your comment. 'Other metabolic disturbances' has been added.
24.	Consultee 2 Fractyl Health	3.5	Bullet 4: We agree with the sentiment of this point but do not think it clearly expresses the training requirement. We think it would be more helpful to say that use of the technology should be by clinicians with experience of advanced endoscopic techniques and who have had specific training in the DMR procedure.	Thank you for your comment. Section 3.5 has been amended, to state that the procedure should be done by clinicians with experience of advanced endoscopic technique and specific training in the DMR procedure.
			Comments on the procedure description	
25.	Consultee 2 Fractyl Health	Overview (procedure technique)	Circumferential ablations are done for the length of the duodenum distal to the Ampulla of Vater to the Treitz flexure. A typical DMR procedure averages 6 ablations.	Thank you for your comment. This section is intended to describe the common approach to the procedure technique based on the key papers included in the overview. The procedure description has been amended.
26.	Consultee 2 Fractyl Health	Overview (procedure technique)	Duodenal mucosa dysfunction has been shown to contribute to the development of insulin resistance in animal models. In humans with hyperglycemia, increased small intestinal cell mass have been directly correlated to increase HbA1c levels providing a clear link between pathophysiological mucosal changes and metabolism.	Thank you for your comment. This section is intended to describe the procedure technique in the key studies listed on the evidence summary.

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			Aliluev A, Tritschler S, Sterr M, et al. Diet-induced alterations in ISC function underlies obesity and pre-diabetes. Nature Metabolism, in revision. 2021;3(September). doi:10.1038/s42255-021-00458-9 Taylor SR, Ramsamooj S, Liang RJ, et al. Dietary fructose improves intestinal cell survival and nutrient absorption. Nature. 2021;597(7875):263-267. doi:10.1038/s41586-021-03827-2 Verdam FJ, Greve JWM, Roosta S, et al. Small intestinal alterations in severely obese hyperglycemic subjects. The Journal of clinical endocrinology and metabolism. 2011;96(2):E379-83. doi:10.1210/jc.2010-1333	Studies that do not contain clinical information on efficacy and safety outcomes are not included in the overview, and are therefore not considered by the Committee. None of the cited studies meet the inclusion criteria, because they do not describe the intervention that is being assessed.
27.	Consultee 2 Fractyl Health	Overview (procedure technique)	This technique reflects early development of the technology which required 2 catheters to carry out both the saline lift and thermal ablation sequencies of the procedure. Both functions have since been incorporated into 1 catheter which represents the overwhelming majority of procedures done to date. A full DMR procedures is defined as the ablation of the anatomical distance of the duodenum from immediately beyond the ampulla of Vater to the ligament of Treitz. These ablations (usually at least 5) should be conducted a) without overlapping and b) minimizing gaps in between the areas of the mucosa that have been ablated.	Thank you for your comment. Please refer to response 25.
28.	Consultee 2 Fractyl Health	Lay description	The endoscope is only introduced prior to the catheter to conduct endoscopic evaluation and place a hemostasis clip to mark the Ampulla of Vater. The catheter does not go through the working channel of the endoscope, it is introduced prior to the endoscope and sits adjacent to it with the balloon always a few centimeters ahead. Suggested wording: ""In this procedure, a balloon catheter is passed through the mouth into the second section of the duodenum. An endoscope (a long, thin, flexible tube with a small camera and light on the end) is then passed alongside the balloon catheter, remaining just behind the balloon itself. The balloon is then inflated to expand the duodenal mucosa (lining).""	Thank you for your comment. The lay description has been changed in response to the comment.
			Comments on the overview	

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29.	Consultee 2 Fractyl Health	Overview (population and studies description)	Duodenal mucosa dysfunction has been shown to contribute to the development of insulin resistance in animal models. In humans with hyperglycemia, increased small intestinal cell mass have been directly correlated to increase HbA1c levels providing a clear link between pathophysiological mucosal changes and metabolism. Aliluev A, Tritschler S, Sterr M, et al. Diet-induced alterations in ISC function underlies obesity and pre-diabetes. Nature Metabolism, in revision. 2021;3(September). doi:10.1038/s42255-021-00458-9 Taylor SR, Ramsamooj S, Liang RJ, et al. Dietary fructose improves intestinal cell survival and nutrient absorption. Nature. 2021;597(7875):263-267. doi:10.1038/s41586-021-03827-2 Verdam FJ, Greve JWM, Roosta S, et al. Small intestinal alterations in severely obese hyperglycemic subjects. The Journal of clinical endocrinology and metabolism. 2011;96(2):E379-83. doi:10.1210/jc.2010-1333	Thank you for our comment. This section is intended to describe the key points relating to the population and studies included in the key evidence of the overview. Please refer to response 26.
30.	Consultee 2 Fractyl Health	Overview (population and studies description)	The substantially larger improvement seen within the Brazilian subgroup, especially among the sham group, was indicative of a deviation from the approved protocol. Upon further investigation with the sites, it was discovered that medication management was deviated from the protocol. Thus the European and Brazilian populations were analyzed among subgroups to determine if a true effect existed among the European population.	Thank you for your comment. The committee was aware that the Brazilian population had a more intensive approach to treatment of diabetes and dieting, which explains some of the HbA1c treatment effects. This is detailed in the overview.
31.	Consultee 2 Fractyl Health	Overview (validity and generalisability)	The substantially larger improvement in HbA1c seen within the Brazilian subgroup, especially among the sham group, was indicative of a deviation from the approved protocol. Upon further investigation with the sites, it was discovered that medication management was deviated from the protocol. Thus the European and	Thank you for your comment. Please refer to response 30.

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			Brazilian populations were analyzed among subgroups to determine if a true effect existed among the European population.	
32.	Consultee 2 Fractyl Health	Overview (validity and generalisability)	We agree that the DMR procedure itself is novel, but the underlying research for the fundamental principal of duodenal exclusion is robust. The exclusion of the duodenum from the passage of nutrients by surgical diversion results in weight-independent improvements in insulin resistance and insulin levels associated with a reduction in glucose in patients with T2D and reductions in liver fat and fibrosis in patients with NAFLD/NASH. Rubino F, Forgione A, Cummings DE, et al. The mechanism of diabetes control after gastrointestinal bypass surgery reveals a role of the proximal small intestine in the pathophysiology of type 2 diabetes. Annals of Surgery. 2006;244(5):741-749. doi:10.1097/01.sla.0000224726.61448.1b Rubino F, Marescaux J. Effect of duodenal-jejunal exclusion in a non-obese animal model of type 2 diabetes. Annals of Surgery. 2004;239(1):1-11. doi:10.1097/01.sla.0000102989.54824.fc Wickremesekera K, Miller G, DeSilva Naotunne T, Knowles G, Stubbs RS. Loss of insulin resistance after Roux-en-Y gastric bypass surgery: A time course study. Obesity Surgery. 2005;15(4):474-481. doi:10.1381/0960892053723402	Thank you for your comment. None of the cited studies meet the inclusion criteria, because they do not describe the intervention that is being assessed.
33.	Consultee 2 Fractyl Health	Overview (validity and generalisability)	Which includes UK sites and subjects.	Thank you for your comment. The validity and generalisability section already notes that the 2 most recent studies, Mingrone (2022) and van Baar (2022), included centres in the UK.
			Comment relating to a NICE guideline	
34.	Consultee 2 Fractyl Health	NICE guideline	NICE guideline on Obesity: identification, assessment and management (CG189; 2014, updated July 2023). Discusses recommendations for bariatric surgery among certain obese populations with type 2 diabetes.	Thank you for your comment.

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