Dear Editor,

Thank you for taking the time to allow us to revise this work. Enclosed is our detailed response to the reviewers' comments on the manuscript titled: "A Practical Guide for Using GLP-1 and Dual GIP and GLP-1 Receptor Agonists for the Management of Type 2 Diabetes Mellitus".

Additionally, the manuscript also went through professional language editing. Please let us know if we could be of any further assistance.

Sincerely,

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First Reviewer

Comment	Response
Title: The title should be changed. Practical Guide for Using GLP-1 and Dual GIP and GLP-1 Receptor Agonists for the Management of Type 2 Diabetes Mellitus in Clinical Practice. Please consider delete "in Clinical Practice" in the title.	The reviewer's comment has been reviewed, and the title has been changed. Line number 4-5
Abstract: The abstract should be concise. Please delete un-relevant part. Please unify the discerption of T2DM. And add the full name of GIP when it first appears.	The first reviewer's comment has been reviewed and the abstract has been modified and made more concise.

	Line number 68-75.
Background. This part is too long and contains lots of common information. Please delete irrelevant part to make it concise.	The first reviewer's comment has been reviewed and irrelevant information deleted while maintaining a solid background for the readers.
Methods. We searched PubMed using the terms GLP-1 AND (switch OR switching OR switched); and GLP-1 AND (once-daily OR "once daily") AND (once-weekly OR "once weekly") with no lower limit set for the date, using MeSH and free text terms to match relevant articles. No GIP?	The first reviewer's comment has been reviewed and the literature review methods have been clarified. GIP as a search term was used originally (methods section clarified) and has originally retrieved 25 results. All relevant articles were already included in the review. The exception was one article discussing the effect of renal impairment on the safety of Tirzepatide and a conclusion for the article has been added under section 3.6.3 and referenced. Line number 148,149 and Ref #104
Results. Part 3 is too long and this part should re-organize.	The first reviewer comment has been reviewed and part 3 has been modified, re-organized, and made more concise.
Please polish the sentence. Several grammar errors were found in the manuscript.	The first reviewer's comment has been reviewed and the manuscript has been edited by an English language editing service.

Second Reviewer

Comment	Response
Clear presentation that the application conditions of second-line and first-line treatment of GLP-1RA	The second reviewer's comment has been reviewed and text has been clarified. Line numbers 124-131, 134-135.
Not using GIP as a search term. Is it will miss some important articles? I think the number of searched articles is too small. The non-MeSH term "Switch", "once daily" and "once weekly" may also exclude some important articles.	The second reviewer's comment has been reviewed. GIP as a search term was used originally (methods section clarified) and has originally retrieved 25 results. All relevant articles were already included in the review. The exception was one article discussing the effect of renal impairment on the safety of Tirzepatide and a conclusion for the article has been added under section 3.6.3 and referenced. -Also, we used the "Switch" MeSH terms to include articles discussing the main objective of our review. In addition, "once daily" and "once weekly" were used to specify the frequency of drug administration that is commonly used in patients with diabetes. Line numbers 400-404 and Ref #104

-In table 1, the author said Lixisenatide had no dose adjustment for mild or moderate disease. Which kind of disease? - What the meaning of this sentence—"Oral Medications 1 hour before injection"? "Potential decrease in oral medications absorption"—which kind of medication?	- The second reviewer's comment has been reviewed and the point has been modified to mild or moderate renal impairment for more clarity (highlighted in yellow in Table 1). - All orally administered medications, in general, are recommended to be administered 1 hour before the Lixisenatide injection, no agent in particular. Language is now more clear for this sentence.
"In contrast, hypoglycemia risk was observed in 0.4% of individuals who received injectable semaglutide"—what is the dosage of semaglutide?	The second reviewer's comment has been reviewed and we clarified in the 40-week trial that the studied dose for the injectable semaglutide was 1 mg. Line numbers 244 and 250
In 3.1.3, the author said only 5% of patient had loss of appetite, 12% had diarrhea when receiving semaglutide. What is the dosage of semaglutide? Why the percentage is lower than clinical experience? Why diarrhea is more common than appetite loss?	The second reviewer's comment has been reviewed and our clarification is as follows: The semaglutide dose was 1 mg. Line numbers 244 and 250 Regarding the incidence of diarrhea, we found that this incidence varies in different trials and can reach up to 20% as in the STEP2 trial.

	In addition, we believe the incidence of loss of appetite is low since patients are expecting this as part of the goal of therapy, therefore not reporting it as a side effect.
What is the definition of hypersensitivity reactions?	The second reviewer's comment has been reviewed and our clarification is there is no defining features for hypersensitivity reactions were mentioned in the original trial. However, severity grades of the reactions were plainly categorized as mild, moderate, and severe.
In the first paragraph of 3.2, the reference is missing. Is there any reason that levothyroxine, phenytoin, and some antipsychotic medications, such as aripiprazole and olanzapine could decrease the efficiency of tirzepatide?	The second reviewer's comment has been reviewed and it has been deleted as the primary reference could not be found.
The logic of 3.2 should be amended. In the first paragraph of 3.2, the author said tirzepatide's efficacy could be decreased by some medicines. In the second paragraph of 3.2, the author said some other medications may decrease the hypoglycemic activities of GLP-1 RAs again. The same problem still exists in the third paragraph.	The second reviewer's comment has been reviewed and 3.2 section has been modified. Line number 261-274

In 3.3, the author said GLP-1RA could increase heart rate. However, as we all know, increased heart rate is not a protective effect to heart. How to explain it?	The second reviewer's comment has been reviewed and we acknowledged that GLP-1 RA treatment is associated with increased blood flow in various micro vessels, including those in the heart. However, we highlighted that this improved blood flow could be a result of an increased heart rate due to GLP-1 receptor activation. While increased heart rate might enhance blood flow, it doesn't necessarily mean it's a protective effect for the heart. Nevertheless, this part has been omitted to avoid confusion.
In 3.4, a table about the cardiovascular outcome of different hypoglycemia medicine is useful to understand this part of content.	The second reviewer's comment has been reviewed and a table for section 3.4 has been added. Table number 2 (highlighted in yellow) Line number 357
In 3.6, GLP-1 RA is contraindicated in acute pancreatitis. Is it necessary that GLP-1 RA should not be used in patients with a past history of pancreatitis?	The second reviewer's comment has been reviewed and our clarification is as follows: It was stated that GLP-1 RA should not be used in patients with history of pancreatitis in this article:

	(Collins L, Costello RA. Glucagon-Like Peptide-1 Receptor Agonists. 2023; PMID:31855395) "GLP-1 agonists should not be prescribed in patients with a history of pancreatitis and should be discontinued in those who develop pancreatitis while taking this medication". Section 3.6 subtitle was edited to clarify and include precautions to go in line with package insert information as well. Line numbers 385-391
In 3.6.3, the author said--In patients with renal insufficiency, liraglutide and dulaglutide should be used with caution. What grade of renal insufficiency should be descripted. Liraglutide and dulaglutide could be used in patients with eGFR above 15 ml/min according to drug instructions. It is not consistent with the second word of 3.6.3.	The second reviewer's comment has been reviewed and 3.6.3 section has been modified for clarity. Line numbers 400-404
In 3.6.5, what is the meaning of the last sentence? I think the description is confusing. In addition, there is new evidence to about the relationship of GLP-1 RA and papillary thyroid cancer. The author could add it.	The second reviewer's comment has been reviewed and 3.6.5 has been modified for clarity.

	-New evidence regarding the relationship of GLP-1 RA and papillary thyroid cancer has been added. Line number 417-434
-In 3.6.6, which kind of gallbladder disease should be avoid in the use of GLP-1 RA? -There is no adequate evidence that GLP-1 RA will worsen diabetic retinopathy.	The second reviewer's comment has been reviewed and 3.6.6 has been modified for clarity. -Acute gallbladder disease, like acute cholecystitis. -In the SUSTAIN 6 trial, worsening diabetic retinopathy and significant increase in diabetic retinopathy complications was reported with semaglutide use. Line number 440-441
I did not see enough data to support the conclusion in Table 2 in this manuscript. For example, why dulaglutide 1.5mg is equivalent to semaglutide 0.5mg? What is the efficiency of lowering HbA1c of dulaglutide 4.5mg or semaglutide 2mg?	The second reviewer's comment has been reviewed and our clarification is as follows: There is a lack of consensus on how to switch between the different GLP-1 and dual GIP GLP-1 RAs and there is no evidence on how to switch, so we highlighted clinical practice experiences in

	different practices at different settings inside and outside Saudi Arabia, hence this consortium research group. This was described in table 3. More text was added in the opening paragraph of section 4 to further clarify this regard. Line number 458-461
In section 4, the sixth paragraph, is the maximum therapeutic dose used for lowering glucose or losing weight? Make it clear please.	The second reviewer's comment has been reviewed, it is for lowering glucose (clarified) Line number 499
In 5.1, the first paragraph, if the inhibitory effect of GLP-1RAs on gastric emptying might be diminished or absent in patients with diabetic-related dysautonomia, why GLP-1RA should be contradicted in gastroparesis?	The second reviewer's comment has been reviewed and our clarification is as follows: Although the degree of gastric emptying effect of GLP-1RAs varies between patients, it is a dose-dependent effect, hence, the dose titration weight loss observed with these agents. In patients with gastroparesis, further worsening of gastroparesis symptoms is expected with GLP-1RAs therapy, and that's a main reason to avoid their use in this population.

In 5.5, which kind of bariatric surgery was done in the research?	The second reviewer's comment has been reviewed and our clarification is as follows: Regarding the hyperinsulinemia (hypoglycemia) effect, it is mentioned that the type is gastric bypass surgery. Regarding the psoriasis remission, it's modified now, and we mentioned that it's roux Y gastric bypass. Line number 584-587
Actually, there is no data support the use of GLP-1RA in hemodialysis patients as the author said. So the title of 5.6 should be revised.	The second reviewer's comment has been reviewed and our clarification is as follows: In this point, the author didn't mention that there is a benefit from using GLP-1RA in hemodialysis patient, but mentioned that there is some benefit of adding GLP-1RA in patient who have different levels of kidney dysfunctions. However, the title might have been confusing, so the title has been modified to: Use of GLP-1 or dual GLP-1/GIP Receptor Agonists in patients with renal insufficiency to further clarify this point.

	Line number 617
What is the percentage of hypoglycemia in Ramadan when using GLP-1RA?	The second reviewer's comment has been reviewed. All percentages are not significant (according to the reference), so we didn't add them previously, they are now added. Line number 674-678
There are many wrong gramma or improper description in this manuscript. For example, in abstract section, the second line, GLP-1Ras should be corrected to GLP-1 Ras. In the third line, Type should be in lower case. In the fourth line, "In addition to this class safety, they pose no risk related to hypoglycemia"- this sentence should be rephrased. In the fifth line, metformin is not a second-line agent. In the sixth line, there is an extra "is" in the sentence. In the seventh line, "We aim to provide a comprehensive guide regarding GLP-1 RAs and dual GIP and GLP-1 RA use in daily clinical practice" - this sentence should be rephrased.	The second reviewer's comment has been reviewed and this sentence is now rephrased. Line number 73-75

There are many similar problems in other sections. I think the writing should be major revised.	

***** END OF COMMENTS *****

Dear Editor,

Thank you for taking the time to allow us to revise this work. Enclosed is our detailed response to the reviewers' comments on the manuscript titled: "Practical guide: Glucagon-like peptide-1 and dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonists in diabetes mellitus".

Additionally, the manuscript also went through professional language editing. Please let us know if we could be of any further assistance.

Sincerely,

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Comment	Response
P3 in the introduction. -The fact that 'long-acting' GLP-1RA's have essentially replaced 'short-acting' should be stated-although exenatide BID is now 'off-patent'. - Induction of satiety may be unrelated to slowing of gastric emptying (eg Nutrients 2020:12;1962) - the potential implications of slowing of gastric emptying to alcohol absorption could be alluded to (eg Brit J Clin Pharmacol 2022:88;3421-7	-The reviewer's comment has been reviewed and the introduction has been modified. - The reviewer's comment has been reviewed and the satiety part has been deleted. - The reviewer's comment has been reviewed and slowing of gastric emptying effect on alcohol absorption has been added.
P14 - This discussion should acknowledge the lack of measurements of gastric emptying using precise methodology with longer-acting GLP-1RA's and the suboptimal assessment of gastrointestinal adverse effects by 'self-report' (eg Ann Int Med 2023:176;1542-3) Gastroparesis can only be determined by direct measurement (Diabetologia 2022;65;1981-93). - Recent evidence that GLP-1RA's may lead to intragastric retention of food at surgery/endoscopy despite 'adequate' fasting should be referred to.	- The reviewer's comment has been reviewed and the discussion of (Gastroparesis & inflammatory bowel disease) under the "Contraindications and precautions for GLP-1 and dual GIP and GLP-1 RA use" section has been modified accordingly. - This area has already been addressed in the section (Preoperative management of patients on GLP-1 or dual GLP-1/GIP Ras) under "other considerations".
p15 Cost considerations should include the use of exenatide BID compared to long-acting drugs	- The reviewer's comment has been reviewed and cost considerations of exenatide vs semaglutide use has been added.
p20 There is additional evidence that post-bariatric hypoglycaemia is related to elevated GLP-1 secretion (Rev Endocr Metab Disord 2023:24;1075-98)	- The reviewer's comment has been reviewed and the additional evidence has been added.
Throughout the review the authors must clarify the evidence base underpinning recommendations.	- The reviewer's comment has been reviewed and the review does point to where the evidence for recommendations came from with consideration to the fact that this is a rapidly developing field, with some areas not yet fully investigated or reported well in the literature.

***** END OF COMMENTS *****