Responding to Manuscript Reviewers: An Insider's Insight

Few manuscripts are accepted on first submission and eventual acceptance often depends on providing adequate responses to points raised by the editor and/or the reviewers. Ideally, the review will improve the quality of your work. Certainly, evidence suggests that manuscripts that undergo several peer review rounds perform better in terms of the number of citations they receive after publication [1].

A well-constructed response to the reviewers is the key to how well your 'corrected' manuscript will be received. Authors often focus heavily on providing a revised manuscript, whereas they rarely invest time devising a comprehensive document that summarises the changes made and the rationale behind the responses you make. We call this the response-to-reviewers document. Here we provide the collective insights from the Niche Science & Technology Medical Writing Team on how to create a winning response.

Before you start

Be grateful for the free review and suggestions on how to improve your manuscript

Adopt the position that responding to referee comments is just part of the publication process

Prepare to explain everything as thoroughly as you can

Track every change

Ensure you keep to the journals timelines

Prepare to succeed

Thank everyone (editor and referees)

As far as you can, accept the suggestions made by the referees

Adopt a logical and structured approach to your responses

Be succinct

Provide clear reasoning behind the rebuttal of specific points

Key Insights

When you submit a manuscript to a journal you can expect one of two responses: acceptance or rejection. Previously in our Insider's Insights we have dealt with how to handle rejection [2]. Here we give guidance on how best to address the required changes that more often than not accompany an acceptance for publication.

Peer review plays a vital role in research publishing and a revision of your manuscript is a key step in the process. However, knowing how to respond to reviewer's comments isn't always easy – get it right and you will see your manuscript published – promptly. Getting it wrong leads to rejection . So what can you do to increase your chances of success? Most importantly, clearly acknowledge the reviewer's time, comments and expertise. Thanking the reviewers in your response sets a positive tone at the outset, providing a base for an ongoing amicable exchange.

Timelines

When you do decide to revise and resubmit your manuscript, try very hard to meet whatever deadline the editor establishes. If you meet the editor's deadline, he or she may accept the manuscript forthwith. Or, if the modification has been substantial, the editor may return it to the same reviewers. Your manuscript will probably be accepted if you have clearly met or defended your paper against the previous criticisms.

On the other hand, if you fail to meet the deadline, your revised manuscript may be treated as a new manuscript and again subjected to full review, possibly by a different set of reviewers. It is wise to avoid this double jeopardy, plus additional review time.

Gatekeepers

Perhaps the most important point to remember when dealing with a request to modify your manuscript is that the editor is a mediator between you and the reviewers. If you deal with the editor respectfully, and if you can defend your work scientifically, most of your 'requests to modify' and even your 'rejections' will in time become published papers.

The editor and the reviewers are usually on your side. Their primary function is to help you express yourself effectively and provide you with an assessment of the science involved. It is to your advantage to cooperate with them in all ways possible.

Responding to referees is all about constructing a rational and succinct story. In providing the editor with a clear guide to the thinking behind your responses to the editor, you markedly reduce the potential for misunderstanding and therefore possible rejection. There are 10 important points to consider when preparing your response to reviewers.

The package

When replying to the editor you should view the response as a package composed of a letter to the editor, a response-to-reviewers document and a new version of the manuscript with the changes tracked (you may also want to submit a new 'clean' version of the manuscript).

In the letter to the editor, remember to thank them and the reviewers for their time and consideration. A template for your response letter can be found on page 6 and a response document from page 10 onwards. The response letter should provide a brief outline of how you have responded to the points raised, noting where new data and/or blocks of text have been added, data have been analysed differently and where you provided rebuttal to specific points.

Manuscript rejection is common

Pierson DJ. Respir Care 2004; 49:1246

Be comprehensive

Respond to every point raised by the reviewers [3]. Ensure that the editor can see that no point has been missed. Some reviewers raise complex issues that may require you to construct multi-component responses, teasing out single points to provide unambiguous answers for each. Miss nothing out – not even the most trivial point that might be addressed with one word answers. You may need to consider numbering the comments. Note that you should mimic any numbering system used by the reviewers when preparing your responses.

Gutted

Be prepared for reviewers to ask for great tracts of your carefully crafted manuscript to be gutted leaving the manuscript, in your opinion, lesser for the removal. This type of redaction often centres on the discussion and speculation over the contribution of your findings in the context of everyone else's observations.

Don't be despondent, it is an opportunity to provide a more succinct version of your argument after reflection – make sure you point this out in your response. However, it can also provide you with an opportunity to introduce more text in response to the omission in your previous manuscript that was identified by the reviewer.

At least 62% of published papers have been rejected at least once

Hall SA, et al., Epidemiol 2007; 18:262–265

Politeness

Always be polite in your responses but don't grovel. Particularly thank reviewers in those circumstances where they make an insightful suggestion that you incorporate into your work. You might even consider including a "thank you" in the manuscript's acknowledgements – though this may not be permitted by the journal – there is no harm in suggesting to the editor.

Authors often comment (off the record) on how one or other reviewer failed to demonstrate the intellectual capacity to make valid comment on their work [4]. Most probably this is not helped when reviewers have clearly not taken the care to construct full sentences or rational arguments to support their criticisms. In some cases the criticisms by reviewers feel biased leading to a feeling that they may be following their own agenda or have some conflict of interest. Your responsibility is to remain respectful. Remember that reviewers may very well read your response.

Be specific

Provide self-contained responses when making changes to any part of your manuscript – text, tables or figures. Give a detailed description as to where in the (original) manuscript your response refers to.

This makes it much easier for the editor to understand exactly what you changed without having to flick back and forth between the manuscript, your response and the reviewers comments. Resist the temptation to simply write "This has been addressed" or "Done" in all but the simplest responses to the simplest requests.

Response style

Adopt a response style and stick to it. At Niche Science & Technology the response-to-reviewers is often a complex document. In cases where several reviewers provide comprehensive comments on a reasonably long manuscript your response may be longer than the paper you submitted.

You can use changes in font to differentiate between different elements; such as the reviewer's comments, your responses and critical changes to the text in the manuscript. You may even use colour (judiciously). Give page and paragraph numbers for all changes you make. Help yourself further by providing a key to the response convention you have used in the letter to the editor or at the front of the response document.

If you are unable to address a point raised in the reviewer comments, explain your reasons for evasion. Do not blatantly ignore reviewer comments, while selectively answering a few.

Repeat yourself

When you have two or more seasoned reviewers they are likely to identify the same weak points of your manuscript, You may feel that you shouldn't need to repeat yourself. However, consider with care whether you refer the reviewer back to the original answer you made or provide the same answer twice. It could be that the points being made by the two reviewers are ever so slightly different.

Complete (all) requests

Incorporating all the requested changes should be your fall-back position, even if you feel that the reviewer is asking for an analysis or modification that is uninformative or otherwise flawed. All this puts you in a good position when the reviewer suggests something that is a step too far and asks for a modification that goes beyond what you feel is the scope of your work.

I expect the editor to accept all my papers, accept them as they are submitted, and publish them promptly. I also expect him to scrutinize all other papers with the utmost care, especially those of my competitors.

Earl H Wood

Mindful rebuttal

You may, on occasion, feel that a reviewer simply asks too much of you (or the work). In such cases it is acceptable to provide a reasoned and logical rebuttal. A general acquiescence on 95%+ of other requests will certainly support your case in these circumstances. Pick your battles carefully and provide a logical argument as to why you should not make the requested modification.

In some cases you may want to appeal to the editor's discretion – though this approach can delay publication unless you give them sufficient evidence to accept your argument without further consideration.

It is entirely possible that both reviewers and the editor seriously misread or misunderstood your manuscript. Even though you know that their criticisms are almost totally erroneous you might want to consider just how long it is going to take you to respond. Remember that you always have the option of submitting your manuscript to another journal, hoping that it will be judged more fairly.

Navigate opposing opinions

In some cases reviewers make recommendations for modifications that are diametrically opposed. For example, one reviewer may ask for data to be added to a table, whereas a second reviewer may ask for the table to be removed completely. In such situations you will need to consider both sides of the argument and select the option that best improves your manuscript. In some cases you may find that one reviewer takes issue with what you consider to be a critical point and the second has no issue with it.

Resist any temptation to play one reviewer off against the other. Reviewers are often selected because of their different areas of expertise, sinking your whole argument.

An interview with our Head of Medical Writing

Q What is the question about handling journal responses that writers ask you most often?

A When we prepare our response to reviewers we transcribe the points they raise into our response-to-reviewers document. For one reason or another these responses may include typo's, spelling mistakes and nonsensical statements. Our team often ask me if they should correct these before providing a response. I always tell our writers to copy the text exactly as it is supplied by the journal. This way the editor gets a better understanding of the challenge faced by the team in preparing its responses.

Q What is the best approach when preparing responses?

A People often say that less is more. And in many cases this is true. However, when responding to reviewers more is definitely more. The more time you give yourself the better your responses will be. More detail in your response will foster better understanding by your reviewers and the journal's editorial team. The more you incorporate your reviewers insights into the final manuscript the better it will be and the faster it will be published. However, keep your letter to the editor brief, they are usually very busy and have limited time

Clarity

Reception of your returned manuscript and responses at the editorial office will most likely be managed by a busy member of the editorial team who will get a first impression of the appropriateness of your responses. Facilitate the process of review by starting all your answers with a simple 'yes' or 'no' (where possible).

Background information and rationale for your response should follow but only after you have clearly stated your acceptance (or rejection). The process of final acceptance becomes more of a tick box exercise and expedited if the editorial team assume you have responded appropriately in most (if not all) cases.

Q What is your biggest bugbear with the review process?

A I am a believer in authors providing well-reasoned (and fully referenced) arguments when interpreting the findings of their study. This often involves a level of understanding and background knowledge that the reviewer may not have. This tends to result in journals adopting a conservative approach for all the wrong reasons, watering down speculation. I feel this stifles discussion and inhibits progress. For my part, I have always found these discussions helpful in pointing to where research should go next.

Reject and resubmit

Many journals have adopted a 'reject and resubmit' policy where previously they have simply asked authors to revise their manuscripts. This certainly helps journals with their time to publication from submission statistics but are there any benefits for the author?

This approach should help authors appreciate that their manuscript needs more than simple linguistic modification. And it ensures that the journal's performance is not based on the speed with which their authors respond – making figures quoted a more realistic representation of the journal's performance [5].

Team up

More often than not research is a team effort and, apart from review articles by eminent scientists, manuscripts tend to be submitted by a group of authors. Responding to referees should be a group exercise in the same way that multiple authors are responsible for writing the original manuscript. However, it is useful to identify one member of the team (possibly the corresponding author of their PhD student) to coordinate the various activities involved in preparing the response. This person can transfer the comments from the referees to the response template, identify members of the team best suited to addressing each point and manage the timelines.

Be thorough, expect to prepare several drafts of your response, circulate it among the team for feedback,improving the language and refining your arguments with each new iteration.

The modern metaphor for editing would be a car wash through which all cars headed for a goal must pass. Very dirty cars are turned away; dirty cars emerge much cleaner, while clean cars are little changed.

Morgan P. 1986 An insider's guide for medical authors and editors. Philadelphia: ISI Press

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To:
Alison Brown
Managing Editor
Diabetes Therapy

1 May 2011

Submission of revised manuscript DIAT-D-10-00032: Development and potential role of type-2 sodium-glucose transporter inhibitors for management of type 2 diabetes.

Dear Dr Brown,

We write to acknowledge safe receipt of your email and would like to thank you and the reviewers for the care and effort they have taken in reviewing the manuscript. We have gone over all the points that they have raised and I attach an annotated version of the full reports of each referee so that you can readily follow our responses in context. In addition, we have uploaded our corrected manuscript incorporating responses to the reviewer comments to the journal's website.

I hope that you will be pleased with the outcome and that you will feel that we have done justice to the various criticisms and suggestions. Thank you in advance for your continued consideration and support for our manuscript. If you have any further questions, please feel free to contact me directly.

Yours Sincerely,

Dr Tim Hardman
Managing Director

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Letter to the Editor

The letter that heralds how you you have responded to the challenges raised during the review process is a key tool for achieving your goal [6,7]. Getting the balance right may see you rewarded with approval for publication without further modification.

Address your letter to the editorial staff member who sent you the reviewers' comments. Be sure to include the manuscripts ID number and provide a succinct summary of the approach you have adopted. Remember to answer any issues that may have been raised by the editor. These may have been brief and only appeared in the editor's initial communication – but don't just ignore them. In terms of success these may be more important than the reviewer's comments.

Be careful of how you end your letter. Express how you hope that you have done enough to achieve approval rather than suggesting that, as all the requested corrections have been made, the manuscript should be accepted without further changes.

And finally….

The process of responding to the issues raised by reviewers is (perhaps) the most stressful part of the publication process. But it is inescapable – a few rare manuscripts are accepted without modification. Here we have summarised the limited information provided in the literature on how to respond to reviewers and combined it with our own experiences [8–14].

It is role of the peer reviewer and the editor to point out what is 'wrong' with your manuscript (or where it can be improved), making sure, on behalf of the journal that the final paper is scientifically valid, clear, original and complete. Referees provide review in their own time and therefore it can seem that their comments are abrupt and ill thought out.

At least 50% of rejected manuscripts are published within 2 years of first journal submission

Wager E. Getting research published. Oxon, 2005

It can be hard to face such (perceived) criticism when we have invested so much time and effort in performing the research and drafting the manuscript. However inconvenient the wording of a specific comment may feel, do not rephrase a referee's point so that it might be interpreted in a way that you would find it easier to address.

The whole process becomes so much more bearable when you accept responding to the journals review (occasionally including some unnecessary or ill-considered comments) as just another step on the road to publication. Rather than being irritated by the 'criticisms' it is much easier to simply transcribe the comments into your standard response-to-reviewers document and start the process of modification. It is further helpful if you keep in mind that, in most cases, reviewers were well-meaning colleagues who freely gave their time to ensure that the findings of your research are reported in the most appropriate fashion. Everyone in the process is working to ensure that your research appears in the literature in a format that contributes best to science as a whole.

A well prepared response document should be complete, polite and based on evidence, not emotion!

Williams HC, et al. How to reply to referee's comments when submitting manuscripts for publication. J Am Acad Dermatol 2004;51:79-83

If you find the exercise of addressing the comments of referees to be overwhelming, you might find some light relief in RL Glass's humorous 'A letter from the frustrated author of a journal paper' [15]. The tone will resonate with anyone with experience of responding to journals and is sure to make you chuckle.

If, however, you have just received a outright rejection or a rejection accompanied by overtly irritating critiques from the referees, cheer up! You may someday collect enough rejection letters to be able to write a book about it. You will certainly come to appreciate the deeper meaning of the delicate phrasing that is sometimes used. Hopefully though you will not receive a rejection like the one below allegedly used by the editors of a Chinese economics journal [16].

"We have read your manuscript with boundless delight. If we were to publish your paper, it would be impossible for us to publish any work of a lower standard. And as it is unthinkable that, in the next thousand years, we shall see its equal, we are, to our regret, compelled to return your divine composition, and to beg you a thousand times to overlook our short sight and timidity."

On the next page we provide some responses we hope you will find useful in replying to the editor (and a few humorous interpretations of what you would like to say).

Useful responses to awkward comments….

When responding to reviewers you may not want to accept fully their position. Be sure that the tone you adopt is collegial and balanced. Here are some useful phrases (and a semi-humorous) interpretation:

Original response	What we meant to say
"We were also disappointed by these results/low levels of…"	"This took my PhD student 3 years. Thanks for pointing out our failures, very kind of you"
"We agree that our results would be enhanced by incorporating bovine model data, however…"	"What on Earth makes you think I have access to a cow?!"
"We thank the reviewer for pointing out the flaw in our experimental design"	"Damn, we were hoping you wouldn't notice that…"
"Although the reviewer makes a good point…"	"We don't agree with you at all and I'm about to embarrass you with the reasons why"
"We thank the reviewer for their suggestion, however…"	"Your way is rubbish and our way is better…"
"We thank the reviewer for suggesting references for this section"	"These are your papers, aren't they…?"
"We believe the reviewer has misunderstood this statement"	"You didn't even read this, did you?"

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Next steps

We created this Insider's Insight so that we could share some helpful pointers and key learnings that we have gained over the last few decades. We have also shared a template you can use to respond to the journal, which we hope will give you a great start to finally getting your article published.

We hope you found this guide useful, if you would to discuss support with any of your publishing challenges please contact us at info@niche.org.uk.

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Get in touch

COMMENTS FROM THE REVIEWER #1:

Comment 1. On page 2: Introduction: the sentence, "Diagnosis usually occurs some time after development of the disease" is vague.

Response from authors. We respectfully suggest that the reviewer might be taking our comment out of context; the statement is made in conjunction with our comment that pathology often precedes diagnosis. In diabetes, the very nature of diagnosis can be vague and our reliance on serendipitous detection serves as a reminder of how poorly we understand the disease. A detailed review of the current literature describing the perceived time-frames for disease development and diagnosis could be provided but we feel that this would be beyond the scope of our article.

Comment 2. Please discuss why specifically current treatments fail, i.e. adverse effects such as hypoglycemia and weight gain - this can lead into more of a substantive discussion of how SGLT2 inhibitors are novel. What is different about SGLT 2 inhibitors? Stating that using renal glucose excretion as a potential therapeutic target represents a paradigm shift (glucosuria is now being viewed differently than traditionally), would be an important item to point out to the reader.

Response from authors. We feel that we have provided a succinct description of how SGLT2 inhibitors are novel in terms of their mechanism of action. Differential effects on hypoglycemia and the clinical profiles of other antidiabetic agents are dealt with adequately elsewhere in the literature. We cited two excellent review articles that discuss some of the limitations of existing therapies. Providing additional information would unnecessarily increase the length of the article.

Comment 3. Consider discussing glucose toxicity and the specific complications in the Introduction.

Response from authors. We gave some consideration to including information on glucose toxicity and specific complications associated with chronic hyperglycaemia. However, we felt that the general readership would already appreciate the need to address hypoglycaemia and that including any additional information would affect the concise style of the manuscript.

Comment 4. Suggest decreasing the amount of space devoted to discussing SGLT1 in this review.

Response from authors. Although the article is intended to inform the reader about SGLT2 inhibitors, we feel that it is not possible to appreciate the difficulty faced by developers in delivering a specific inhibitor without properly describing the nature of the challenge posed to this objective by the SGLT1 transporter.

Comment 5. On page 5, under the SGLT2 Inhibitors section: please mention phlorizin's enzymatic degradation as a drawback.

Response from authors. We have amended the sentence:

It has poor bioavailability, potential toxicity and is non-selective – in that it inhibits the function of both SGLT1 and SGLT2 transporters.

to read

Tending to be hydrolysed to phloretin in the gut, phlorezin has poor bioavailability, is potentially toxic and is non-selective – in that it inhibits the function of both SGLT1 and SGLT2 transporters.

Comment 6. On page 8, last sentence of the first paragraph - strongly consider including clinical trials data in some form, whether in graphs, tables, or in text, but it seems too incomplete to merely refer readers to another paper, especially since there have been trials published since Chao and Henry's review.

Response from authors. We didn't want to include an extensive review of the clinical studies conducted with SGLT2 inhibitors; inclusion of this sort of data within review articles quickly becomes outdated. When reporting on a new agent class many early publications are Phase I trials that were conducted to establish the safety and pharmacokinetic profiles of new molecules. They often provide little data on efficacy or pharmacodynamic properties. However, on the request of the reviewer we have added a table summarising current studies recorded on the ClinTrials.gov website and published articles.

Comment 7. Define more explicitly FRG in the Safety section on page 10.

Response from authors. We have added more information on FRG. The text has been amended from:

Classed as a benign disease, these people do not appear to suffer any ill consequences, suggesting that blockade of the transporter per se in T2DM patients would offer no immediate risk. It is not clear whether familial glucosuria (due to SGLT2 mutation) protects those with familial renal glucosuria against T2DM. Neither could we find any recorded evidence of an increased disposition to urinary tract or vulvovaginal infections, although identification and study of these subjects is difficult due to the rarity of the disease.

to read:

Both an autosomal recessive and dominant pattern of inheritance have been reported. Classed as a benign disease, these people do not appear to suffer any ill consequences, suggesting that blockade of the transporter per se in T2DM patients would offer no immediate risk. Patients have decreased renal tubular reabsorption of glucose from the urine in the absence of hyperglycemia or any other signs of tubular dysfunction. Glucosuria can range from 1 - 150 grams/1.73m² per day. It is not clear whether familial glucosuria (due to SGLT2 mutation) protects those with

familial renal glucosuria against T2DM. Neither could we find any recorded evidence of an increased disposition to urinary tract or vulvo-vaginal infections, although identification and study of these subjects is difficult due to the rarity of the disease.

Comment 8. Stating that "Treatment of T2DM follows a defined pathway of therapy described by treatment guidelines" implies that treatment is straightforward and negates the multiple approaches and combinations used in clinical practice. Clarifying this sentence would be useful.

Response from authors. We have amended the text:

While treatment of T2DM follows prescribed guidelines, there are many approaches and permutations to their application in clinical practice.

COMMENTS FROM THE REVIEWER #2:

Comment 1. In general, the paper's discussion of renal mechanisms seems largely reasonable and factual (except for a few discrepancies/errors regarding the figures that need to be clarified). However, the discussion of clinical applications seems to interject points that are based more on conjecture and/or hypotheses that are unsupported by experimental or clinical evidence. This normally would be acceptable if such points were clearly stated as hypotheses and/or relative uncertainties, but reconsider the tone of some of these passages, and the relative lack of supporting references, as it gives the impression of a greater certainty and thus appear to be an over-interpretation of the available evidence. There are also numerous spelling and grammatical errors throughout the paper that should have been detected on a more careful proofreading.

Response from authors. We thank the reviewer for their kind comments and have attempted to be less ambiguous as to where we have made speculation. However, we would like to express our disappointment in their failure to understand the purpose of our article. Our intent was to provide the reader with information on a new class of agents that is not yet available for use in clinical practice. Thus, the novelty of the class means that information available in the scientific literature is limited. Currently, we can only speculate how this will new treatment paradigm will affect the way we view and/or treat the disease and whether or not it will empower us to deliver control to patients who fail to respond to all other treatments. Our title states that we are discussing the POTENTIAL role of SGLT2 inhibitors and we feel this makes our speculations obvious and “acceptable”. In addition, we feel that the inclusion of 47 references in an article of this length is an adequate level of support.

We searched for the numerous typographical and grammatical errors. It would have been helpful if the reviewer had been more specific. We have corrected the few errors where they have been apparent.

Comment 2. Abstract and Page 12: I disagree with the use of the adjective "ultimate" in relation to SGLT2 inhibitors, and I am unclear as to the authors' intended meaning

in this context. The dictionary defines "ultimate" as "best or most extreme; most basic or fundamental; being or happening and the end of a process; final". I do not see how SGLT2 inhibitors, given our current knowledge or clinical experience, could qualify under any of these definitions. In what way are SGLT2 inhibitors "best" or "most extreme"? There is no evidence of their superiority since there have been very few head-to-head comparison trials against other agent classes. In what way are they "basic" or "fundamental"? They do not address any of the underlying factors contributing to diabetes development, but rather mask the problem of hyperglycemia by perturbing normal renal glucose handling. In what way is their use "final" or the "end of a process"? They may fall into our armamentarium as the "final" drug choice to be added, simply by virtue of being the newest class, but does that role merit such a positive description? If the authors are proposing that they should have a preferred status by virtue of their relative safety and "insulin-independent" mechanism (as alluded to on page 12), it should be noted that their relative safety has yet to be truly tested in widespread post-marketing studies (which may be very different than the experience of selected subjects from a clinical trial), and their insulin-independent mechanism of action, while unique, is not sufficient by itself to propel them to the top of any list of preferred agents. This whole description needs to be reconsidered. If the authors wish to editorialize the potential role of SGLT2 inhibitors, a more moderate and balanced description that reflects the prevailing evidence should be provided.

Response from authors. The wording has been changed – perhaps ‘ultimate’ could be considered too strong – the intent was to express how the combination of properties ‘expected’ with SGLT2 inhibitors may be considered to reflect the properties of the ‘perfect’ combinatorial antidiabetic agent.

Comment 3. Introduction, Page 2, 2nd paragraph: "Intense efforts?.frequently fail. This pattern is repeated when management involves the use of antidiabetic drugs". This statement is too broad a generalization. Not all patients treated with combination oral agents achieve optimal control, but in the hands of high quality

healthcare, many patients do. Failure is not a given. This statement needs to be reconsidered.

Response from authors. We would contest that although this statement might be considered 'general', it well reflects the ultimate fate of patients. Treatment follows best practice guidelines and we state that in the hands of high quality healthcare professionals many patients achieve optimal glycaemic control. Nevertheless, despite the best efforts of the best physicians, the most optimistic outcome for all diabetic patients is that they maintain their status at the time of their diagnosis. Type 2 diabetes is a progressive disease and the majority of patients face an ever worsening symptomology that accompanies increasing morbidity and eventually premature mortality. Analysis of some of the most respected population data sets, such as the UKPDS data, show that even long-term aggressive treatment strategies are associated with almost certain pathology. These accounts are well-documented in the literature and most patients would **not** view this as representing a "good prognosis".

Comment 4. SGLTs and renal physiology, Page 4, top: The text in this paragraph says that the S1 segment reabsorbs 90% of filtered glucose, while Figure 1 itself shows that both S1 and S2 segments together reabsorb 90% of filtered glucose. Please reconcile.

Response from authors. The figure has been amended.

Comment 5. SGLTs and renal physiology, Page 5, middle: The text in this paragraph says that the Na/K-ATPase pump returns Na to the nephron lumen, while Figure 2 itself shows the Na/K-ATPase pump moving Na out the basolateral aspect to the bloodstream. Please reconcile.

Response from authors. The figure has been amended.

Comment 6. SGLTs and renal physiology, Page 4, last sentence of first paragraph: This sentence seems to refer to the GLUT2-mediated glucose transport shown in Figure 2, not Figure 3. In fact, there is nothing in Figure 3 that relates to the transport of glucose out to the bloodstream. Please clarify.

Response from authors. Reference in the text to Figure 3 has been changed to Figure 2.

Comment 7. SGLT2 inhibitors, Page 6, 2nd paragraph, last sentence: "They might also be used in combination with all currently available treatments." This statement remains conjecture, and it should be pointed out that SGLT2 inhibitors have so far only been studied in combination with some, but certainly not all available treatments.

Response from authors. The text has been amended to read:

First indications suggest that the mechanism of action independent of insulin be of value for use with other, traditional antidiabetic treatments

Comment 8. SGLT2 inhibitors, Page 7, middle: The O-linkage is a target of <beta>-glucosidase enzymes, not "<beta>-glucosides".

Response from authors. Corrected.

COMMENTS FROM THE EDITOR:

Editor comments #1. Clinical expectations, Efficacy, Page 8, middle: "short-term benefits are modest." The term "modest" in this context is a matter of interpretation. The HbA1c lowering on the order of 0.5-0.9% that has been observed with SGLT2 inhibitors is actually comparable to that of other marketed oral agents, such as DPP-4 inhibitors. The authors should specify their interpretation of what constitutes a "modest" versus a more-than-"modest" treatment effect.

Response from authors. We would contest that a 0.5% reduction in HbA1c should be termed "modest" as, in great number of patients, a reduction of this size will often require combinatorial therapy to return patients to normoglycaemia. We have added a sentence that better defines the expected impact of these drugs on glycaemia. Our assumption appears to be in line regulatory agencies, who require reductions in HbA1c of at least 0.5% for an agent to be considered as a new antidiabetic treatment. Obviously, the few available reports on the clinical application of SGLT2 inhibitors to date relate to studies that have been conducted as part of ongoing regulatory programs – and as such they reflect investigations in patients selected to be most likely to demonstrate a glycaemic response. The authors have been party to Advisory Board and Key Opinion Leader meetings where discussions have focused on the expected clinical benefits of SGLT2 inhibitors in the 'general' diabetic population. In these meetings, leading diabetologists and pharmaceutical industry representatives have voiced the expectation that SGLT2 inhibitors are unlikely to produce reductions of more than 0.5%. These meeting have been conducted under strict confidentiality agreements but have served to provide us with an insight into expectations for this class of drugs that we wish to share with the journals readers.

Editor comments #2. Clinical expectations, Efficacy, Page 8, middle: "It remains to be seen whether promoting glucose excretion will result in long term benefits for the patient in terms of returning metabolic balance or even weight loss." Please clarify what is meant by "metabolic balance" (balance of what?). "Long-term" in this

context is also a matter of interpretation. Studies to date have lasted as long as 24 weeks, which is a common study duration used in diabetes trials. Weight loss is definitely seen over this time period, and is also not an uncommon study duration used in major trials of weight loss interventions. The authors should specify what they would consider to be "long-term".

Response from authors. SGLT2 inhibitors have two practical outcomes. First, by applying a simplistic mass-balance logic it is easy to accept that loss of calories (however small) will result in weight loss. Second, loss of glucose will serve to correct (at least in part) the metabolic disturbances associated with diabetes – thus introducing the potential for return to metabolic balance. We feel that the average reader will appreciate this point.

Benefits delivered by a new drug once it reaches the clinic do not always reflect the potential implied from data provided from clinical studies conducted in specific populations for regulatory purposes. In terms of practical disease management, 24 weeks represents a fraction of the time a patient suffers with the disease. In all but the setting of clinical trials we would suggest that clinicians interpret 'long-term' as being relevant to the time a patient suffers with the disease.

In the case of SGLT2 inhibitors, we still don't know whether patients will adapt to chronic calorie loss by increasing intake or whether the body will respond to chronic SGLT2 inhibition by an increase in SGLT2 expression.

Points 3 – 6 have been answered together

Editor comments #3. Clinical expectations, Efficacy, Page 8, last sentence: The authors point out that, based on their mechanism of action, SGLT2 inhibitors will be more efficacious at higher levels of hyperglycemia. However, this phenomenon is almost universally seen with all diabetes therapies, in that the degree of absolute HbA1c lowering is directly correlated with the absolute elevation of HbA1c level at

baseline. In this context, the authors' point does not appear to be a unique trait of SGLT inhibitors.

Editor comments #4. Clinical expectations, Efficacy, Page 9, top, first sentence: "The benefit to those patients in whom treatment has provided mild-to-moderate glycaemic control might be questioned as the potential for glucose excretion would be relatively low." If I interpret this sentence correctly, it is trying to make the same point as the previous sentence. However, lesser glucose lowering might not be a shortcoming of SGLT2 inhibitors, but may be a phenomenon that is common to all glucose lowering therapies.

Editor comments #5. Clinical expectations, Efficacy, Page 9, middle: "?SGLT2 inhibitors might attenuate the impact of post-prandial glucose spikes." This is a given. SGLT2 inhibitors will not discriminate between hyperglycemia in the preprandial versus postprandial phase. They will lower both, regardless.

Editor comments #6. Clinical expectations, Efficacy, Page 9, last two sentences of first paragraph: Aside from the grammatical errors here, the authors are making the point that agents that only target postprandial glucose elevations have less overall HbA1c lowering efficacy and are therefore "disappointing" in their lack of "long-term outcome benefits". While this is not untrue, to be fair, "disappointing" is another relative term. Patients who are not far from target and who then reach target with meglitinides would not consider their meglitinides to be "disappointing". If the authors are arguing that SGLT2 inhibitors may be "weaker" than other oral agent classes, this argument must remain as conjecture until proper, head-to-head comparison trials against other agents are performed. And whether a treatment is "weaker" or not has little to do with whether it translates into long-term benefits. Exactly what kind of "long-term outcome benefits" are the authors referring to? If it's a sustained glucose lowering, that is more a function of compliance. If it's long-term end-organ complications, that's a whole different argument for which only a few currently available treatments have been shown to impact, so SGLT2 inhibitors should not be singled out.

Response from authors. The four points (above) raised by the editor attempt to deconstruct a paragraph that was provided to put into context the possible clinical consequences of the simple physiological process of blocking the SGLT2 inhibitor in a logical step-by-step fashion.

- High plasma glucose ≡ steep concentration gradient to drive renal excretion of glucose;
- Glucose tends to be highest after eating ≡ excretion is likely to be greatest;
- Patients with mild-to-moderate glycaemic control will tend to have only moderately raised glucose ≡ drive to excrete glucose is not so great;
- Patients with mild-to-moderate glycaemic control still experience post-prandial spikes that have been associated with severity of secondary complications;
- Metabolic pathways targeted by currently available insulin-dependent therapies are incapable of responding to acute spikes as they are already exerting the best effect they can;
- SGLT2 inhibitors permit spikes to be attenuated because increased plasma glucose ≡ increased renal excretion = spike attenuation.

Thus, the inhibitor per se doesn't actively discriminate in terms of how the body responds it simply allows the body to respond in an appropriate fashion.

In terms of disappointment with the clinical promise of meglitanides, we refer to their failure to address the clinical consequences of the disease rather than their modest effect on HbA1c that the editor recognises. The clinical potential of blunting post-prandial spikes has been a point of discussion for some years. Despite having been available for more than a decade, treatment with meglitanides have failed to demonstrate any associated improvements in the morbidity or mortality believed to be associated with loss of the 'early phase' insulin response and consequent post-prandial glucose excursions.

We replaced the missing text on Page 9 and thank the editor for spotting our error.

Editor comments #7. Clinical expectations, Safety, Page 10, bottom: "It is not clear whether familial glucosuria (due to SGLT2 mutation) protects those with familial renal glucosuria against T2DM." Please clarify the meaning of this sentence. Are the authors referring to the potential for diabetes prevention? If so, SGLT2 inhibitors are not unlike the many other drug classes that have not yet been shown to reduce diabetes incidence in pre-diabetic cohorts. Also, some appropriate references should be cited in this discussion regarding FRG.

Response from authors. The Editor appears confused; the sentence refers to familial renal glucosuria and not SGLT2 inhibitors. There has been some speculation about this but there is insufficient data to make any conclusion. The amendment to the text that we made in response to Reviewer #1 (Comment 7) makes this point clearer.

Editor comments #8. Positioning SGLT2 inhibitors, Page 11, bottom paragraph: "Treatment of T2DM follows a defined pathway of therapy described by treatment guidelines." It should be pointed out that the ADA and AACE guidelines, for example, have very distinct approaches and follow very different "pathways". Broadly speaking, treatment pathways for T2DM are far from being well-defined.

Response from authors. The amendment to the text that we made in response to Reviewer 1 (Comment #8) clarifies this point.

Editor comments #9. Positioning SGLT2 inhibitors, Page 12 onwards: There are several references in this section to a "synergistic" effect when used together with other agents. This should be more appropriately stated as an "additive" effect, since synergism implies more than the sum of individual contributions, for which there is no evidence with SGLT2 inhibitors.

Response from authors. We agree with the Editor that the effects of SGLT2 inhibitors with other antidiabetic agents are likely to be additive. However, although combination therapy results in reductions in HbA1c above those seen with single

agent treatment, they have infrequently been shown to have additive effects. Furthermore, some antidiabetic agents work antagonistically and care must be taken when engaging in combinatorial therapy.

Unlike most other agents, SGLT2 inhibitors are non-insulin dependent in their action and we feel that the combination of two different approaches to glycaemic control may be considered synergistic. The Cassell Concise English Dictionary (1994 Ed) defines 'synergistic' as "the combined action between two organs". We would prefer to keep the original wording unless the Editor remains adamant that the use of 'synergistic' is deliberately misleading.

Editor comments #10. Positioning SGLT2 inhibitors, Page 12, bottom: "Insulin-dependent therapies become less effective with the development of insulin resistance and/or deterioration of <beta>-cell function; particularly in patients with low insulin resistance (high glucose) or poorly controlled disease." This sentence is not true! Subcutaneous insulin is a powerful therapy, particularly for severe insulin resistance where other agents at maximum dose may not be sufficient, for any insulin-deficient state due to <beta>-cell loss, and especially for cases of severe hyperglycemia.

Response from authors. Though we recognise the ability of regular insulin injections to reduce plasma glucose, the main thrust of our article involves looking forward to possible future benefits for patients. One might argue that insulin per se represents hormone replacement therapy rather than an insulin-dependent treatment. Considering the ingenuity of man, it seems a somewhat defeatist that we still need to resort to sticking needles into patients several times a day. Data from bariatric surgery studies on serves to underline how there are alternatives to treatment of T2DM that we have failed to fully consider. There are also the arguments that increased exposure to insulin can have an associated long-term morbidity and employing insulin-dependent mechanisms to dispose of pathological levels of glucose to elsewhere within the body may eventually recruit more pathology than it aims to prevent.

Editor comments #11. Positioning SGLT2 inhibitors, Page 13, 2nd paragraph, 1st sentence: The authors argue that by its mechanism of action, SGLT2 inhibitors might lead patients to disregard their dietary carbohydrate restrictions. This is purely hypothetical; if the authors have evidence to back this up, they should cite it; otherwise they should clarify that it is strictly hypothetical. The converse is conceivable too: A patient treated with SGLT2 inhibitors who ingests unrestricted glucose may develop worsening polyuria, and with the osmotic diuresis that would ensue, might then be dissuaded from following such a callous dietary pattern. In the absence of any behavioural evidence, both of these competing hypotheses may have equal merit.

Response from authors. We feel that by stating "it has yet to be established" we make it clear to the reader that we are speculating. I would suggest that this question will be at the forefront of the mind of someone reading about SGLT2 inhibitors for the first time. I contest the Editors converse argument. It would seem highly unlikely that the said "escape" mechanism would not negate any benefits of SGLT2 inhibitors. However, good science requires that we must first pose the hypothesis and then develop robust methods of testing it.

Editor comments #12. Positioning SGLT2 inhibitors, Page 13, 2nd paragraph, 2nd sentence: What's the evidence that marked and rapid glucose lowering or rapid negative caloric balance affects appetite? The authors should cite some evidence to support this argument (not including catabolic states like ketoacidosis that are known to be associated with nausea). Clinically, it is certainly not uncommon to see patients in poor control (who are no doubt catabolic and polyuric) who have no problems continuing with high calorie dietary habits on a daily basis!

Response from authors. Evidence in the form of supportive reference has been provided in the text. Most patients with T2DM are overweight and any excess weight or weight gain, adversely affects glycaemic control. Paradoxically, drugs used to improve glycaemic control are associated with weight gain - particularly insulin

therapy. This weight gain adversely affects glycaemic control and increases insulin resistance. We need to better understand body weight regulation in T2DM to better adapt for the effect of such medication on weight. In terms of energy, weight gain results from positive energy balance, which in T2DM is often attributed to decreased energy expenditure and the cessation of glycosuric energy loss on starting hypoglycaemic treatment. The current literature (now cited) suggests that these two factors, even in combination, cannot completely explain observed weight gain. Rather, the exact contribution of "energy intake" and appetite remains unknown.

Editor comments #13. Positioning SGLT2 inhibitors, Page 13, bottom: What is the evidence that the efficacy of SGLT2 inhibitors is actually attenuated in renal insufficiency, via the mechanism that is proposed? I am not aware of any such evidence in humans, so either an appropriate reference should be cited, or this should be more clearly indicated as hypothetical. The next sentence then makes the argument that the clinical action of SGLT2 inhibitors might actually be more optimal in states of mild-to-moderate renal impairment. Please clarify these conflicting arguments, and provide some supporting evidence to back up either of these claims.

Response from authors. The text has been removed leaving a simple clear proposition that renal impairment may affect response to treatment with SGLT2 inhibitors.

Editor comments #14. Conclusion, Page 14: The conclusion does not mention SGLT2 inhibitors at all - please clarify why this is?

Response from authors. The text has been amended to include direct reference to SGLT2 inhibitors.

Editor comments #15. Figure Legends, Page 25: It appears that the legends for Figures 2 and 3 have been interchanged. Figure 2 depicts the glucose transport cascade at the luminal surface and the Na/K-ATPase pump, while Figure 3 depicts the Na-glucose 1:1 co-transporter. The latter figure also needs to be properly

labeled with the luminal vs. cytosolic sides of the membrane, and the legend should explain the sequence of panels (a) through (c).

Response from authors. The legend and figures have been amended.

Editor comments #16. Table 1: "oligonucleotides" is misspelled.

Response from authors. The text has been corrected.