

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Diabetes-related symptoms, acute complications and management of diabetes mellitus of patients who are receiving palliative care: a protocol for a systematic review.
AUTHORS	Bettencourt-Silva, Rita; Aguiar, Beatriz; Sá-Araújo, Vânia; Barreira, Rosa; Guedes, Vânia; Marques Ribeiro, Maria João; Carvalho, Davide; Östlundh, Linda; Paulo, Marília Silva

VERSION 1 - REVIEW

REVIEWER	trisha Dunning Barwon health and Deakin University Australia
REVIEW RETURNED	28-Jan-2019

GENERAL COMMENTS	<p>The systematic review protocol is well described and meets relevant criteria.</p> <p>specific comments</p> <p>The term glucose lowering medicines in replacing antidiabetic drugs, but the former should be used in the search strategy.</p> <p>Amend ethical approvable to ethics approval (page 3).</p> <p>Page 4</p> <p>Clarify bullet point 2. It is ambiguous. The systematic review does not interview or collect evidence directly from clinicians.</p> <p>page 6 The main concern of palliative care is to manage the whole person, not just their diabetes. Thus pain, depression and distress are also essential.</p> <p>Interdisciplinary team care and early referral to relevant clinicians are important.</p> <p>Page 8 Other important outcomes to consider are advance care planning and documented advance care plans.</p> <p>Note HbA1c is an average measure of blood glucose and many factors can affect the accuracy.</p> <p>Death could be due to causes other than diabetes-complications.</p> <p>Will ICD-10 codes, comorbidity burden and other relevant information be collected.</p> <p>Page 8 states the search will be conducted in December 2018.</p> <p>Indicate how the grey literature will be searched and included/excluded.</p> <p>Some key references are missing from the reference list and these include guidelines for managing diabetes at the end of life.</p>
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REVIEWER	Shirley Chambers Queensland University of Technology, Australia
REVIEW RETURNED	06-Feb-2019

GENERAL COMMENTS	<p>The topic of the protocol for this review is certainly interesting and needs to be addressed. A little more explanation is needed here and there - keep in mind not every reader is not going to be up to speed in regards to DM or palliative care so both concepts need to be explained well and how each relates to/impacts on the other. You will see on the attached PDF (of my manual edits and comments - too many to list) that much that I have picked up are minor edits or places where a little more information is needed to clarify. I will be interested to see your work completed and published. Please have a colleague whose first language is English to have a look at your next draft before submitting. Good luck.</p> <p>Review Checklist – questions to which I responded NO</p> <p>Q2. Is the abstract accurate, balanced and complete? No</p> <ul style="list-style-type: none"> • Q1 Response: The abstract needs to be reviewed by the authors for clarity. <p>Q4. Are the methods described sufficiently to allow the study to be repeated? No</p> <ul style="list-style-type: none"> • Q4: Response: <ul style="list-style-type: none"> o Quality Assurance Exercise: The quality assurance exercise (detecting bias) needs to be reported more clearly, and there has been no mention made of how results from this quality assurance exercise will impact on the review, such as, if papers score beneath a particular number - they will be excluded from the review, or alternatively, papers will not be excluded on the basis of the quality assurance checks rather this exercise will allow the authors to describe the quality of the papers found on this topic. o Abstract Review: The abstract reviewing exercise is barely mentioned and needs to be outlined much more, such as tailoring an abstract assessment tool (e.g., tick and flick style which provides basic statements of what included papers will contain, such as sample parameters, aim/purpose of the study, relevant findings etc) for the purpose of this study – this would make the process much more systematic – particularly when more than one researcher is reviewing abstracts. <p>Q8. Are the references up-to-date and appropriate? No</p> <ul style="list-style-type: none"> • Q8 Response: More in-text referencing is needed throughout the paper. I question the use of Ref [3] (p, 5 line 42) – I do not think this is the best reference to use here or at least use at least 1 academic reference of an epidemiological study as well. <p>Q13. Is the supplementary reporting complete (e.g. trial registration; funding details; CONSORT, STROBE or PRISMA checklist)? No</p> <ul style="list-style-type: none"> • Q13 Response: In the PRISMA-P 2015 Checklist: <ul style="list-style-type: none"> o Registration (2) – that the PROSPERO registration number is missing in text o Eligibility Criteria (8) - the study designs which will be accepted for this review are not outlined.
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	<p>Q15. Is the standard of written English acceptable for publication? No</p> <ul style="list-style-type: none"> Q15 Response: As the paper is at present the written English of this paper is not acceptable for publication. <p>More specific edits and comments: Please see attached PDF of manual edits and comments inserted onto the hardcopy of this document.</p> <p>The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 1	
The systematic review protocol is well described and meets relevant criteria.	We thank Reviewer 1 for the time taken to review our manuscript.
The term glucose lowering medicines in replacing antidiabetic drugs, but the former should be used in the search strategy.	We thank Reviewer 1 for the very valid suggestion. We will update our search strategy including 'glucose lowering medicines'. In the manuscript, we have substituted the term antidiabetic drugs to glucose lowering medicines. Please see "Supplements".
Amend ethical approvable to ethics approval (page 3).	We thank Reviewer 1 for capturing this error, we have amended it. Please see page 3.
Page 4 Clarify bullet point 2. It is ambiguous. The systematic review does not interview or collect evidence directly from clinicians.	We thank reviewer 2 for their comment. As per the Editor's request, we have amended point 2 to be specific related to the methods. Please see page 4.
Page 6 The main concern of palliative care is to manage the whole person, not just their diabetes. Thus pain, depression and distress are also essential. Interdisciplinary team care and early referral to relevant clinicians are important.	We thank Reviewer 1 for their comment, we have better explained these concepts in the manuscript. Please see page 6.
Page 8 Other important outcomes to consider are advance care planning and documented advance care plans.	We thank Reviewer 1 for their suggestion. We have added it to our type of outcomes. Please see page 8.
Note HbA1c is an average measure of blood glucose and many factors can affect the accuracy.	We thank Reviewer 1 for their very valid comment. We acknowledge the use of HbA1c as a limitation of our systematic review. Although, due to the nature of our study that will review data of studies already published, we consider that the use of HbA1c will be the most effective way. We will have its limitation in consideration during risk of bias assessment and quality evidence. We have described this in the limitations. Please see page 4.

<p>Death could be due to causes other than diabetes-complications.</p>	<p>We thank Reviewer 1 for their comment. As mentioned in the “type of outcome, page 8” just deaths due to DM-related complications will be reported. For example, if a diabetic patient dies of cancer this will not be included.</p>
<p>Will ICD-10 codes, comorbidity burden and other relevant information be collected.</p>	<p>We thank Reviewer 1 for their comment. If studies included in our qualitative synthesis provide the ICD-10 codes of comorbidity burden these will be reported as part of our findings.</p>
<p>Page 8 states the search will be conducted in December 2018.</p>	<p>We Thank Reviewer 1 for noticing this. In the initial plan, the research team thought to start the search for literature in December 2018. Although, being aware that having peer-review comments in our manuscript would strengthen our study, we have decided to wait until the protocol publication to start the search. Information was amended. Please see page 8.</p>
<p>Indicate how the grey literature will be searched and included/excluded.</p>	<p>We Thank Reviewer 1 for their comment. We have described that we will search for grey literature using the Grey Literature Report and Open Grey databases. We will apply the same inclusion and exclusion criteria of the medical electronic databases. Please see page 8 and 9.</p>
<p>Some key references are missing from the reference list and these include guidelines for managing diabetes at the end of life.</p>	<p>We Thank Reviewer 1 for their comment. We have tried to upgrade the references complementing our manuscript.</p>
<p>Reviewer 2</p>	
<p>The topic of the protocol for this review is certainly interesting and needs to be addressed. A little more explanation is needed here and there - keep in mind not every reader is not going to be up to speed in regards to DM or palliative care so both concepts need to be explained well and how each relates to/impacts on the other. You will see on the attached PDF (of my manual edits and comments - too many to list) that much that I have picked up are minor edits or places where a little more information is needed to clarify. I will be interested to see your work completed and published. Please have a colleague whose first language is English to have a look at your next draft before submitting. Good luck.</p>	<p>We thank Reviewer 2 for the time taken to review our protocol for a systematic review.</p>
<p>Title</p>	<p>We thank Reviewer 2 for their suggestion and we have accepted it. Please see page 1, title.</p>

Abstract	We thank Reviewer 2 for the thorough abstract revision and we have accepted their suggestions. Please see page 3, abstract.
Introduction	We thank Reviewer 2 for the thorough Introduction revision. We have accepted the English language suggestions and justified/provided more insight where appropriate. Please see pages 5 and 6.
Objectives	We thank Reviewer 2 for suggestion. We have accepted it. Please see page 6.
Methods and analysis	We thank Reviewer 2 for the thorough methodological revision. We have accepted the English language suggestions and justified/provided more insight where appropriate. Specifically we have better described the titles and abstracts screening stage. Please see pages 6 to 10.
PRISMA-P 2015 Checklist	We thank Reviewer 2 for their comments. We have inserted the PROSPERO registration number under "methods and analysis" and the type of studies included in this review is presented in "type of studies" Please see page 7 and 8.

VERSION 2 – REVIEW

REVIEWER	Trisha Dunning Barwon Health and Deakin University Australia
REVIEW RETURNED	20-Mar-2019

GENERAL COMMENTS	No further comments To the editors The authors appear to have addressed the reviewers' questions. It does still require copy editing - presumably that can be done in house?
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REVIEWER	Shirley Chambers Queensland University of Technology, Australia
REVIEW RETURNED	20-Mar-2019

GENERAL COMMENTS	Thank you for revising this manuscript well - it reads much better, just a few more tweaks to do. Please see my suggested edits and
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comments below which I trust will make this a much better piece of work. Well done, this will be a very good review to do and I am sure the results will certainly assist palliative clinicians who have patients with DM in their care.

Review Checklist:

Questionable Areas

- Q8: I am concerned that the references list is light on and not really up to date, particularly with respects to the palliative care area. I am sure more appropriate references could be found.
- Q13: Areas of PRISMA checklist questionable
 - o Amendments #4 – N/A rather than No
 - o Data: Synthesis: #15c – This was basic, is this enough
- Q15: The standard of the English in this manuscript is acceptable for publication upon the incorporation of my suggested edits.

Abstract:

Page 3

- Line 12: 'rising burden on DM worldwide – change 'on' to 'of'
- Line 16: 'expert opinion. There' – join these sentences together, i.e., 'expert opinion as there is a lack of a suitable evidence base'
- Line 20: aim of review 'is to assess the best ' – suggest change to 'is to identify the best' as I assume you are doing the review to certainly assess the literature to identify the best practices – so maybe could say 'to identify and assess' – or are you assessing so that you can identify?
- Line 26: 'approaches employed in palliative care adult patients' - always best to put the patient first then the disease etc, so I suggest 'employed to treat adult patients who are receiving palliative care', I realise you are limited by word counts – if all else fails maybe 'employed to treat adult palliative patients'
- Line 35: Primary outcomes – do you mean the outcome is the alleviation of symptoms due to DM management practices – as how it is written presently does not really align with the aim. I would have thought the primary outcomes would be something to do with the DM management practices.

Page 4

- Line 10 (dot point 2): This needs to be written more clearly – text suggestion 'Limitations of this review include the exclusion of papers reported in languages other than English, Portuguese or Spanish and those published prior to 1990'
- Line 14 (dot point 3) I do not understand this point – is it a limitation or a strength
- Line 21 (Dot point 4) 'will make this study wider in terms of' – replace with 'will broaden this study in terms of'
- Line 23: (Last dot point) 'include studies' - replace with 'include primary studies'

Introduction:

Page 5

- Line 16: 'to patients at end of life' – replace with 'to patients who are actively dying' (many people think palliative care is only for those last day, hrs of life- which is the actively dying stage – but there is evidence to suggest that earlier referral to and introduction of palliative cares services benefits the patient and their family carers) – alternatively 'to patients who have a very short prognosis'
- Line 18: 'Palliative care should be applicable early' - change to 'Palliative care is best introduced early'
- Lines 46-48: sentence starting 'However, in patients receiving...'
- this point was already noted above in line 35, if this is not making a new point, remove

- Line 48: sentence starting 'Furthermore, DM is, by itself' – the 'why' of this sentence sediment needs to be stated
- Page 6
- Line 9: after word 'considerations' - need an in-text reference for this point
 - Line 26: 'also treating' - replace with 'also treats'
 - Line 28: 'As such, treatment' - replace with 'As such, the appropriate treatment'
 - Lines 28-32: Check font size
 - Line 32: 'admission' - change to 'admissions'
 - Line 43: Aim of review is to access – should be at least 'assess' – I suggested in Abstract to replace with 'identify and assess'
- Page 7
- Line 10: 'the International prospective register of systematic reviews' – either remove capitalisation of the 'I' in international or make each first letter of each word here capitals.
 - Line 22: 'with the pediatric population' – replace with 'with pediatric samples' alternatively, 'exclude studies of pediatric populations'
 - Line 47 on: not sure of primary outcomes – see comment in abstract section above, this could be remedied with a little more wording
- Page 8
- Line 26: 'will be searched at the Grey' – replace with 'will be searched using the Grey'
 - Lines 29-31: sentence starting 'The inclusion and exclusion' – I do not think you need this here – as you have already stated your eligibility criteria
 - Line 39: 'The search strategy will include only terms relating to or describing the intervention' - ? your search terms also include the patient population/context – i.e., palliative care, terminal etc. I am not sure what you mean by this statement.
- Page 9
- Lines 22-24: sentence 'The two independent reviewers will screen all titles and abstracts' – remove this and join remaining of this sentence to the prior sentence
 - Line 22: from "titles and abstracts will be screened by two independent reviewers' - add text who will take into consideration the inclusion and exclusion criteria outlined.'
 - Line 24: Delete: 'The two independent reviewers will screen all titles and abstracts'
 - Line 29-30: 'Based on that they will vote the potentially eligible study to be included or excluded' – replace with 'Based on these criteria, the studies will be accepted for full text review or rejected.'
 - Line 31: remove 'and' starting this line. Start sentence with 'Conflicts'
- Page 10
- Line 27: 'different DM approaches' what are these – can you give an example
 - Line 31: 'when' - replace with 'where'
 - Line 37: 'as mentioned on the type of outcomes,' - replace with 'as mentioned in the type of outcomes section',
 - Line 56: 'we will just describe it' – replace with 'we will describe the quality of the included studies'.
- Page 11:
- Line 12: move apostrophe from before the s to after the ', i.e., from (patient's) - to (patients')
 - Lines 12-13: 'data from the disease' – replace with 'details of the disease for which the patient was referred to palliative care' or just 'disease details'

	<ul style="list-style-type: none"> • Line 29: 'Patients and the public were not involved in this study' – replace with 'Patients and the public will not be involved in this study' – as this is a protocol, write in the present tense • Line 41-43: 'and approved the final manuscript' – is this needed seeing below you state that all authors read and approved the final manuscript <p>Reference List</p> <ul style="list-style-type: none"> • Ref 2: take out excessive capitalisation • Ref 6: reference is not complete
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VERSION 2 – AUTHOR RESPONSE

Reviewer 1

No further comments.

We thank Reviewer 1 for the time taken to review our manuscript, valuable comments and insightful suggestions to our work.

Reviewer 2

Thank you for revising this manuscript well - it reads much better, just a few more tweaks to do. Please see my suggested edits and comments below which I trust will make this a much better piece of work. Well done, this will be a very good review to do and I am sure the results will certainly assist palliative clinicians who have patients with DM in their care.

We thank Reviewer 2 for the time taken to review our manuscript, valuable comments and insightful suggestions to our work.

Q8: I am concerned that the references list is light on and not really up to date, particularly with respects to the palliative care area. I am sure more appropriate references could be found. We thank reviewer 2 for this comment. We added new references to the manuscript.

Q13: Areas of PRISMA checklist questionable

o Amendments #4 – N/A rather than No

o Data: Synthesis: #15c – This was basic, is this enough We thank reviewer 2 for this comment. We amended the PRISMA checklist.

The standard of the English in this manuscript is acceptable for publication upon the incorporation of my suggested edits.

We thank Reviewer 2 for valuable help.

Abstract:

Page 3 - Line 12: 'rising burden on DM worldwide – change 'on' to 'of'

We thank reviewer 2 for the comment. We have changed it.

Page 3 - Line 16: 'expert opinion. There' – join these sentences together, i.e., 'expert opinion as there is a lack of a suitable evidence base'

We thank reviewer 2 for the comment. We have changed it.

Page 3 - Line 20: aim of review 'is to assess the best' – suggest change to 'is to identify the best' as I assume you are doing the review to certainly assess the literature to identify the best practices – so maybe could say 'to identify and assess' – or are you assessing so that you can identify?

We thank reviewer 2 for the comment. We have changed the sentence as suggested.

Page 3 - Line 26: 'approaches employed in palliative care adult patients' - always best to put the patient first then the disease etc, so I suggest 'employed to treat adult patients who are receiving palliative care', I realise you are limited by word counts – if all else fails maybe 'employed to treat adult palliative patients'

We thank reviewer 2 for the comment. We have replaced it.

Page 3 - Line 35: Primary outcomes – do you mean the outcome is the alleviation of symptoms due to DM management practices – as to how it is written presently does not really align with the aim. I would have thought the primary outcomes would be something to do with the DM management practices.

We thank reviewer 2 for the thoughtful comment. We tried to explain the sentence a better, the primary outcomes and secondary outcomes are specific measures that will allow us to compare the BM management approaches.

Please see page 3.

Page 4 - Line 10 (dot point 2): This needs to be written more clearly – text suggestion 'Limitations of this review include the exclusion of papers reported in languages other than English, Portuguese or Spanish and those published prior to 1990'

We thank reviewer 2 for the comment. We have changed it.

Page 4 - Line 14 (dot point 3) I do not understand this point – is it a limitation or a strength

We thank reviewer 2 for the comment. We have included this point as a limitation as per the suggestion of Reviewer 1 comment in the first round of peer-review. Although, we have discussed this following your comment, and we have decided to delete the point as HbA1c will not be that important in short-term palliative care and perhaps it should not be highlighted here.

Page 4 - Line 21 (Dot point 4) 'will make this study wider in terms of' – replace with 'will broaden this study in terms of'

We thank reviewer 2 for the comment. We have replaced it.

Page 4 - Line 23: (Last dot point) 'include studies' - replace with 'include primary studies'

We thank reviewer 2 for the comment. We have added it.

Introduction:

Page 5 - Line 16: 'to patients at end of life' – replace with 'to patients who are actively dying' (many people think palliative care is only for those last day, hrs of life- which is the actively dying stage – but there is evidence to suggest that earlier referral to and introduction of palliative cares services benefit the patient and their family carers) – alternatively 'to patients who have a very short prognosis'

We thank reviewer 2 for the valid suggestion. We have amended the sentence as suggested.

Page 5 - Line 18: 'Palliative care should be applicable early' - change to 'Palliative care is best introduced early'

We thank reviewer 2 for the comment. We have changed it.

Page 5 - Lines 46-48: sentence starting 'However, in patients receiving...' - this point was already noted above in line 35 if this is not making a new point, remove We thank reviewer 2 for capturing this error. We have removed the sentence.

Page 5 - Line 48: sentence starting 'Furthermore, DM is, by itself' – the 'why' of this sentence sediment needs to be stated

We thank reviewer 2 for the suggestion. We amended it.

Page 6 - Line 9: after word 'considerations' - need an in-text reference for this point We thank reviewer 2 for capturing this comment. We added a new reference.

Page 6 - Line 26: 'also treating' - replace with 'also treats' We thank reviewer 2 for the comment. We have replaced it.

Page 6 - Line 28: 'As such, treatment' - replace with 'As such, the appropriate treatment'

We thank reviewer 2 for the comment. We have replaced it.

Page 6 - Lines 28-32: Check font size We thank reviewer 2 for capturing the error. We have changed the font size.

Page 6 - Line 32: 'admission' - change to 'admissions'

We thank reviewer 2 for the comment. We have changed it.

Page 6 - Line 43: Aim of review is to access – should be at least 'assess' – I suggested in Abstract to replace with 'identify and assess'

We thank reviewer 2 for the comment. We do agree with you very valid point made earlier about the differences of "assess" and "identify" and we will change it.

Page 7 - Line 10: 'the International prospective register of systematic reviews' – either remove capitalisation of the 'I' in international or make each first letter of each word here capitals.

We thank reviewer 2 for the comment. We have removed the capitalization of the I.

Page 7 - Line 22: 'with the pediatric population' – replace with 'with pediatric samples' alternatively, 'exclude studies of pediatric populations'

We thank reviewer 2 for the valid suggestion. We have amended the sentence.

Page 7 - Line 47 on: not sure of primary outcomes – see comment in abstract section above, this could be remedied with a little more wording We thank reviewer 2 for the comment. We have better explained the sentence.

Please see page 7-8.

Page 8 - Line 26: 'will be searched at the Grey' – replace with 'will be searched using the Grey'

We thank reviewer 2 for the comment. We have changed it.

Page 8 - Lines 29-31: sentence starting 'The inclusion and exclusion' – I do not think you need this here – as you have already stated your eligibility criteria

We thank reviewer 2 for the comment. We have deleted the sentence.

Page 8 - Line 39: 'The search strategy will include only terms relating to or describing the intervention' - ? your search terms also include the patient population/context – i.e., palliative care, terminal etc. I am not sure what you mean by this statement.

We thank reviewer 2 for the comment. We better explained the sentence "The search strategy will include terms defined in accordance to population, intervention, comparator and outcomes as described above".

Please see page 8.

Page 9 - Lines 22-24: sentence 'The two independent reviewers will screen all titles and abstracts' – remove this and join remaining of this sentence to the prior sentence

We thank reviewer 2 for the suggestion. We have changed the sentence as suggested.

Page 9 - Line 22: from "titles and abstracts will be screened by two independent reviewers' - add text who will take into consideration the inclusion and exclusion criteria outlined.' We thank reviewer 2 for the comment. We better explained the sentence.

Please see page 9

Page 9 - Line 24: Delete: 'The two independent reviewers will screen all titles and abstracts'

We thank reviewer 2 for the suggestion. We have removed it.

Page 9 - Line 29-30: 'Based on that they will vote the potentially eligible study to be included or excluded' – replace with 'Based on these criteria, the studies will be accepted for full text review or rejected.' We thank reviewer 2 for the comment. We have replaced it.

Page 9 - Line 31: remove 'and' starting this line. Start sentence with 'Conflicts' We thank reviewer 2 for the comment. We have amended it.

Page 10 - Line 27: 'different DM approaches' what are these – can you give an example

We thank reviewer 2 for the suggestion. We explained with more detail DM approaches such as different insulin regimens.

Page 10 - Line 31: 'when' - replace with 'where'

We thank reviewer 2 for the comment. We have changed it.

Page 10 - Line 37: 'as mentioned on the type of outcomes,' - replace with 'as mentioned in the type of outcomes section', We thank reviewer 2 for the comment. We have replaced it.

Page 10 - Line 56: 'we will just describe it' – replace with 'we will describe the quality of the included studies'.

We thank reviewer 2 for the comment. We have replaced it.

Page 11 - Line 12: move apostrophe from before the s to after the ', i.e., from (patient's) - to (patients')

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Page 11 - Line 29: 'Patients and the public were not involved in this study' – replace with 'Patients and the public will not be involved in this study' – as this is a protocol, write in the present tense

We thank reviewer 2 for the comment. We have changed it.

Page 11 - Line 41-43: 'and approved the final manuscript' – is this needed seeing below you state that all authors read and approved the final manuscript We thank reviewer 2 for the comment. We have removed this sentence.

Reference List

Ref 2: take out excessive capitalization We thank reviewer 2 for the comment. We have removed the excessive capitalization.

Ref 6: reference is not complete

We thank reviewer 2 for the comment. We have included a few more reference in the area of Diabetology and oncology.