PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cost of Oropharyngeal Dysphagia after Stroke: protocol for a systematic review.
AUTHORS	Marin, Sergio; Serra-Prat, Mateu; Ortega, Omar; Clave, Pere.

VERSION 1 – REVIEW

REVIEWER	Jessica Beavan Royal Derby Hospital Derby United Kingdom
REVIEW RETURNED	12-Apr-2018

GENERAL COMMENTS	This is a generally well written protocol, but I wonder whether it would have made more sense submitting it as a whole protocol for the full steps of the project rather than for the literature review which is the first part of a much bigger project? This protocol would benefit from review by a health economist. I would have recommend more detail on the items which contribute to the costs of dysphagia-for instance tube feeding , PEG insertion (Endoscopy services), antibiotic use and other pneumonia related costs (Admission to ITU).Pressure areas are not mentioned. One of the challenges here will be looking at sources describing different health systems (are the authors going to limit to english text journals only?), and what is defined as health and social costs-how will this be corrected for? Are the chosen items based on papers already reviewed but not referenced?(Patel 2018?) The authors limit this review to published data, but I wonder if combining the first 2 sections to gain unpublished medicare, health care system data would be a much greater resource and give a better idea of additional cost of post stroke dysphagia. This is a very important area where savings and quality improvement could be potentially be made with simple measures and the whole project would be a great interest.

REVIEWER	Heather Flowers Heather Flowers, MEd, MHSc, PhD, CCC-SLP, S-LP(C), Reg CASLPO Professeure adjointe | Assistant Professor Université d'Ottawa | University of Ottawa École des sciences de la réadaptation | School of Rehabilitation Sciences Institut de Recherche sur le Cerveau de l'uOttawa | uOttawa Brain & Mind Research Institute Affiliate Investigator | Chercheur affilié Ottawa Hospital Research Institute Chercheur | Scientist Institut du Savoir - Montfort | Montfort - A Knowledge Institute
REVIEW RETURNED	13-May-2018

GENERAL COMMENTS	This protocol for a systematic review considering direct and indirect economic costs of oropharyngeal dysphagia will ultimately provide new knowledge and could have far-reaching practice implications.

	Key elements of the manuscript require clarification and/or restructuring. Examples of some overarching issues, which seem entirely rectifiable include: 1. Use of the word “additional” in “additional” costs attributable to oropharyngeal dysphagia. Does this mean “over and above” the cost of a comparison group without oropharyngeal dysphagia? 2. I am not familiar with categories of economic burden, such as “partial”, “direct”, “indirect”, “hospital”, “health care system”, “social perspectives”. Clarifying each type of burden/cost with a definition (and references if applicable) and ideally providing an example of each type would help the naïve reader and improve the flow of the manuscript. 3. I have made some language edits, only because there were few vocabulary/style points that could be improved. Therefore, I don’t think that the manuscript will require additional attention in this respect. Page 3. Line 50. Should you state age >17 years rather than 18 years? Page 4. Line 9. What are controlled and not-controlled studies? I didn’t note definitions for each type in the methods, so this distinction is unclear. Page 4. Line 9. LANGUAGE EDIT – I would say “perspective from which…” not “in which” Page 4. Line 52 – LANGUAGE EDIT – I would say “incite” rather than “induce” changes in the provision…. Page 5. Line 7 – LANGUAGE EDIT – I would say “identified” rather than “encountered” Page 5. Line 7 – I would say that your strategy is “well-developed” rather than “developed” Page 5. Line 10 – Explain what type of publication bias could affect results. Would it be a bias towards studies demonstrating high costs of OD? Page 6. Line 16 – I think where you’ve used the word “efficacy” multiple times (here and later on in the manuscript), it should be “efficiency”. Page 6. Line 25-27 – The comment about OD being easy to diagnose is an overstatement. You might want to declare rather that there are well-established processes for its accurate diagnosis, such as routine screening followed by expert assessment. Then, the next sentence about the position statement follows nicely. Page 6. Line 34-37 – I think there needs to be a more comprehensive explanation of dysphagia treatment. It sounds like the only way to treat is with modified diets, and that is certainly not the case. It might be better to describe behavioural treatment as compensatory (and modified diets are only one example) or restorative (e.g., use of exercises, maneuvers).

	Page 6. Line 39 – I think this sentence is long, coupling malnutrition and dehydration with good oral health practices. Maybe these two concepts should be placed in two different sentences, especially since the oral pathogens would related primarily to the oral health point. Page 6. Line 46-47 – LANGUAGE EDIT – I would say “diminish” instead of “avoid” Page 7. Line 4. It is not clear to me what sanitary costs are. Page 7. Line 11. – LANGUAGE EDIT - I would say “acute hospital setting” instead of “attention” Page 7. Line 13 – LANGUAGE EDIT – I would start the sentence with “Knowing” instead of “The knowledge of”. Page 7. Lines 25-28 – Are there any citations that could be used alongside the statement that OD costs are not well known? Page 7. Line 51 – Why not search both Medline and EMBASE through OVID? Does it not have a better search platform for MEDLINE than Pubmed? Page 8. Line 16. – Do you mean an abstract screening phase and a subsequent full article review phase (I’m not familiar with the term “posterior selection”). Page 8. Lines 25-27. I think the title and abstract screening phase could be better defined. How will abstracts be systematically eliminated? Would they be excluded if there were no mention of certain words such as “stroke”, “OD”, and “costs”? How many screeners will be involved for this stage? Page 8. Paragraph starting at line 34. Are all study designs permissible? If not, which ones would not be included? Also, is there a minimum number of enrolled patients for included studies? Page 9. Lines 49-50. What is a temporary discount rate? Why would sensitivity analysis be used in an economic study design? Page 10. Line 11. Canadian Neurological Scale (full title should be used). Page 10. Lines 18. What is a “nutritional assessment”? Is this an evaluation of three-day intake quantity or is there another type of routine nutritional assessment of interest? Page 10. Lines 47-48. What is an example of quantities of health and social resource consumption? How is this measured typically? Visit frequency? Page 13. Lines 41-50. This sentence is very long. Page 14. Lines 13-14. Raise awareness on “minimal care”. Does this mean the need for at least minimal care? Page 25-26. What are “active” interventions? I presume they are restorative and functional (used during swallowing)?

	General Methods: I think that the quality appraisal for individual articles should be in the section on quality assessment (so risk of bias and individual GRADE in same section). General Methods: PRISMA statement – I think this should be placed at the beginning of the methods as it projects the whole plan for your protocol and systematic review. It seems like a bit of an addendum otherwise. General Methods: Good information is provided about steps beyond the systematic review itself for a more comprehensive project. Table 1. Other than clearly defining which terms are [Mesh] terms, the other terms are not defined as to their nature. Which other terms are exploded (sometimes denoted with EXP or /)? Which terms are sought in the title, abstract, and/or keywords? Often, there are designated extensions such as “ti”, “ab”, “kw”, or “tw”. It would be helpful to identify the extensions or if they are not needed, how the term is being used to conduct the search. For example, when I try the term “Oropharyngeal Dysphagia” in OVID EMBASE, it assigns the extension “mp”. Also, presenting a sample search with the number of total hits per term (and overall) would be informative as part of the protocol. So, for example, when the search is run in EMBASE, how many citations are identified at this point in time? The information would provide some knowledge of scope/breadth of the proposed search. Figure 1. In the box, “FULL-TEXT ARTICLES EXLUDED”, the information about inclusion criteria does not need to be restated. The points were clear in the methods.

VERSION 1 – AUTHOR RESPONSE

2. Answers to reviewer1:
-This is a generally well written protocol, but I wonder whether it would have made more sense submitting it as a whole protocol for the full steps of the project rather than for the literature review which is the first part of a much bigger project?

- ANSWER: It is true that this is the first stage of a larger project, which is the doctoral thesis of one of the authors (SM) aimed at calculating the cost of oropharyngeal dysphagia. This thesis is structured in different parts including a systematic review and a prospective original study with data from our hospital. We think that these two main parts of the project cannot be integrated in a single protocol. Moreover, the results of this systematic review will provide relevant data on the cost of dysphagia and has a great value “per se” in an area of great uncertainty. We understand that BMJ open journal accepts protocols for systematic reviews. Thank you for your interest.

-I would have recommend more detail on the items which contribute to the costs of dysphagia for instance tube feeding, PEG insertion(Endoscopy services), antibiotic use and other pneumonia related costs (Admission to ITU).Pressure areas are not mentioned. One of the challenges here will be looking at sources describing different health systems (are the authors going to limit to english text journals only?), and what is defined as health and social costs-how will this be corrected for?Are the chosen items based on papers already reviewed but not referenced?(Patel 2018?)
ANSWER:
- We have revised the section “Elements of cost considered” and as the reviewer suggest we have

specifically included some new items such as “tube-feeding, PEG-insertion, antibiotic use, pneumonia related costs and admission to intensive care unit.”
- Regarding language, we do not establish any language limitation in our bibliographic search.
- We will gather and report information about the country where the study was performed. Each country has its own health care system. No correction will be performed but just a description and a narrative comparison of the results from each country/healthcare system.
- The study by Patel et al, 2018, was published once we had finished this protocol. We appreciate your suggestion and we have reviewed and included this interesting article in the references section of our manuscript. Thank you.
-The authors limit this review to published data, but I wonder if combining the first 2 sections to gain unpublished medicare, health care system data would be a much greater resource and give a better idea of additional cost of post stroke dysphagia.
- ANSWER: We appreciate the reviewers comment but as most systematic reviews we will consider only published data from indexed journals because of the enormous difficulty of obtaining unpublished data from all around the worldin a systematic way.
-This is a very important area where savings and quality improvement could be potentially be made with simple measures and the whole project would be a great interest.
-ANSWER: Thank you for your comment on this project. Our strategy to explore this area is first to do this systematic review and then to study the costs of post stroke OD from a hospital perspective by analyzing from an economic perspective the results of a clinical series recently published by our group.[1]
1. Rofes L, Muriana D, Palomeras E, et al. Prevalence, risk factors and complications of oropharyngeal dysphagia in stroke patients: A cohort study. Neurogastroenterol Motil. 2018.
Thank you for your positive comments.

3. Answers to reviewer 2:
1. Use of the word “additional” in “additional” costs attributable to oropharyngeal dysphagia. Does this mean “over and above” the cost of a comparison group without oropharyngeal dysphagia?
-ANSWER: Yes, the reviewer is right. Our main objective is to determine the costs attributable to oropharyngeal dysphagia in stroke patients, so we look for studies with a comparison group of stroke patients without dysphagia. However, studies focused on the main determinants of the cost of treatment and care of stroke patients will also be considered in this review. In these studies multivariate analyses could offer the independent effect of oropharyngeal dysphagia on total costs in the care of post-stroke patients. Perhaps, the use of the word “additional” might not be the most suitable one, so we have decided to change it by “related to”. Thank you very much for this important suggestion that will make our work more accurate.
2. I am not familiar with categories of economic burden, such as “partial”, “direct”, “indirect”, “hospital”, “health care system”, “social perspectives”. Clarifying each type of burden/cost with a definition (and references if applicable) and ideally providing an example of each type would help the naïve reader and improve the flow of the manuscript.
- ANSWER: Thank you for this suggestion. These are terms and concepts used in health-economics. According to this reviewer’s comment we have added a brief “glossary term” section to the manuscript with some references.
3. I have made some language edits, only because there were few vocabulary/style points that could be improved. Therefore, I don’t think that the manuscript will require additional attention in this respect.
- ANSWER: Thank you, we have changed them in the manuscript.
Page 3.Line 50.Should you state age >17 years rather than 18 years?

- ANSWER: We have changed 18 for >17 (age). Thank you.
Page 4.Line 9. What are controlled and not-controlled studies? I didn’t note definitions for each type in the methods, so this distinction is unclear.

-ANSWER: We have modified the text in order to clarify this question. We have avoided the term “controlled” when referring to studies that report incremental costs.

Page 4.Line 9. LANGUAGE EDIT – I would say “perspective from which…” not “in which”
- ANSWER: We changed “in which” for “perspective from which.”
Page 4. Line 52 – LANGUAGE EDIT – I would say “incite” rather than “induce” changes in the provision….
- ANSWER: We eliminated this sentence according to theeditor’s suggestion.
Page 5. Line 7 – LANGUAGE EDIT – I would say “identified” rather than “encountered”
- ANSWER: We changed “encountered” for “identified.”
Page 5. Line 7 – I would say that your strategy is “well-developed” rather than “developed”
- ANSWER: We changed “developed” for “well-developed.”.
Page 5. Line 10 – Explain what type of publication bias could affect results. Would it be a bias towards studies demonstrating high costs of OD?
-ANSWER: the reviewer is right; we have clarified in the text what type of publication bias couldaffect results.

Page 6. Line 16 – I think where you’ve used the word “efficacy” multiple times (here and later on in the manuscript), it should be “efficiency”.
ANSWER: We reviewed all the parts in the manuscript where the word “efficacy” appeared and we changed it for “efficiency” when possible. Thank you.

Page 6. Line 25-27 – The comment about OD being easy to diagnose is an overstatement. You might want to declare rather that there are well-established processes for its accurate diagnosis, such as routine screening followed by expert assessment. Then, the next sentence about the position statement follows nicely.
- ANSWER: the reviewer is right; we have rewritten this concept according to reviewer’s recommendation.
Page 6. Line 34-37 – I think there needs to be a more comprehensive explanation of dysphagia treatment. It sounds like the only way to treat is with modified diets, and that is certainly not the case. It might be better to describe behavioural treatment as compensatory (and modified diets are only one example) or restorative (e.g., use of exercises, maneuvers).
Thank you for this important comment. Treatment of post-stroke OD is a relevant area of our research, and these are our thoughts:
- There is an evidence-based and effective treatment for OD in these patients mainly oriented to compensating swallow impairments through adaptation of fluid viscosity and solid food textures to avoid aspiration and chocking, and improving nutritional status and oral health to avoid respiratory infections. This has been defined as the minimal effective treatment to be provided to this population or “minimal-massive intervention”[2]. The aim of this compensatory intervention is to avoid the complications of OD.
- However, advances in treatment for swallow dysfunction among post-stroke patients include improvements in compensatory strategies but are mainly focused on (1) peripheral stimulation strategies and (2) central, non invasive stimulation strategies that provide us with methods to stimulate the swallow response with pharmacological or physical stimuli with evidence of their clinical benefit. Among these methods, transcutaneous and intrapharyngeal electrical stimulation, pharmacological stimulation through TRPV agonists and non invasive brain stimulation techniques (NIBS) such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation.[3] The aim of these interventions are to restore the swallow function.
- We believe that these two strong tendencies and the results of new randomized control trials will bring about a lot of changes in the management of poststroke OD in the near future. This has a strong implication for healthcare professionals involved in the care of these patients, as education and

research in these new technologies is a cornerstone to allowing maximal potential recovery of stroke patients with OD. Therefore, combining the new pathophysiological and therapeutic tendencies may achieve specific neurorehabilitation treatment for these patients.
2. Martín A, Ortega O, Roca M, Arús M, Clavé P. Effect of A Minimal-Massive Intervention in Hospitalized Older Patients with Oropharyngeal Dysphagia: A Proof of Concept Study. J Nutr Health Aging. 2018.
3. Cabib C, Ortega O, Kumru H, et al. Neurorehabilitation strategies for poststroke oropharyngeal dysphagia: from compensation to the recovery of swallowing function. Ann N Y Acad Sci. 2016

Page 6. Line 39 – I think this sentence is long, coupling malnutrition and dehydration with good oral health practices. Maybe these two concepts should be placed in two different sentences, especially since the oral pathogens would related primarily to the oral health point.
- ANSWER: We appreciate your suggestion and have separatedthe concepts into different sentences. Thank you.
Page 6. Line 46-47 – LANGUAGE EDIT – I would say “diminish” instead of “avoid”
- ANSWER: We changed “avoid “for “diminish.”
Page 7.Line 4. It is not clear to me what sanitary costs are.
- ANSWER: We have changed this term to “healthcare costs”. Thank you.
Page 7.Line 11. – LANGUAGE EDIT - I would say “acute hospital setting” instead of “attention”
- ANSWER: We changed “attention” for “acute hospital setting.”.
Page 7. Line 13 – LANGUAGE EDIT – I would start the sentence with “Knowing” instead of “The knowledge of”.
- ANSWER: We changed “The knowledge of” for “knowing.”.
Page 7. Lines 25-28 – Are there any citations that could be used alongside the statement that OD costs are not well known?
-ANSWER: Yes, we can cite a recent study published by our group found that presenting OD after stroke was associated with high mortality rates during hospital stay and was an independent risk factor for prolonged length of hospital stay and to be institutionalized after hospital discharge; OD was also an independent risk factor for poorer functional capacity and increased risk of mortality 3 months after the stroke episode. This study stated these factors are of a great importance not only from the perspective of the patient health, but also because they represent a major social and economic burden.[1]

1. Rofes L, Muriana D, Palomeras E, et al. Prevalence, risk factors and complications of oropharyngeal dysphagia in stroke patients: A cohort study. Neurogastroenterol Motil. 2018.
Page 7. Line 51 – Why not search both Medline and EMBASE through OVID? Does it not have a better search platform for MEDLINE than Pubmed?

- ANSWER: Unfortunately we have access to OVID only for short periods of time in our institution, while Medline is a more accessible tool we can use to develop the search and indefinitely in the future.
Page 8.Line 16. – Do you mean an abstract screening phase and a subsequent full article review phase (I’m not familiar with the term “posterior selection”).

- ANSWER: Yes, the reviewer is right. We meant to say abstract screening phase and subsequent full article review phase. We have now deleted the term“posterior selection”,thank you.
Page 8.Lines 25-27. I think the title and abstract screening phase could be better defined. How will abstracts be systematically eliminated? Would they be excluded if there were no mention of certain words such as “stroke”, “OD”, and “costs”? How many screeners will be involved for this stage?

- ANSWER: We have rewritten the screening process following this comment. The screening will be done by one reviewer, and checked by a second reviewer. Studies will be selected if they have

relevant economic terms such as “costs” or “resources consumption” as well as relevant health terms such as “dysphagia” or “malnutrition, dehydration, frailty, respiratory infections and pneumonia” with “stroke” in the abstract or title.
Page 8.Paragraph starting at line 34. Are all study designs permissible? If not, which ones would not be included? Also, is there a minimum number of enrolled patients for included studies?

- ANSWER: Regarding the study type, we do not expect to eliminate any study because of its design. Regarding the type of economic study, we willnot consider those studies that do not provide data about the cost of the disease or its complications Wewill not eliminate any study because of the number of patients included. We have clarified this in the manuscript: “no restrictions related to the size of the sample will be imposed.”
Page 9.Lines 49-50. What is a temporary discount rate? Why would sensitivity analysis be used in an economic study design?

- ANSWER: Temporary discount rate: discounting is a technique usedin cost of illness studies and economic evaluations. In economic studies, the use of a temporary discount rate is important for direct and indirect costs that accrue past the first year. It enables the calculation at present values of benefits that accrue in the future. Discounting is explained as a time preference; for benefits, individuals prefer to renounce a part of benefits in an uncertain future and accrue them now; for costs, individuals prefer to delay them instead of incurring them in the present. In economic studies, a discount rate value is used to discount the future monetary amounts. Some tools for assessing the internal validity of economic studies (e.g. Drummond’s checklist) insist on the importance of applying a discount rate in these studies for costs that accumulate beyond one year. Importance of sensitivity analysis in an economic study design: economic studies in healthcare are very context-specific and some methodological decisions may affect results. Sensitivity analysis on certain parameters can help to apply economic assessments in other contexts, that is, to make them more transferable. Sensitivity analysis tests the robustness of the results by varying the items around which there is uncertainty.
Page 10.Line 11. Canadian Neurological Scale (full title should be used).
- ANSWER: Thank you.
Page 10.Lines 18. What is a “nutritional assessment”? Is this an evaluation of three-day intake quantity or is there another type of routine nutritional assessment of interest?
-ANSWER: Assessment of nutritional status is not an easy issue because there is not a single way to measure it. There are different indicators of nutritional status such as a) anthropometric measures (weight, weight loss, height, body mass index), b) assessment of body composition (fat mass, lean mass, muscle mass) by bioelectrical impedance or DEXA, c) biochemical indicators (albumin, prealbumin, …), and d) some validated questionnaires such as the Mini Nutritional Assessment (MNA) which screen for the risk of malnutrition. In addition, some dietary questionnaires have been developed to assess dietary habits and food intake but, although related to nutritional status, they do not directly evaluate nutritional status.

Page 10.Lines 47-48. What is an example of quantities of health and social resource consumption? How is this measured typically? Visit frequency?
-ANSWER: Typical examples of health resource consumption are the number of visits to primary care and the emergency department, number of outpatient visits and hospital stays. It also includes cost of medication and other types of treatment (such as rehabilitation or nutrition) and transport. Social resource consumption refers mainly to hours of formal or informal carers.
Page 13.Lines 41-50. This sentence is very long.
-ANSWER: We have divided it into two sentences.
Page 14.Lines 13-14. Raise awareness on “minimal care”. Does this mean the need for at least minimal care?

-ANSWER: We have recently defined the term minimal care for patients with OD.

Complications of OD are related to three main risk factors: a) impaired safety of swallow, causing the aspiration of respiratory pathogens to the airway; b) impaired nutritional status, leading to malnutrition, impaired immunity and frailty; and c) poor oral health (OH) and hygiene, associated with oral colonization by respiratory pathogens. Several interventional studies aiming at improving older patients'oral hygiene have significantly reduced the incidence of respiratory infections and pneumonia. However, it is necessary to treat these three main risk factors simultaneously in a minimal-massive intervention (MMI).

The aim of this kind of intervention (MMI) is to maximize the number of patients treated with simple and cost-effective measures based on the best scientific evidence. MMI is based on compensatory interventions such as fluid and food texture adaptation to avoid aspirations, nutritional supplementation to improve nutritional status, and oral hygiene to reduce the load of respiratory pathogens inthe oral cavity.

We have recently shown thatimplementation of MMI in hospitalized older patients with OD improvednutritional status and functionality and reducedhospital readmissions, respiratory infections and mortality. MMI might become a new simple and cost-effective strategy to avoid OD complications in the geriatric population admitted with an acute disease to a general hospital.[2]

2. Martín A, Ortega O, Roca M, Arús M, Clavé P. Effect of A Minimal-Massive Intervention in Hospitalized Older Patients with Oropharyngeal Dysphagia: A Proof of Concept Study. J Nutr Health Aging. 2018.
Page 25-26. What are "active" interventions? I presume they are restorative and functional (used during swallowing)?

-ANSWER: Active interventions are ODtreatments that aim to restore the impaired swallow function. For patients with post-stroke OD, we have recently published a review describing these treatments[3]. Characterization of post-stroke OD is evolving from the assessment of impaired biomechanics to the sensorimotor integration processes involved in deglutition. Treatment is also changing from compensatory strategies to promoting brain plasticity, both to recover swallow function and to improve brain-related swallowing dysfunction.

3. Cabib C, Ortega O, Kumru H, et al. Neurorehabilitation strategies for poststroke oropharyngeal dysphagia: from compensation to the recovery of swallowing function. Ann N Y Acad Sci. 2016

General Methods: I think that the quality appraisal for individual articles should be in the section on quality assessment (so risk of bias and individual GRADE in same section).

- ANSWER: We agree with the changes you are proposing onquality appraisal in this systematic review and will include both concepts in a larger section referring to the quality of the assessed evidence in this systematic review. Thank you.
General Methods: PRISMA statement – I think this should be placed at the beginning of the methods as it projects the whole plan for your protocol and systematic review. It seems like a bit of an addendum otherwise.

- ANSWER: We agree withputting PRISMA data at the beginning of the methods.. Thank you.
Table 1. Other than clearly defining which terms are [Mesh] terms, the other terms are not defined as to their nature. Which other terms are exploded (sometimes denoted with EXP or /)? Which terms are sought in the title, abstract, and/or keywords? Often, there are designated extensions such as "ti", "ab", "kw", or "tw". It would be helpful to identify the extensions or if they are not needed, how the term is being used to conduct the search. For example, when I try the term "Oropharyngeal Dysphagia" in

OVID EMBASE, it assigns the extension “mp”. Also, presenting a sample search with the number of total hits per term (and overall) would be informative as part of the protocol. So, for example, when the search is run in EMBASE, how many citations are identified at this point in time? The information would provide some knowledge of scope/breadth of the proposed search.

-ANSWER: Regarding Table 1: Thank you for your suggestions onthe identification of the terms used in the search strategy. We consulted an expert librarian in order to improve this section. We really appreciate all information provided to improve the way in which we are reporting such an important section of this work. Terms different than Mesh havebeen redefined:we have specified terms forwhich extensions are not needed (e.g. Dysphagia therapy/). We have specified in the manuscript the number of total articles founded at this point of time in Medline using Pubmed “Using this search strategy tosearch MEDLINE using Pubmed, a total of seventy articles were found in June 2018.”
Figure 1. In the box, “FULL-TEXT ARTICLES EXLUDED”, the information about inclusion criteria does not need to be restated. The points were clear in the methods.
- ANSWER: regarding Figure 1, we agree with your comment and have removed inclusion and exclusion criteria in this figure.

VERSION 2 – REVIEW

REVIEWER	Jessica Beavan Royal Derby Hospital, United Kingdom
REVIEW RETURNED	18-Jul-2018

GENERAL COMMENTS	This is a well written protocol, although I think it may be extremely difficult to gain data to answer the overall complicated question, but an important one to try and do. There are a couple of minor issues-describing dysphagia as an illness rather than an impairment; not defining TRPV, making clear that dysphagia is often a marker of severe stroke with other severe impairments and how that would be tackled (i.e. corrected for stroke severity-e.g. by NIHSS, MRS, BI, OCSP?). Pressure areas are also again not mentioned, which can be a consequence of malnutrition. Overall these are minor issues.

VERSION 2 – AUTHOR RESPONSE

Reviewer Name: Jessica Beavan. Institution and Country: Royal Derby Hospital, United Kingdom
This is a well written protocol, although I think it may be extremely difficult to gain data to answer the overall complicated question, but an important one to try and do.
ANSWER: Thank you very much for your positive comments.
There are a couple of minor issues-describing dysphagia as an illness rather than an impairment;
ANSWER: Although there is a debate regarding the consideration of OD as an illness or as animpairment, as the reviewer suggest we will refer to OD as a condition or a dysfunction in this protocol. However, as explained in the introduction section, OD is included in the International Classification of Diseases developed by the Wolrd Health Organization with specific codes.
Not defining TRPV,
ANSWER: Thank you for this suggestion, we have now defined this acronym in the text.
Making clear that dysphagia is often a marker of severe stroke with other severe impairments and how that would be tackled (i.e. corrected for stroke severity-e.g. by NIHSS, MRS, BI, OCSP?).
ANSWER: The reviewer is right indicating that OD could be a marker of stroke severity. We also recognize the difficulty to differentiate the costs attributable to OD from those attributed to stroke severity. This can only be assessed if individual studies report the independent or adjusted effect of OD and severity of stroke through multivariate analysis. By using this approach, we have recently

found OD after stroke was an independent risk factor for prolonged hospital stay (P = .049; β = 0.938) and institutionalization after discharge (OR = 0.47; CI = 0.24-0.92); OD was an independent risk factor for poorer functional capacity (OR = 3.00; CI = 1.58-5.68) and increased mor tality (HR = 6.90; CI = 1.57-30.34) 3 months after stroke.1 In our analysis we will consider the adjusted effect of OD when possible. We have introduced a sentence in the methodology to clarify this point. Thank you.

1: Rofes L, Muriana D, Palomeras E, Vilardell N, Palomera E, Alvarez-Berdugo D, Casado V, Clavé P. Prevalence, risk factors and complications of oropharyngeal dysphagia in stroke patients: A cohort study. Neurogastroenterol Motil. 2018 Mar 23:e13338. doi: 10.1111/nmo.13338. [Epub ahead of print] PubMed PMID: 29573064.

Pressure areas are also again not mentioned, which can be a consequence of malnutrition. Overall these are minor issues.

ANSWER: Thank you very much. Malnutrition may favour pressure sores, as well as many other clinical conditions such as sarcopenia, oedema or infectious diseases. In this regard, and as the reviewer suggest, we have introduced a sentence in the introduction section mentioning that treating malnutrition in poststroke patients reduces the risk of pressure sores documented by a systematic review that has been introduced in the reference section.