Author's response to reviews

Title: Oral disease in adults treated with hemodialysis: Prevalence, predictors, and association with mortality and adverse cardiovascular events: The rationale and design of the ORAL Diseases in hemodialysis (ORAL-D) study, a prospective, multinational, longitudinal, observational, cohort study

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Author's response to reviews: see over
Dear Editor,

We now wish to submit our revised protocol for the Oral Diseases in hemodialysis (ORAL-D) study to *BMC Nephrology* after consideration of comments from the editorial team and two expert reviewers. We have included a point-by-point discussion of the issues raised by reviewers and indicated any changes made to the manuscript.

Please note we have also taken the opportunity to add an additional author, Ms Patrizia Natale, MSc, who fulfils the criteria for authorship on this manuscript. We trust this addition is acceptable to the editorial board for this manuscript revision.

Thank you for your further consideration and we hope this protocol is now acceptable for publication on *BMC Nephrology*.

Sincerely

Giovanni FM Strippoli

On behalf of the authors
Responses to reviewers:

Reviewer 1:

1. Can the authors please check and correct the grammar in the first sentence of the background section as “People with end-stage kidney disease treated with dialysis experience high rates of deaths…”

We have amended this sentence as suggested.

2. Could authors mention the possible link among poor health, atherosclerosis and malnutrition in terms of increased cardiovascular risk in dialysis patients as a novel cardiovascular risk factor?

We have amended the introduction (paragraph 2 of introduction) to include a reference linking malnutrition to oral health and completed this paragraph stating the following:

“The relative contributions of socioeconomic disadvantage, malnutrition and cardiovascular disease to the prevalence of oral disease and associated outcomes for people who have kidney disease require analysis in a large longitudinal study, ahead of potential interventional trials.”

3. The authors mentioned in the method/design section that they will recruit 4500 dialysis patient from randomly selected pool of outpatient dialysis clinics in Europe and South America. I would appreciate if they would give some more detail about this pool and why these countries were selected for the study.

The clinics included in this study involved a large number of dialysis communities in countries with heterogeneity in social and economic circumstances. In addition, the ORAL-D study included sites in which investigators had committed to providing good-quality data for the study. All clinics were operating within a collaborative dialysis network administered by a large dialysis provider, Diaverum. We have added these specific details to the Methods section as appropriate.

4. The authors mentioned in the method/design section that dental surgeon will assess and examine the dental and periodontal status of the dialysis patients. I would appreciate if they would explain their choice about dental surgeon instead of periodontologist.

We thank the reviewer for pointing this out. All analyses-oral visits were conducted in all countries by dentists with training and experience in periodontology. We have amended the text.

5. Self-administered Questionnaires Section: I would appreciate if the authors would use “mouth wash use” or “mouth rinse use” instead of “mouth use”

We have corrected this.

6. Background section: I would appreciate if the authors mention the possible mechanisms about the association of periodontal and cardiovascular disease in detail. I would appreciate if they would also consider a recent and detailed review about the systemic

Inflammation has a central role in the pathogenesis of atherosclerotic complications in people who have chronic kidney disease. [Blood Purification 20:454, 2002] Periodontitis is a state of chronic infection of oral tissues that may contribute to atherosclerosis progression via pro-inflammatory pathways [AJKD 2006;47(5):815]. Notably, successful treatment of periodontitis is associated with lower levels of inflammatory cytokines including interleukin-6 and tumor necrosis factor-alpha and may attenuate endothelial dysfunction [J Dent Res 2004,83:156-160]. Accordingly, periodontitis may contribute to vascular injury and disease via inflammation. We have added additional relevant text of paragraph 2 of the Background section.

7. I would appreciate if the authors would consider malnutrition, inflammation and atherosclerosis (MIA) syndrome.

We have specifically commented on and referenced malnutrition, inflammation and atherosclerosis [MIA] syndrome as a potential link between oral disease and clinical outcomes in chronic kidney disease in the revised introduction (paragraph 2).

8. I would also appreciate if the authors would consider a recent and detailed review about the nomenclature and diagnostic criteria of “protein-energy wasting” term by Fouque D et al (Fouque D et al. Kidney International 2007).

We have now considered and referenced the protein-energy wasting syndrome in the Background of the revised manuscript.

9. I would appreciate if the authors mention the exclusion criteria as diabetes, patient treated with radiation to head and neck region, patients with advance age, handicapped patients in terms of searching thirst and preventive oral habits.

Study enrolment and baseline data capture have been completed and the exclusion criteria have already been defined. We deliberately took a broad population-based approach to inclusion criteria.

10. I would appreciate if the authors mention about the patients’ medication possibly related with dry mouth. I would appreciate if the authors give some detail which biochemical (including parameters related with inflammation as CRP) and clinical parameters will be used as searching the relationship between biochemical and clinical performance.

We have now referred specifically to our collection of medications associated with dry mouth in the Methods section [p 9].

We will not be collecting data for C-reactive protein specifically for this study. We will be collecting and analyzing data for albumin and protein catabolic rate as well as body weight parameters, in addition to other clinical parameters. We have now added protein catabolic rate to the parameters we have collected data for that are already listed in the Methods [p 9].

11. In the Oral Examination Section: I would appreciate if the authors give more detail about the oral examination day (dialysis-free day or dialysis day and pre or post-dialysis)
examination place (dialysis unit or dental clinic) and the standard instruments used in the dental examination as lights...

We have now added more specific information about the detailed of the oral examination to the Methods [p 10].

12. I would appreciate if the authors give some detail the data collection about patients’ medication possibly affected the oral bleeding indices as aspirin, warfarin.

We have added that we are collecting data for oral anticoagulants in the patient cohort in the Methods [p 9].

13. I would appreciate if the authors give some more details about the characteristics of the oral pain (tooth pain, temporomandibular joint pain?).

We have not specifically sought details on the source of oral pain experienced.

14. Salivary indices section: I would appreciate if the authors give some more detail about the collection of the saliva and containers (metal or plastic) as a methodology.

We have added more details on the evaluation of salivary indices in the Methods [pp 12 and 13].

Reviewer 2:

1. A causal relationship is proposed between oral disease and poor health in dialysis. Does scientific evidence exist for this relationship?

We note in our Abstract that we have highlighted potential causes for any link (lower use of dental services) and have now added to the Abstract the increased presence of inflammation and malnutrition as out potential causes for oral disease in this clinical setting. In addition, in response to both reviewers, we have been more specific about potential mechanisms that might explain any link between advanced kidney disease and poorer oral health which will be explored in part by our large study.

2. The abstract is written in the future, while it had happened in the past (July 2010-February 2012), please change... will assess in ... had assessed and so on.

We have altered the tense throughout to correspond to the completed enrolment.

3. Are control patients enrolled in this study, since the study takes place in many different countries? It enriches the scientific quality of this study if the authors do

We have not included control patients in this study.

4. Correlations will be explored between HD patients and clinical factors. Will this be a fishing experiment? Which clinical factors will be explored?

We have now defined the potential correlates of oral disease in this population based on hypotheses that oral health is related to nutrition, socioeconomic status and inflammation. Given we have
included a large number of participants we will be able to control for relevant clinical and demographic variables in multivariate analysis.

We will include as potential variables in analysis: age, sex, ethnicity, country or residence, educational status, living situation, occupation status, smoking, BMI, self-reported appetite, income, financial strain, comorbidity score, diabetes, existing cardiovascular disease, depression score, blood pressure, protein catabolic rate, hemoglobin, albumin, phosphorus, cholesterol, ferritin, parathyroid hormone, and duration on dialysis. We have listed these variables in the manuscript.

5. An association between periodontal etc. and premature mortality will be explored, do the authors expect a biological and logical causal relationship between one of the oral health variables.

In response to both reviewers, we have been more specific about the potential mechanisms by which oral health might be increased and be associated with important cardiovascular events in people treated with dialysis.

6. Experiences of xerostomia: xerostomia is already an experience, this word can be deleted.

Xerostomia is now not included in the manuscript.

7. Page 7: since several countries will be included, a statistical analysis should be carried out to exclude the effect of the country on the oral health.

We will control for country of origin in analyses.

8. How do the authors make sure that the intra-oral assessment is calibrated?

Dental surgeons in each country were trained according to the centralized and standardized protocol and methods used in the study.

9. Why did the authors decide to use stimulated saliva instead of unstimulated saliva (which is more representative for the feelings of oral dryness)?

We thank the reviewer for this question. A choice was made by the steering committee of the study to use stimulated instead of unstimulated saliva. The evidence for comparative efficacy of these two clinical methods remains sparse (Löfgren CD, Wickström C, Sonesson M, Lagunas PT, Christersson C. A systematic review of methods to diagnose oral dryness and salivary gland function. BMC Oral Health. 2012 Aug 8;12:29. doi: 10.1186/1472-6831-12-29). In a systematic review conducted by our group, of all studies assessing xerostomia in people of hemodialysis, 70% were done using stimulated saliva (data not shown, in press). Finally, we aim to evaluate not only saliva volumes but also pH and buffer capacity on the same saliva samples, and stimulated saliva is richer in protein and non-protein components.
10. Figure 2: the Xerostomia Inventory is not the original questionnaire. Please add information that the XI questionnaire was altered and adapted. This raises the question if the questionnaire needs to be validated again.

We thank the reviewer for pointing this out. During the preparation of the study, some questions were erroneously removed from the validated xerostomia inventory. As the study recruitment is now completed, the appropriate questionnaire cannot now be used. We have now removed references to study of xerostomia from the protocol.