Application for amendment to YODA project application 2017-1746

1. Purpose and date of amendment

Amendment proposed 25th November 2019.

Our current permissions are to analyse heterogeneity in treatment effects by ‘comorbidity’. We would like to request an amendment to our existing protocol to broaden the definition of ‘comorbidity’ to include functional deficits.

The overall aim of the project remains the same: to assess heterogeneity in treatment effectiveness for comorbid patients who, by definition, have multimorbidity. Our current applications seeks to quantify comorbidity using “a combination of demographic, past medical history, lifestyle (eg smoking) and drug variables as well as information from trial protocols (ie inclusion and exclusion criteria).” – page 4, paragraph 9. We would now like to additionally define comorbidities/deficiencies using elements from trial questionnaires so that we can also capture whether patients also have functional impairments. The purpose of this change is to assess whether, compared to the measures outlined in the initial application, adding functional deficits better identifies frailer multimorbid/comorbid patients, in whom we hypothesise that treatment efficacy may differ.

2. Modifications to protocol

We propose to identify functional deficits using baseline quality of life questionnaire data such as EQ-5D and SF-36. For example, if participants report ‘difficulty climbing stairs due to health’ from SF-36, or ‘I am unable to wash or dress myself’ from EQ-5D we would define these as deficits. As before, we would then seek to report the levels of comorbidity (eg https://rdcu.be/bXAzn), and to examine heterogeneity in treatment effects (not yet submitted).

However, to avoid potential disclosure, we would only use these additional functional measures as a part of a comorbidity/deficit count (e.g. a patient with two comorbidities on medical history and who had difficulty climbing the stairs would have a count of three). We would not seek to report the proportion of participants responding yes to these specific questions (or to report on the heterogeneity in effects according to the responses to these specific questions). Rather the comorbidities and functional deficits would be used to calculate a total ‘deficit count’, which would be used as a composite measure. This deficit count will be analysed in the same manner as the existing analyses, by inclusion as a treatment-covariate interaction in regression models.

As a check on the validity of the deficit count, we also wish to examine the association between the overall score and a subset of the score defined using the smaller set of variables previously defined. We will also assess the relationship of the count to the severity of the index condition at baseline.

3. Additional requested studies

We also wish to access the following additional studies. These meet the inclusion criteria for our earlier trial selection (they are all trials of type 2 diabetes, one of our exemplar conditions), but have been added to YODA since our initial application. Out purpose and analysis plan for these studies is the same as our original protocol, plus the amendment described above. List of trials - NCT01989754, NCT01809327, NCT01381900, NCT01032629 and NCT00642278.