D2d Publication and Presentation Proposal Submission Form

Office Use
Submission Number PR16-07 Date Submitted (MM/DD/YYYY) 08/15/2016

To: D2d Publications and Presentations Subcommittee

Re: D2d Publications and Presentations Preliminary Concept Proposal

Title of Proposal *(81 character limit)*: Baseline characteristics that predict pre-diabetes eligibility in the D2d study

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If Lead Author is not a member of the D2d study group, please specify:
D2d Co-Investigator
Institutional Affiliation

Proposed Writing Group (name and D2d role)

List one author per line. Indicate who will do the statistical analysis.

Larry Phillips- Atlanta VA
Others
To be determined once the writing group is formed

Scope of Project Proposal

- (●) D2d-wide
- ( ) Site-specific
- ( ) Other, specify

Publication Tier Designation (see D2d Publications and Presentations Policy)

- ( ) Tier 1
- (●) Tier 2
- ( ) Tier 3

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Significance, proposed central hypothesis and specific aims of analysis/preliminary abstract

D2d is one of the largest prospective studies enrolling subjects with pre-diabetes or "at risk for diabetes". It is the only large study enrolling patients using an inclusion criteria of meeting at least two-out-of-three of Hemoglobin A1c (A1c), impaired fasting glucose(IFG), and/or imparied glucose tolerance (IGT). The Diabetes Prevention Study did not use A1c as a inclusion criteria. Hence the population being studied may be different to that of DPP. Factors and variables that predict the progression to diabetes in this population could be very different. Since A1c is widely used clinically to screen patients for pre-diabetes, it is really important to study the prognostic ability of A1c in the setting of the D2d study to predict progression to diabetes, when combined with IGT or IFG.

Another factor that may effect the diagnosis of pre-diabetes and the prediction of diabetes are high and low glycators which result in over and under diagnosis of pre-diabetes if A1c is used alone. There are racial differences in ability to glycate. In the ACCORD study intensive treatment was associated with improved primary outcomes in the low hemoglobin glycation index (HGI) group verses the high HGI group (1).

Other important factors that contribute to the diagnosis of pre-diabetes and the diabetes prediction models are age, sex,race, duration of pre-diabetes, systolic BP,BMI, Triglycerides and LDL (Nichols GA). Some novel factors that may also contribute are, anemia, depression and elevations in AST/ALT.

These variables in relation to the conversion to diabetes as discussed above will be analyzed in another paper when all the diabetes outcomes have been reached for the D2d study. However at this time it would be useful to see if there are baseline characteristics that predispose subjects to have a positive A1c and IFG or IGT. The A1c or FBS is often used ALONE to determine a pre-diabetes diagnosis in the community. It would be useful to to see if the D2d enrolled population is different since they have both positive. It will be useful to see how the HGI affects the diagnosis of pre-diabetes as it is defined for the D2d study

Hypothesis: The D2d enrolled subjects will have unique glycation and baseline characteristics that predispose them to have a positive A1c and IFG or IGT

Specific Aim 1: To determine the baseline characteristics that predict that a subject will have both A1c and IFG or IGT at baseline

Specific Aim 2: To determine if glycation (high vs low glycaters) influences enrollment into the D2d study

Ref (1)The hemoglobin glycation index identifies subpopulations with harms or benefits from intensive treatment in the ACCORD trial. Hempe JM, Liu S, Myers L, McCarter RJ4, Buse JB, Fonseca V. Diabetes Care. 2015 Jun;38(6):1067-74. doi: 10.2337/dc14-1844. Epub 2015 Apr 17

Identify variables to be used in the analyses

Variables to be used

Baseline variables:

Laboratory variables- A1c, fasting plasma glucose, 2-hour post OGTT plasma glucose, triglycerides, total cholesterol, HDL, LDL, Hb/Hct, AST/ALT- collected at baseline

Non- laboratory variables- Age, gender, race, systolic BP, BMI, h/o of depression, h/o CVD, smoking- collected at screening/baseline

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Description of analysis plan (if desired, may include envisioned tables, figures)

1) The hemoglobin glycation index calculation: Screening and baseline FPG and HbA1c data from D2d participants will be used to estimate the linear relationship between FPG and HbA1c in the study population. Using this information predicted A1c for the observed FBS for participants will be calculated. Baseline HGI will be calculated by subtracting the predicted HbA1c from the observed HbA1c. HGI can then be analyzed either continuously or as upper and lower quartiles to separate high and low glycaters. This will then be analyzed to determine if HGI high or low HGI influences the diagnosis of prediabetes as defined in D2d.

2) Multivariate analysis will also be done to gauge the independent contribution of Race, sex, age,systolic BP, BMI, h/o of depression, h/o CVD, triglycerides, total cholesterol, HDL, LDL, Hb/Hct, AST/ALT to the HGI and the diagnosis of pre-diabetes as defined by D2d.

Proposal Type

Type of proposal (check all that apply)

- [x] Manuscript – analysis
- [ ] Manuscript – methodology
- [ ] Manuscript – validation
- [ ] Manuscript – other
- [ ] Letter to the Editor
- [ ] Abstract/Extended Abstract
- [ ] Oral Presentation (e.g. Powerpoint)
- [ ] Poster Presentation

Abstract and Presentations only

Intended meeting _____

Submission due date _____

Meeting date _____

Publications only

Intended journal Diabetes Care

Describe timeline for submission

Specific Aim 3 and four could be a separate paper and be done soon after close of all recruitment. For specific aims one and two we would have to wait till the end of the study.

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Acknowledgement of D2d Publications and Presentations Policy

I have read and agree to abide by the policies and procedures for D2d Publications and Presentations as described in the document titled: *D2d Publication and Presentation Policy*.

Lead Author Signature *(e-signature accepted)* Cyrus V. Desouza 440875

Digitally signed by Cyrus V. Desouza 440875
DN: dc=gov, dc=va, o=internal, ou=people, 0.9.2342.19200300.100.1.1=cyrus.desouza@va.gov, cn=Cyrus V. Desouza 440875
Location: OFFICE
Date: 2016.08.13 11:56:31 -05'00'

Date 08/15/2016

Note: After a proposal is submitted to the PPS and if approved, the lead author has nine months to submit a draft to the subcommittee for review. Should the lead author fail to submit a draft within nine months, the subcommittee may assign the proposal to other members of the D2d Research Group for completion.

Final steps to submission:
Save a copy of this form to your computer.
Click on the "Submit" button and follow the directions to submit electronically. Alternatively, you may attach the file manually to an email and send to: D2d@TuftsMedicalCenter.org.

Submit