Dataset Integrity Check for Effect of Oral Insulin on Prevention of Diabetes in Relatives of Patients With Type 1 Diabetes Krischer

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Contents

1 Standard Disclaimer

The intent of this DSIC is to provide confidence that the data distributed by the NIDDK repository is a true copy of the study data. Our intent is not to assess the integrity of the statistical analyses reported by study investigators. As with all statistical analyses of complex datasets, complete replication of a set of statistical results should not be expected in secondary analysis. This occurs for a number of reasons including differences in the handling of missing data, restrictions on cases included in samples for a particular analysis, software coding used to define complex variables, etc. Experience suggests that most discrepancies can ordinarily be resolved by consultation with the study data coordinating center (DCC), however this process is labor-intensive for both DCC and Repository staff. It is thus not our policy to resolve every discrepancy that is observed in an integrity check. Specifically, we do not attempt to resolve minor or inconsequential discrepancies with published results or discrepancies that involve complex analyses, unless NIDDK Repository staff suspect that the observed discrepancy suggests that the dataset may have been corrupted in storage, transmission, or processing by repository staff. We do, however, document in footnotes to the integrity check those instances in which our secondary analyses produced results that were not fully consistent with those reported in the target publication.

2 Study Background

The objective of the study was to determine whether oral insulin delays onset of type 1 diabetes in autoantibody-positive relatives of patients with type 1 diabetes. Between March 2, 2007, and December 21, 2015, relatives with at least 2 autoantibodies, including insulin autoantibodies and normal glucose tolerance, were enrolled in Canada, the United States, Australia, New Zealand, the United Kingdom, Italy, Sweden, Finland, and Germany. The main study group (n = 389) had first-phase insulin release on an intravenous glucose tolerance test that was higher than the threshold. The 55 patients in the secondary stratum 1 had an identical antibody profile as the main study group except they had first-phase insulin release that was lower than the threshold. Secondary strata 2 (n = 114) and strata 3 (n = 3) had different autoantibody profiles and first-phase insulin release threshold combinations. Follow-up continued through December 31, 2016.

3 Archived Datasets

All the SAS data files, as provided by the Data Coordinating Center (DCC), are located in the TrialNet_07/private_orig_data/Data.Extraction.7/7/sasv9/ folder in the data package. For this replication, variables were taken from the sas7bdat datasets ae, autoab, bmi, cpepm, cpepo, gtt hba1c, hla, insulin, mastable, rel, and rx.

4 Statistical Methods

Analyses were performed to duplicate results for the data published by Kirscher et al [1] in the journal JAMA Care in 2017. To verify the integrity of the dataset, descriptive statistics were computed.

5 Results

For Figure 1 in the publication [1], <u>Participant Flow Through Type 1 Diabetes TrialNet Study</u>, Table A lists the variables that were used in the replication and Table B compares the results calculated from the archived data files to the results published in Figure 1.

For Table 1 in the publication [1], <u>Distribution of Participant Characteristics by Treatment Group and Strata</u>, Table C lists the variables that were used in the replication and Table D compares the results calculated from the archived data files to the results published in Table 1.

6 Conclusions

The NIDDK repository is confident that the TrialNet_07 data files to be distributed are a true copy of the study data.

7 References

[1] Writing Committee for the Type 1 Diabetes TrialNet Oral Insulin Study Group. Effect of Oral Insulin on Prevention of Diabetes in Relatives of Patients With Type 1 Diabetes A Randomized Clinical Trial. *JAMA.* 2017;318(19):1891–1902. doi:10.1001/jama.2017.17070.

Table A: Variables used to replicate Figure 1: Participant Flow through Type 1 Diabetes TrialNet Study

Table Variable	dataset.variable
Randomized	mastable.reg
Randomized to receive	mastable.rxdesc
Stratum	mastable.stratum2

Table B: Comparison of values computed in integrity check to reference article Figure 1 values

REG value	RXDESC value	STRATUM2 value	MS n	IMS n	Diff n (%)
Randomized	-	-	560	560	0 (0)
	Oral Insulin	-	283	283	0 (0)
		Primary Stratum	203	202	1 (0.49)
		Secondary Stratum 1	28	30	2 (7.4)
		Secondary Stratum 2	51	51	0 (0)
		Secondary Stratum 3	1	0	1 (100)
	Placebo	-	277	277	0 (0)
		Primary Stratum	186	190	4 (2.2)
		Secondary Stratum 1	27	26	1 (3.7)
		Secondary Stratum 2	63	59	4 (6.3)
		Secondary Stratum 3	1	2	1 (100)

Table C: Variables used to replicate Table 1: Distribution of Participant Characteristics by Treatment Group and Strata

Table Variable	dataset.variable
Randomized	mastable.reg
Randomized to receive	mastable.rxdesc
Stratum	mastable.stratum2
Sex	mastable.sex
Race	mastable.race
Ethnicity	mastable.ethnicity
Height	bmi.heightcm
Weight	bmi.weightkg

Table D: Comparison of values computed in integrity check to reference article Table 1 values

STRATUM2 value (cohort)	RXDESC value (active/placebo)	Participant Characteristic	MS n (%) or mdn (IQR)	IMS n (%) or mdn (IQR)	Diff n (%)
Entire cohort	Oral insulin (active)	-	283	283	0
Entire cohort	Oral insulin (active)	Age (median (IQR))	8.2 (5.9-12.5)	8.2 (5.9-12.6)	0 (0-0.1)
Entire cohort	Oral insulin (active)	Gender = Boys	170 (60.1)	170 (60.1)	0 (0)
Entire cohort	Oral insulin (active)	Race = White	252 (95.5)	252 (95.5)	0 (0)
Entire cohort	Oral insulin (active)	Race = Black	8 (3.0)	8 (3.0)	0 (0)
Entire cohort	Oral insulin (active)	Race = Asian/PacIslander	4 (1.5)	4 (1.5)	0 (0)
Entire cohort	Oral insulin (active)	Ethnicity = Non-Hispanic	256 (90.5)	256 (90.5)	0 (0)
Entire cohort	Placebo	-	277	277	0
Entire cohort	Placebo	Age (median (IQR))	8.2 (5.4-11.5)	8.2 (5.4-11.5)	0 (0-0)
Entire cohort	Placebo	Gender = Boys	170 (61.4)	170 (61.4)	0 (0)
Entire cohort	Placebo	Race = White	249 (94.3)	250 (94.3)	1 (0)
Entire cohort	Placebo	Race = Black	9 (3.4)	9 (3.4)	0 (0)
Entire cohort	Placebo	Race = Asian/PacIslander	6 (2.3)	6 (2.3)	0 (0)
Entire cohort	Placebo	Ethnicity = Non-Hispanic	252 (91.0)	253 (91.3)	1 (0.3)
Primary Stratum	Oral insulin (active)	-	203	202	1
Primary Stratum	Oral insulin (active)	Age (median (IQR))	8.6 (6.1-12.8)	8.6 (6.1-12.7)	0 (0-0.1)
Primary Stratum	Oral insulin (active)	Gender = Boys	128 (63.1)	126 (62.4)	2 (0.7)
Primary Stratum	Oral insulin (active)	Race = White	181 (95.3)	180 (95.2)	1 (0.1)
Primary Stratum	Oral insulin (active)	Race = Black	6 (3.2)	6 (3.2)	0 (0)
Primary Stratum	Oral insulin (active)	Race = Asian/PacIslander	3 (1.6)	3 (1.6)	0 (0)

STRATUM2 value (cohort)	RXDESC value (active/placebo)	Participant Characteristic	MS n (%) or mdn (IQR)	IMS n (%) or mdn (IQR)	Diff n (%)
Primary Stratum	Oral insulin (active)	Ethnicity = Non-Hispanic	182 (89.7)	181 (89.6)	1 (0.1)
Primary Stratum	Placebo	-	186	190	4
Primary Stratum	Placebo	Age (median (IQR))	8.2 (5.5-11.8)	8.2 (5.5-11.5)	0 (0-0.3)
Primary Stratum	Placebo	Gender = Boys	117 (62.9)	119 (62.6)	2 (0.3)
Primary Stratum	Placebo	Race = White	172 (94.5)	176 (94.6)	4 (0.1)
Primary Stratum	Placebo	Race = Black	4 (2.2)	4 (2.2)	0 (0)
Primary Stratum	Placebo	Race = Asian/PacIslander	6 (3.3)	6 (3.2)	0 (0.1)
Primary Stratum	Placebo	Ethnicity = Non-Hispanic	171 (91.9)	174 (91.6)	3 (0.3)
Secondary Stratum 1	Oral insulin (active)	-	28	30	2
Secondary Stratum 1	Oral insulin (active)	Age (median (IQR))	9.1 (5.9-13.7)	8.9 (6.1-14.2)	0.2 (0.2-0.5)
Secondary Stratum 1	Oral insulin (active)	Gender = Boys	19 (67.9)	21 (70.0)	2 (2.1)
Secondary Stratum 1	Oral insulin (active)	Race = White	25 (96.2)	27 (96.4)	2 (0.2)
Secondary Stratum 1	Oral insulin (active)	Race = Black	0	0	0
Secondary Stratum 1	Oral insulin (active)	Race = Asian/PacIslander	1 (3.8)	1 (3.7)	0 (0.1)
Secondary Stratum 1	Oral insulin (active)	Ethnicity = Non-Hispanic	26 (92.9)	28 (93.3)	2 (0.4)
Secondary Stratum 1	Placebo	-	27	26	1
Secondary Stratum 1	Placebo	Age (median (IQR))	8.5 (6.5-10.8)	8.5 (6.7-10.7)	0 (0.2-0.1)
Secondary Stratum 1	Placebo	Gender = Boys	19 (70.4)	18 (69.2)	1 (1.2)
Secondary Stratum 1	Placebo	Race = White	25 (100)	24 (100)	1 (0)
Secondary Stratum 1	Placebo	Race = Black	0	0	0
Secondary Stratum 1	Placebo	Race = Asian/PacIslander	0	0	0
Secondary Stratum 1	Placebo	Ethnicity = Non-Hispanic	26 (96.3)	25 (96.2)	1 (0.1)

STRATUM2 value (cohort)	RXDESC value (active/placebo)	Participant Characteristic	MS n (%) or mdn (IQR)	IMS n (%) or mdn (IQR)	Diff n (%)
Secondary Stratum 2 & 3	Oral insulin (active)	-	52	51	1
Secondary Stratum 2 & 3	Oral insulin (active)	Age (median (IQR))	7.3 (5.1-10.3)	7.2 (4.7-10.2)	0.1 (0.4-0.1)
Secondary Stratum 2 & 3	Oral insulin (active)	Gender = Boys	23 (44.2)	23 (45.1)	0 (0.9)
Secondary Stratum 2 & 3	Oral insulin (active)	Race = White	46 (95.8)	45 (95.7)	1 (0.1)
Secondary Stratum 2 & 3	Oral insulin (active)	Race = Black	2 (4.2)	2 (4.3)	0 (0.1)
Secondary Stratum 2 & 3	Oral insulin (active)	Race = Asian/PacIslander	0	0	0
Secondary Stratum 2 & 3	Oral insulin (active)	Ethnicity = Non-Hispanic	48 (92.3)	47 (92.2)	1 (0.1)
Secondary Stratum 2 & 3	Placebo	-	64	61	3
Secondary Stratum 2 & 3	Placebo	Age (median (IQR))	8.3 (5.1-11.5)	8.3 (5.4-11.7)	0 (0.3-0.2)
Secondary Stratum 2 & 3	Placebo	Gender = Boys	34 (53.1)	33 (54.1)	1 (1.0)
Secondary Stratum 2 & 3	Placebo	Race = White	52 (91.2)	50 (90.9)	2 (0.3)
Secondary Stratum 2 & 3	Placebo	Race = Black	5 (8.8)	5 (9.1)	0 (0.3)
Secondary Stratum 2 & 3	Placebo	Race = Asian/PacIslander	0	0	0
Secondary Stratum 2 & 3	Placebo	Ethnicity = Non-Hispanic	55 (85.9)	54 (88.5)	1 (2.6)

Attachment A: SAS Code

```
options mprint nocentre linesize=163 validvarname=upcase;

%let rundate = y2018m11d19;
%let olddate = yYYYYmMMdDD;

title "Program:
/prj/niddk/ims_analysis/TrialNet_07/prog_initial_analysis/Data.Extraction.7/7/DSIC.paper.review.&
rundate..sas";
title2 "This program reviews TrialNet_07/Data.Extraction.7/7 data for level 1 PII";

/********************************************************************

programmer:  Jane Rideau Demuth

platform:  LINUX SASv9.4

date:  06 September 2018

purpose:  See title2.

********************************************************************/

**************;
*** formats ***;
**************;
proc format;
  value nmsgf
    . = ' '
    low-high = '###'
    ;
  value $cmsgf
    ' ' = ' '
    other = '$$$'
    ;
  value $stratumf
    'Primary' = 'Primary'
    'Secondary 1' = 'Secondary 1'
    'Secondary 2','Secondary 3' = 'Secondary 2&3'
    ;

******************;
*** input files ***;
******************;
libname tn777 "/prj/niddk/ims_analysis/TrialNet_07/private_orig_data/Data.Extraction.7/7/sasv9/";
data mastable;
  set tn777.mastable;
title3 "Input file:
/prj/niddk/ims_analysis/TrialNet_07/private_orig_data/Data.Extraction.7/7/sasv9/mastable.sas7bdat
";
proc contents data=mastable varnum;

%macro readin(ds);
data &ds.;
  set tn777.&ds.;
title3 "Input file:
/prj/niddk/ims_analysis/TrialNet_07/private_orig_data/Data.Extraction.7/7/sasv9/";
title4 "                ~&ds..sas7bdat";
proc contents data=&ds. varnum;
%mend readin;
%readin(ae);
%readin(autoab);
%readin(bmi);
%readin(cpepm);
%readin(cpepo);
%readin(gtt);
%readin(hba1c);
%readin(hla);
%readin(insulin);
```

9

```
%readin(rel);
%readin(rx);

**********************;
*** check figure 1 ***;
**********************;
proc freq data=mastable;
  title3 'Figure 1';
  tables reg*rxdesc*stratum2 / missing list;

*******************;
*** check table ***;
*******************;
data mastable;
  set mastable;

  *** calculate age ***;
  age = (dtreg-dtbirth)/365.25;

proc sort data=mastable;
  by stratum2;

proc freq data=mastable;
  title3 'Table';
  where reg = 0;
  tables rxdesc*(sex race ethnic) / missing;

proc freq data=mastable;
  title3 'Table';
  where reg = 0;
  by stratum2;
  tables rxdesc*(sex race ethnic) / missing;
  format stratum2 $stratumf.;

proc sort data=bmi;
  by maskid dtexam;

data bmi1st(keep=maskid bmi);
  set bmi(keep=maskid dtexam weightkg heightcm);
  by maskid dtexam;
  if first.maskid;

  *** calculate BMI ***;
  bmi = weightkg / ((heightcm/100) ** 2);

proc sort data=mastable;
  by maskid;

data mastable;
  merge mastable(in=keepthese)
        bmi1st(in=inbmi keep=maskid bmi);
  by maskid;
  if not(keepthese and inbmi) then abort;

proc sort data=mastable;
  by rxdesc;

proc univariate data=mastable noprint;
  var age bmi;
  by rxdesc;
  output out=mastableuni
        median=age_mdn bmi_mdn
        q1=age_q25 bmi_q25
        q3=age_q75 bmi_q75;

proc print data=mastableuni noobs;
  title3 'Table - Entire Cohort by Treatment';
  var rxdesc age_q25 age_mdn age_q75 bmi_q25 bmi_mdn bmi_q75;
  format age_q25 age_mdn age_q75 8.1;

proc sort data=mastable;
```

```
   by stratum2 rxdesc;
   format stratum2 $stratumf.;

proc univariate data=mastable noprint;
   var age bmi;
   by stratum2 rxdesc;
   output out=mastableuni2
          median=age_mdn bmi_mdn
          q1=age_q25 bmi_q25
          q3=age_q75 bmi_q75;
   format stratum2 $stratumf.;

proc print data=mastableuni2 noobs;
   title3 'Table - Entire Cohort by Stratum, Treatment';
   var stratum2 rxdesc age_q25 age_mdn age_q75 bmi_q25 bmi_mdn bmi_q75;
   format age_q25 age_mdn age_q75 8.1;

endsas;
```