

# Dataset Integrity Check for Islet Transplantation in Type 1 Diabetes (CIT-07)

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**August 9, 2018**

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## **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 National Institutes of Health established the Clinical Islet Transplantation (CIT) Consortium to evaluate more rigorously the risks and benefits associated with islet transplantation in T1D. The CIT-07 trial was designed to be a license enabling multicenter phase 3 clinical trial of a standardized, well-defined islet product, using a stringently defined, clinically relevant primary end point. Study participants had T1D of >5 years duration, and had persistent IAH and SHEs despite expert management by a diabetologist or endocrinologist for at least 1 year prior to study enrollment.

Participants in the CIT-07 study received up to three separate islet transplants and a regimen of immunosuppressive medications, including antithymocyte globulin (ATG), sirolimus, and tacrolimus, to support the engrafting of the islets into the beta-cell mass. Participants who did not achieve or maintain insulin independence by Day 75 post-transplant were considered for a second islet transplant, and participants who showed partial graft function and who remained dependent on insulin for longer than 1 month following the second transplant were considered for a third islet transplant. Basiliximab was used in place of ATG for the second and third transplants, if necessary. Following each transplant, study visits were conducted to perform a physical exam, review adverse events, and collect blood samples and information on quality of life. Participants were required to test their blood glucose levels throughout the study. Subjects were followed for 24 months after the participant's last transplant.

## **3 Archived Datasets**

All the SAS data files, as provided by the Data Coordinating Center (DCC), are located in the CIT-07 folder in the data package.

## 4 Statistical Methods

Analyses were performed to duplicate results for the data published by Hering et al [1] in Diabetes Care in 2016. To verify the integrity of the dataset, descriptive statistics were computed.

## 5 Results

For Table 1 in the publication [1], Recipient, donor, and graft characteristics, Table A lists the variables that were used in the replication and Table B compares the results calculated from the archived data file to the results published in Table 1. The results of the replication are almost an exact match to the published results, with some discrepancies in data presentation.

## 6 Conclusions

The NIDDK repository is confident that the CIT-07 data files to be distributed are a true copy of the study data.

## 7 References

[1] Hering, B.J., Clarke, W.R., Bridges, N.D., Eggerman, T.L., Alejandro, R., Bellin, M.D., Chaloner, K., Czarniecki, C.W., Goldstein, J.S., Hunsicker, L.G., Kaufman, D.B., Korsgren, O., Larsen, C.P., Luo, X., Markmann, J.F., Najj, A., Oberholzer, J., Posselt, A.M., Rickels, M.R., Ricordi, C., Robien, M.A., Senior, P.A., Shapiro, A.M.J., Stock, P.G., Turgeon, N.A., and the Clinical Islet Transplantation Consortium. "Phase 3 Trial of Transplantation of Human Islets in Type 1 Diabetes Complicated by Severe Hypoglycemia". Diabetes Care (2016) 39:1230-1240.

**Table A:** Variables used to replicate Table 1: Recipient, donor, and graft characteristics

<b>Table Variable</b>	<b>dataset.variable</b>
Gender	demographics_cit07.gender
Age	demographics_cit07.agetx1
Weight	demographics_cit07.weight
BMI	demographics_cit07.bmi
Duration of diabetes	demographics_cit07.duration
HbA1c (%)	hba1c_share_cit07.hba1c
HbA1c (mmol/mol)	round(((hba1c_share_cit07.hba1c - 2.152) * 10.931), 1)
Insulin requirement	
Units/day	Insulin_cit07.insulin
Units/kg/day	Mean_insulin_cit07.ins_kg
Autoantibodies	autoantibodies_cit07.posiaa, autoantibodies_cit07.posgad65, autoantibodies_cit07.posica512
Anti-insulin	autoantibodies_cit07.posiaa
Anti-GAD65	autoantibodies_cit07.posgad65
Anti-ICA512	autoantibodies_cit07.posica512
Clarke score	Clarke_cit07.clarke_score
HYPO score	Hypo_cit07.hypo_score
SHE 1 year pretx	
Glycemic LI	li_cit07.li_score
GFR	gfr_cit07.gfr
Nonproliferative retinopathy	retinopathy.(StageRetOS and StageRetOS)
Proliferative retinopathy	retinopathy.(StageRetOS and StageRetOS)
Microalbuminuria	Albumin_Crea_GFR_Components.UMALI
Donor age	manufacturing.age
Donor BMI	manufacturing.donorbmi
Donor sex	manufacturing.donorsex
Pancreas cold ischemia time	manufacturing.coldischtime
PHPI lot characteristics	
Total IEQ transplanted (per lot)	manufacturing.TotalPostTransplantIEQ
Tissue volume (mL/lot)	manufacturing.PackTissueVol
Total dose/subject	
Total IEQ transplanted (per subject)	ShareIEQ_Infused.PostTransplantIEQ
Total IEQ/kg transplanted (per subject)	ShareIEQ_Infused.PostTransplantIEQ_kg

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

Recipient characteristics	Observations (n) Manuscript	Observations (n) DSIC	Diff.	Median (minimum-maximum) or N (%) Manuscript	Median (minimum-maximum) or N (%) DSIC	Diff.
Gender (% male)	48	48	0	19 (39.6)	19 (39.6)	0 (0)
Age (years)	48	48	0	48.4 (26.2-65.5)	48.4 (26.2-65.5)	0 (0-0)
Weight (kg)	48	48	0	68.8 (48.0-111.1)	68.8 (48.0-111.1)	0 (0-0)
BMI (kg/m <sup>2</sup> )	48	48	0	25.1 (18.9-29.8)	25.2 (18.9-29.8)	0.1 (0-0)
Duration of diabetes (years)	48	48	0	28.5 (11-57)	28.5 (11-57)	0 (0-0)
HbA1c (%)	48	48	0	7.2 (5.7-9.2)	7.2 (5.7-9.2)	0 (0-0)
HbA1c (mmol/mol)	48	48	0	55 (39-77)	55 (39-77)	0 (0-0)
Insulin requirement	48	48	0			
Units/day				32.6 (11.4-62.1)	32.6 (11.4-62.1)	0 (0-0)
Units/kg/day				0.5 (0.2-0.8)	0.5 (0.2-0.8)	0 (0-0)
Autoantibodies	45	45	0			
Anti-insulin (% positive)				44 (97.8)	44 (97.8)	0 (0)
Anti-GAD65 (% positive)				29 (64.4)	29 (64.4)	0 (0)
Anti-ICA512 (% positive)				20 (44.4)	20 (44.4)	0 (0)
Clarke score	48	48	0	6 (3-7)	6 (3-7)	0 (0)
HYPO score*	48	40	8	1,253.5 (58-8,467)	1,253.5 (58-8,467)	0 (0-0)
SHE 1 year pretx	48	48	0	6.5 (0-336)	6.5 (0-336)	0 (0-0)
Glycemic LI*	48	40	8	622 (100-1,500)	622.3 (100.1-1,500.2)	0.3 (0.1-0.2)
GFR (mL/min/1.73 m <sup>2</sup> )	48	48	0	102 (80-130)	102 (80-130)	0 (0-0)
Diab Microvasc Complic	48	48	0			
Nonproliferative retinopathy (%)				16 (33.3)	16 (33.3)	0 (0)
Proliferative retinopathy (%)				6 (16.7)	6 (16.7)	0 (0)
Microalbuminuria (%)				5 (10.4)	5 (10.4)	0 (0)
Donor/pancreas characteristics						
Donor age (years)	75	75	0	42.8 (18.6-60.7)	42.8 (18.6-60.7)	0 (0-0)
Donor BMI (kg/m <sup>2</sup> )	75	75	0	33.4 (20.9-50.3)	33.4 (20.9-50.3)	0 (0-0)
Donor sex (% male)	75	75	0	53 (70.7)	53 (70.7)	0 (0)
Pancreas cold ischemia time (h/per isolation)**	75	75	0	7.7 (3.7-13.0)	7.7 (3.9-13.0)	0 (0.2-0)

Recipient characteristics	Observations (n) Manuscript	Observations (n) DSIC	Diff.	Median (minimum-maximum) or N (%) Manuscript	Median (minimum-maximum) or N (%) DSIC	Diff.
PHPI lot characteristics						
Total IEQ transplanted (per lot)	75	75	0	480,500 (282,156-1,005,822)	480,500 (282,156-1,005,822)	0 (0-0)
Tissue volume (mL/lot)	75	75	0	4.0 (0.8-11.5)	4.0 (0.8-11.5)	0 (0-0)
Total dose/subject						
Total IEQ transplanted (per subject)	48	48	0	820,286 (286,565-1,562,425)	820,286 (286,565-1,562,425)	0 (0-0)
Total IEQ/kg transplanted (per subject)	48	48	0	11,972 (5,227-25,553)	11,97 (5,227-25,553)	0 (0-0)

\*Note that the number of subjects presented in the manuscript represents the number of patients in CIT-07. The values calculated in the DSIC represent the number of subjects with observations for that variable.

\*\*Note that the number presented as the minimum in the manuscript is a typo. The correct value for minimum pancreas cold ischemia time is 3.9.

## Attachment A: SAS Code

```
*****
***Programmer: Sabrina Chen
***Date Created: 5/21/2018
***Purpose: Compare the data received from the CIT-07 DCC to a published paper.
***
*****;

title1 "%sysfunc(getoption(sysin))";
title2 " ";

options nocenter validvarname=upcase;
title 'prj/niddk/ims_analysis/CIT_07/prog_initial_analysis/cit07_dsic.2018.sas';
run;

proc format;
    value visitf 1 = 'Baseline'
                2 = 'Day 75'
                3 = 'Day 365'
                4 = 'Day 730';

    value $insulinf 'Failure' = 0
                  'Failure(termination)' = 0
                  'Insufficient data' = 0
                  'Success' = 1;

    value genderf 1 = 'Male'
                 2 = 'Female';

run;

libname datadict "/prj/niddk/ims_analysis/CIT_07/private_orig_data/Data_Dictionaries/";
libname pclib v9 '/prj/niddk/ims_analysis/CIT_07/private_created_data/sas_data';

data demographics_cit07;
    set pclib.demographics_cit07;
run;

proc contents data=demographics_cit07;
run;

data autoantibodies_cit07;
```



```

        set pclib.autoantibodies_cit07;
run;

proc contents data=autoantibodies_cit07;
run;

data Dictionary;
    set datadict.Data_Dictionary_V1;
run;

proc contents data=dictionary;
run;

proc freq data=dictionary;
    tables table_name*variable_name/list missing;
run;

data gfr_cit07;
    set pclib.gfr_sharev2_cit07;
run;

proc contents data=gfr_cit07;
run;

data retinopathy_cit07;
    set pclib.retinopathy_cit07;
run;

proc contents data=retinopathy_cit07;
run;

data albumin_cit07;
    set pclib.albumin_cit07;
run;

proc contents data=albumin_cit07;
run;

data insulin_cit07;
    set pclib.insulin_cit07;
run;

proc contents data=insulin_cit07;
run;

data mean_insulin_cit07;
    set pclib.mean_insulin_cit07;
run;

```

```
proc contents data=mean_insulin_cit07;
run;

data clarke_cit07;
  set pclub.clarke_cit07;
run;

proc contents data=clarke_cit07;
run;

proc print data=clarke_cit07;
run;

data hypo_cit07;
  set pclub.hypo_cit07;
run;

proc contents data=hypo_cit07;
run;

data li_cit07;
  set pclub.li_cit07;
run;

proc contents data=li_cit07;
run;

data hbalc_share_cit07;
  set pclub.hbalc_share_cit07;
run;

proc contents data=hbalc_share_cit07;
run;

data ieq_infused_cit07;
  set pclub.ieq_infused_cit07;
run;

proc contents data=ieq_infused_cit07;
run;

** Pull the baseline record;
proc sort data = demographics_cit07;
  by ACCESSION ;
run;

proc sort data = autoantibodies_cit07;
  by ACCESSION NUMDAYSINITIAL;
```

```

run;

data autoantibodies_cit07;
  set autoantibodies_cit07;
  by accession;
  if first.accession;
run;

proc sort data = gfr_cit07;
  where          pstintvst=1;
  by ACCESSION;
run;

proc sort data = ieq_infused_cit07;
  where tx=1;
  by ACCESSION;
run;

proc sort data=insulin_cit07;
  by ACCESSION NUMDAYSINITIAL;
run;

data insulin_cit07;
  set insulin_cit07;
  by ACCESSION pstintvst;
  where pstintvst = 1;

  retain total_insulin count_num 0;
  if first.pstintvst then do;
    total_insulin = 0;
    count_num = 0;
  end;

  count_num = count_num + 1;

  total_insulin = sum(insulin, total_insulin);

  if last.pstintvst then do;
    avg_insulin = total_insulin / count_num;
    output insulin_cit07;
  end;
run;

proc sort data=mean_insulin_cit07;
  where          pstintvst=1;
  by ACCESSION NUMDAYSINITIAL;
run;

```

```

proc sort data=clarke_cit07;
  where      pstintvst=1;
  by ACCESSION ;
run;

proc sort data=hypo_cit07;
  where      pstintvst=1;
  by ACCESSION ;
run;

proc sort data=li_cit07;
  where      pstintvst=1;
  by ACCESSION ;
run;

proc sort data=hbalc_share_cit07;
  where      pstintvst=1;
  by ACCESSION;
run;

data table1;
  merge demographics_cit07      (in=indem keep=ACCESSION bmi duration weight gender agetx1)
        autoantibodies_cit07   (keep=ACCESSION posiaa posgad65 posica512)
        gfr_cit07              (keep=ACCESSION gfr)
        ieq_infused_cit07      (keep=ACCESSION posttransplantieq posttransplantieq_kg)
        insulin_cit07          (keep=ACCESSION avg_insulin)
        mean_insulin_cit07     (keep=ACCESSION ins_kg)
        clarke_cit07           (keep=ACCESSION clarke_score)
        hypo_cit07             (keep=ACCESSION hypo_score)
        li_cit07               (keep=ACCESSION li_score)
        hbalc_share_cit07      (keep=ACCESSION hbalc)

  ;
  by ACCESSION;

  if posiaa = . and posgad65 = . and posica512 = . then antibody_data = 0;
  else antibody_data = 1;

  hbalcmmol = round(((hbalc - 2.152) * 10.931), 1);

  if indem then output;
run;

proc freq data = table1;
  tables gender;

```

```

format gender genderf.;
title 'Table 1 - Gender';

proc means data = table1 n median min max;
*   var age;
   var agetx1;
   title 'Table 1 - Age';

proc means data = table1 n median min max;
   var weight;
   title 'Table 1 - Weight';

proc means data = table1 n median min max;
   var bmi;
   title 'Table 1 - BMI';

proc means data = table1 n median min max;
   var duration;
   title 'Table 1 - Duration of Diabetes';

proc means data = table1 n median min max;
   var hbalc;
   title 'Table 1 - HbA1c %';

proc means data = table1 n median min max;
   var hbalcmmol;
   title 'Table 1 - HbA1c mmol/mol';

proc means data = table1 n median min max;
   var avg_insulin;
   title 'Table 1 - Insulin requirements - Units/day';

proc means data = table1 n median min max;
   var ins_kg;
   title 'Table 1 - Insulin requirements - Units/kg/day';

proc freq data = table1;
   tables antibody_data;
   title 'Table 1 - Autoantibodies samples collected';

proc freq data = table1;
   tables posiaa;
   title 'Table 1 - Anti-insulin';

proc freq data = table1;
   tables posgad65;
   title 'Table 1 - Anti-GAD65';

proc freq data = table1;
   tables posica512;
   title 'Table 1 - Anti-ICA512';

```

```

proc means data = table1 n median min max;
    var clarke_score;
    title 'Table 1 - Insulin requirements - Clarke Score';

proc means data = table1 n median min max;
    var hypo_score;
    title 'Table 1 - Insulin requirements - HYPO Score';
/*
proc means data = table1 n median min max;
    var she;
    title 'Table 1 - Insulin requirements - SHE 1 year pretx';
*/
proc means data = table1 n median min max;
    var li_score;
    title 'Table 1 - Insulin requirements - Glycemic LI';

proc means data = table1 n median min max;
    var gfr;
    title 'Table 1 - GFR';

proc means data = table1 n median min max;
    var posttransplantieq;
    title 'Table 1 - Total IEQ transplanted (per subject)';

proc means data = table1 n median min max;
    var posttransplantieq_kg;
    title 'Table 1 - Total IEQ/kg transplanted (per subject)';

```