Restoring Insulin Secretion (RISE)

Data Release Documentation

Adult Medication Study

Prepared by the RISE Coordinating Center

The George Washington University Biostatistics Center
6110 Executive Boulevard, Suite 750
Rockville, MD 20852

Telephone: (301) 881-9260
Fax: (301) 881-8752

Restoring Insulin Secretion (RISE)
Adult Medication Study
Table of Contents

1. Introduction 4

1.1 General 4

1.2 Participants 4

1.3 Visits 4

1.4 Treatment Arms 4

1.5 Primary Measurements 5

1.6 Primary Outcomes 5

1.7 Statistical methods for primary and major secondary outcomes 6

2. Release Information 8

2.1 General Information 8

2.2 Data Location 8

2.3 De-identified Data 8

2.4 Structure of the Datasets 8

2.4.1 Data Files 8

3. Serious Adverse Events 9

4. File Descriptions 9

4.1 Data Forms 9

4.1.1 General 9

4.1.2 Variable Names on Data Forms 9

4.2 Datasets for Non-Form Data 10

4.3 Variables Common to All Datasets 10

4.4 Screening and Run-in Forms 10

4.4.1 SCREEN: Screening Form 11

4.4.2 RUNSTART: Start Of Run-In Visit Inventory 11

4.4.3 RUNEND: End Of Run-In Visit Inventory 11

4.4.4 SLPQ_ADU: Adult Sleep Questionnaire Results 11

4.5 Baseline and Follow-up Forms 11

4.5.1 BASELINE: Baseline Visit Inventory 11

4.5.2 CLAMP: Hyperglycemic Clamp Procedure 11

4.5.3 EXITFORM: Participant Exit Interview 11

4.5.4 HISTORY: Participant Survey And Medical History 12

4.5.5 LOCLAB: Local Lab Results 12

4.5.6 OGTT: Oral Glucose Tolerance Test Procedure 12

4.5.7 SMBG: Self-Monitoring Blood Glucose Form 12

4.5.8 STATUS: Participant Study Status 12

4.5.9 VISIT: Clinical Visit Inventory 12

4.5.10 UNSCHED: Unscheduled Visit Inventory 12

4.6 Laboratory Data 12

4.6.1 RISEADULT_CLAMPDATA: Centrally-Measured Laboratory Data: Hyperglycemic Clamp 12
4.6.2 RISEADULT_OGTTDATA: Centrally-Measured Laboratory Data: 3-Hour Oral Glucose Tolerance Test 14
4.6.3 RISEADULT_OTHERLABDATA: All Other Centrally-Measured Laboratory Results 15
4.7 Other Created Datasets 15
4.7.1 RISEAdult_BASEDATA: Baseline Data 15
5. References: 17

1. Introduction

1.1 General

The Restoring Insulin Secretion (RISE) Study was 3 parallel randomized clinical trials designed to investigate whether early intervention in patients with prediabetes or early type 2 diabetes could restore β-cell function, and whether improved β-cell function is maintained following a 3-month medication washout period. The three studies comprising RISE are:

1) RISE Adult Medication Study, which recruited adult participants at 1) The University of Washington/VA Medical Center in Seattle, WA, 2) Indiana University in Indianapolis, IN and 3) University of Chicago/Jesse Brown VA in Chicago, IL.
2) RISE Pediatric Medication Study, which recruited pediatric participants at 1) University of Colorado, Denver, in Denver CO, 2) University of Pittsburgh in Pittsburgh, PA, 3) Yale University in New Haven CT, and 4) Indiana University in Indianapolis, IN.
3) BetaFat Study, which recruited adult participants at Kaiser Permanente in Los Angeles, CA.

***This data release is relevant to the RISE Adult Medication Study only*.**

Detailed information about RISE including RISE protocols, manuals, references, publication list, and links to abstracts and manuscripts is available at http://risestudy.org. This report describes the complete public release of the RISE Adult Medication Study dataset. A brief description of the trial is given below; further details can be found in Reference 1.

1.2 Participants

Adults aged 20-65 years were eligible for the RISE Adult Medication Study if they had a fasting plasma glucose 95-125 mg/dl plus a 2-hour oral glucose tolerance test (OGTT) glucose ≥140 mg/dl, along with HbA1c ≤7.0%. Detailed eligibility and exclusion criteria can be found in Reference 1.

1.3 Visits

Randomization into the RISE Adult Medication Study began in July 2013 and continued for four years through October 2017. Participants were seen at quarterly visits after randomization for a total of 21 months. Comprehensive 2-day baseline (BAS), Month 12 (M12) and Month 15 (M15) assessments included physical measurements, medical history updates, adverse event assessment, medication adherence and dispensing, questionnaires, a 3-hour 75g oral glucose tolerance test (OGTT) and a 2-step hyperglycemic clamp. Month 6 (M06) and Month 21 (M21) visits were briefer and included a subset of physical measurements, adverse event assessment, medication adherence and dispensing, and a 3-hour 75g OGTT. Quarterly visits at Month 3 (M03), Month 9 (M09) and Month 18 (M18) were very brief and included limited physical measurements, HbA1c, adverse event assessment and medication adherence and dispensing. The study timeline is presented diagrammatically in Figure 1.

1.4 Treatment Arms

At randomization, participants were randomly assigned to one of four treatment groups:

1. insulin glargine for 3 months followed by metformin for 9 months (G/M)
2. liraglutide combined with metformin (L+M) for 12 months
3. blinded metformin for 12 months (M)
4. blinded placebo matched to metformin for 12 months (P).

Participants were given their medication at the randomization visit and at the M03, M06 and M09 quarterly visits. Titration details can be found in Reference 1.

1.5 Primary Measurements

The primary RISE Adult Medication Study aim was to assess the durability of treatment effect 3-months post-medication withdrawal in sustaining improvements in hyperglycemic clamp-measured β-cell function, adjusted for baseline. Specifically, we evaluated the hypothesis that G/M, L+M or M would be superior to P at the M15 assessment.

RISE used a two-step hyperglycemic clamp to directly quantify first phase (first ten minutes after priming glucose bolus) and steady state (at plasma glucose ~200 mg/dl; ~11.1 mmol/l) ß-cell responses to intravenous glucose, and the maximal arginine-stimulated ß-cell response during hyperglycemia (>450 mg/dl; >25.0 mmol/l). A 3-hour OGTT was used to evaluate ß-cell responses in the context of an enterally delivered stimulus. Laboratory outcome measures were measured in a central laboratory.

Hyperglycemic Clamp: A two-step hyperglycemic clamp was performed as described in Reference 1. Participants fasting for 10-hours overnight prior to the visit. Using variable rate 20% dextrose infusions, glucose was clamped using a computerized algorithm combined with bedside blood glucose monitoring every 5-10 minutes. For the first step, a targeted, steady-state plasma glucose concentration of 11.1 mmol/L was achieved and maintained through 120 minutes. Blood samples were drawn through an indwelling intravenous catheter in a warmed hand prior to starting the clamp and at 100, 110 and 120 minutes (steady-state) after commencing the dextrose infusion. Thereafter, the infusion rate was increased to achieve the second step target, which was a plasma glucose >450 mg/dL (>25 mmol/L). After this target glucose had been attained for a minimum of 30 minutes after commencing the second step, a bolus of L-arginine (5 grams) was administered over one minute. Blood samples for subsequent assays were drawn at -5, -1, 2, 3, 4 and 5 minutes relative to the arginine injection.

Oral Glucose Tolerance Test: Following a 10-hour overnight fast, a 3-hour, 75-gram OGTT was performed. Blood samples were obtained -10, -5, 10, 20, 30, 60, 90, 120, 150 and 180 minutes relative to glucose ingestion.

1.6 Primary Outcomes

Hyperglycemic clamp measurements were made at baseline (BAS), after 12 months on-treatment (M12) and 3 months after treatment withdrawal (M15).

Insulin Sensitivity: Insulin sensitivity (M/I) was quantified as the mean of the glucose infusion rate (M) at 100, 110 and 120 minutes of the hyperglycemic clamp corrected for urinary glucose loss, divided by the mean steady-state plasma insulin concentration at these same time points (I). This measure was expressed per kg body weight.

C-peptide and Insulin Responses: From the hyperglycemic clamp, the following measures were calculated.

- Fasting concentrations were the average of the two samples drawn prior to glucose administration.
- Acute (first-phase) C-peptide (ACPRg) and insulin (AIRg) responses to glucose were calculated as the mean incremental response above fasting from samples drawn at 2, 4, 6, 8 and 10 minutes following intravenous dextrose administration.
- Steady-state C-peptide, insulin and glucagon concentrations were calculated as the mean of the respective measurements at 100, 110 and 120 minutes.
- Acute C-peptide (ACPRmax) and insulin (AIRmax) responses to arginine at maximal glycemic potentiation (>450 mg/dl; >25.0 mmol/l) were calculated as the mean concentrations in samples drawn 2, 3, 4 and 5 minutes after arginine injection minus the average concentration of the samples drawn 1 and 5 minutes prior to arginine.

RISE included two co-primary outcome measures derived from the hyperglycemic clamp: 1) the clamp-derived glucose-stimulated steady state C-peptide secretion (SS C-peptide) and maximal C-peptide response to arginine during hyperglycemia (ACPRmax), along with a major secondary outcome of acute (first-phase) C-peptide (ACPRg). Although the primary outcome was assessed 3 months following medication withdrawal at M15, RISE included a major secondary evaluation at the end of the treatment period at M12. Primary and secondary outcome analyses were adjusted for the prevailing insulin

sensitivity.

1.7 Statistical methods for primary and major secondary outcomes

The aim of RISE required that β-cell function appropriately accounts for the reciprocal relationship of insulin sensitivity and the β-cell's insulin response, and thus we must account for movement of both variables simultaneously without forcing a specific relationship between them. This was accomplished by performing the primary and major secondary outcome analyses using two separate models: insulin sensitivity (M/I) at M15 vs. treatment arm (adjusted for baseline) and C-peptide (and insulin) release at M15 vs. treatment arm (adjusted for baseline), where the two models are fit simultaneously using Seemingly Unrelated Regression techniques (2-6). This provides an estimate of the treatment group comparison in insulin sensitivity as well as the treatment group comparison in the release of the β-cell peptides, while allowing for the correlation among the insulin sensitivity and peptide release measures. This yields an estimate of the joint covariance structure of the two models, and allows a joint statistical test of both variables using a 6-DF chi-square test of the treatment arm comparisons in each model. Thus, we tested whether both the insulin sensitivity and C-peptide (and insulin) release variables were different across the 4 treatment groups at M15, adjusted for their baseline value.

This approach provided a clear answer to the question of whether the M15 β-cell function differs by treatment group, adjusted for baseline measures. However, given that an underlying reciprocal relationship is expected, it is possible that a significant difference could be found between groups, but that this represents a proportional shift without a specific improvement in peptide release adjusted for sensitivity. In other words, the data points could lie on a different part of a shared relationship curve such that the change represents a mutually compensated change in these terms without a separate underlying change in beta-cell function. Therefore, if the results of the two-model analysis were significant, further analyses evaluated the patterns of change in either or both variables within each group.

In order to maintain a study-wide α=0.05, a closed testing procedure was be used to assess the primary outcome. The closed testing procedure is a method of hierarchical testing which tests higher-order comparisons before allowing lower-level comparisons, thus controlling the type I error and preserving power. First, ß-cell function was compared across the four treatment groups using an analysis of covariance model adjusted for baseline ß-cell function. From this model, the overall test of equality across the four treatment groups was computed. If that overall test was significant at the α=0.05 level, then each of the four possible sets of three interventions was compared in four separate analysis of covariance models. The final significance testing of any set of two treatment groups is only undertaken if the p-values for each of the two 3-intervention tests which include a particular two intervention group are both p<0.05. For example, for interventions I1, I2, I3 and I4, the first analysis of variance test I1234 assesses whether there are any differences among the four groups. If the overall test across the four groups is not significant, testing concludes and no treatment group is declared different from any other. Alternately, if that initial 4-group test is significant at the α=0.05 level, four separate analysis of covariance models with combinations I123, I124, I134 and I234 are tested. The comparison I12 is only tested if both I123 and I124 are significant at p<0.05 and so forth. The closed testing procedure was chosen as the primary outcome analysis to maintain an overall study-wide α=0.05 while preserving power and allowed each set of interventions to be compared under pre-specified circumstances. The two primary outcomes were analyzed separately with a total type I error probability of 0.05 for each, i.e. without an adjustment for two separate outcomes.

Below is sample Primary Outcome R code used for these analysis.

R code and sample output for primary outcome with Seemingly Unrelated Regression model using systemfit

```
> fit12=systemfit(list(Eq1 = log_mi ~ Treatment + log_mi_base,
                       Eq2 = log_cpeptide_steady ~ Treatment +
                               log_cpeptide_steady_base),
```

```
                method='SUR',
                data=RISEM15)

> linearHypothesis(fit12,test = "Chisq",
                   c('Eq1_TreatmentTreat2=0','Eq2_TreatmentTreat2=0',
                     'Eq1_TreatmentTreat3=0','Eq2_TreatmentTreat3=0',
                     'Eq1_TreatmentTreat4=0','Eq2_TreatmentTreat4=0'))

Hypothesis: Eq1_TreatmentTreat2 = 0    Eq2_TreatmentTreat2 = 0
               Eq1_TreatmentTreat3 = 0    Eq2_TreatmentTreat3 = 0
               Eq1_TreatmentTreat4 = 0    Eq2_TreatmentTreat4 = 0


Model 1: restricted model
Model 2: fit12

  Res.Df   Df   Chisq     Pr(>Chisq)
1   xxx
2   xxx-6   6    xxxx    x.xxx ← pvalue for the joint statistical test of
both sensitivity and secretion variables of the treatment arms across the 4
groups.  If significant, then each 3-arm combination is tested as described
above.
```

2. Release Information

2.1 General Information

- No participant identifying information is included.
- A randomly generated RISE_REPOSITORY_ID uniquely identifies each participant.
- Clinic and all other location identifiers have been removed.
- No dates are included; visit dates are provided as days from randomization.
- Only randomized participants who provided consent to distribute their data to the repository are included. Out of the 267 original RISE Adult Medication Study participants, the 264 participants who consented are included in this release dataset.
- In accordance with HIPAA regulations and to protect the identification of participants, the data has been de-identified to ensure that no participant is identifiable. For example, data was sorted into small, clearly identifiable groups and collapsed if the sample size was small.
- Only research data is included in the released dataset, including data for screening and post-randomization clinic visits, and laboratory data. Non-research data, including tracking forms, are not included. Detailed serious adverse event data were collected but are also not included in the data release to protect participant confidentiality.
- All available data from each form and laboratory is included. Missing data was caused by a variety of reasons: the visit was not completed in its entirety; the variable or blood sample was not collected or measured; the variable was completed incorrectly; the visit was missed, etc.

2.2 Data Location

Data are released from the RISE Coordinating Center at the George Washington University Biostatistics Center to the Data Repository at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health.

2.3 De-identified Data

The RISE Adult Medication Study dataset was de-identified in the following manner.

- All personal identifiers were removed, including participant ID and other personal identifiers, clinical center, and all dates.
- Variables that might identify a particular individual were collapsed into wider groupings.
    - Age at baseline was collapsed into 20-49, 50-59, 60+ year old age groups.
    - Race/ethnicity was coded as non-Hispanic White and all other race/ethnicity groups combined.
- Text string data that include participant or staff names, initials and dates has that PID removed.

2.4 Structure of the Datasets

2.4.1 Data Files

- The files are included as SAS datasets. The contents of variables in each dataset is provided.
- One record exists in each file for each participant for each visit at which that particular form was completed or data was collected. Variable RISE_REPOSITORY _ID is used to identify a particular participant and variable VISIT to identify which visit was completed.
- This dataset includes data collected at all quarterly visits, including screening, run-in, baseline and quarterly visits through M21. Section 3 describes in detail the data included.

3. Serious Adverse Events

As noted, detailed serious adverse events were collected but are not included in the data release to protect participant confidentiality. A complete listing of RISE Adult Medication Study SAEs is below. All SAEs were deemed unrelated to the study interventions by an adjudication committee masked to treatment arm.

RISE Adult Medication Study
All Serious Adverse Events by Treatment Group

Glargine followed by Metformin	Liraglutide with Metformin	Metformin Alone	Placebo
• Hospital admission for chest pain • Two hospital admissions for chest pain and tightness • Severe angioedema attributed to Lisinopril • Syncopy	• Kidney stone removal • Elective spinal decompression surgery • Episode of vertigo • Motor vehicle accident w/head injury • Cholelithiasis/ Cholecystitis • Hospitalization for pain control related to chronic back pain • Sepsis due to scalp cellulitis	• Left knee total arthroplasty • Hospitalization for food poisoning • Hospitalization for pneumonia, bronchitis, respiratory infection • Hospitalization for earaches and numbness • Surgical relief of carpal tunnel nerve pain	• Hospitalization twice due to diminishing ability to support weight and ambulate; ALS diagnosis • Hospitalization for asthma attack • Foot surgery for arthritis

4. File Descriptions

4.1 Data Forms

4.1.1 General

Multiple data collection forms were completed for each participant at every clinical visit. This release includes research data for each data form completed at every visit.

Each form is available as a PDF for use in approved data-release analyses only – ***no form is to be used for primary data collection without specific permission from the RISE Consortium or the original source***. Instructions for completing each form are included in a box at the top of each form, and additional instructions are often included throughout the form as required. The RISE form name can be found at the top-right of all forms.

Data-entry included responses in both the check boxes and the data-boxes on the data collection forms.

Over the course of RISE, several forms were changed – new variables or new codes were added. Only the final PDF version of each form is distributed with this data release, although all data collected are included in the data files. Variables that were added will have missing data prior to the addition of the variable.

4.1.2 Variable Names on Data Forms

- □ Variable names for each released variable are embedded in red on the data form.
- □ All datasets are HIPAA de-identified as described above.
- □ Coding and formats for all variables can be found on the original data form except where described below.

- The numerical value entered for check-box style categorical variables is noted inside the check-boxes.
- Text boxes are data-entered as free text. Underlined freeform text were clinic-use only and not data entry or available for release. Personal identifying information has been removed.

4.2 Datasets for Non-Form Data

Data not collected on forms but for which datasets are included in this release are as follows:

- Hyperglycemic clamp data: One record for each participant for each visit where the hyperglycemic clamp was completed. This includes both the raw glucose, C-peptide and insulin data, along with the key computed variables.
- Oral glucose tolerance test data: One record for each participant for each visit where the OGTT was completed. This includes both the raw glucose, C-peptide and insulin data, along with the key computed variables.
- Other laboratory data: One record for each participant for each visit where additional laboratory measurements were completed.
- A BASEDATA file which includes one record for each participant with randomized treatment assignment, baseline age group, sex, and race-ethnicity.

4.3 Variables Common to All Datasets

Several variables are used to identify a specific participant, visit and time on all datasets. These include:

- RISE_REPOSITORY_ID: This is a randomly generated ID used to link a participant to all other records, and is unique to each participant.
- VISIT: This identifies the visit and is used along with RISE_REPOSITORY_ID to match a participant's visit across the multiple forms completed for that visit. VISIT is coded as follows:
    - SCR: Screening visits (initial visit to determine preliminary eligibility).
    - RST and REN: Run-in start and end visits took place after the screening visit and prior to randomization.
    - BAS: Baseline (randomization) visit.
    - M03, M06, M09, M12, M15, M18, M21: Regularly scheduled post-randomization visits.
    - UNS: Unscheduled) visits.
- DAYSRAND: The number of days a particular visit occurred before (negative numbers), on (0), or after (positive values) randomization.

4.4 Screening and Run-in Forms

All participants completed a screening and run-in period prior to randomization. The screening and run-in period took at least two visits prior to the baseline visit, over a period of 3 to 8 weeks. This period was used to:

- Assess eligibility,
- Determine if the participant was able and willing to complete the study tasks, such as taking medication, performing self-injections, completing logs, and attending visits, and
- Collect baseline data.

The screening visit consisted of eligibility OGTT and body mass index, as well as collection of basic demographic information. Some participants completed a second screening prior to becoming eligible for the RISE. Only the final (eligible) screening data are included in the data release.

After the initial eligibility was confirmed, participants entered a 3-week run-in period during which time the

participants' ability to complete the various tasks of the study was assessed. Participants were allowed a 2nd run-in if eligibility tasks weren't completed satisfactorily. Only the final run-in assessment is included in the data release.

4.4.1 SCREEN: Screening Form

RISE Form SCREEN was used to record information collected at the initial screening visit. This form records demographic information, physical measurements, diabetes information, and eligibility criteria. The SCREEN form also records local laboratory results, and data related to collection of the screening 2-hour OGTT. The final section of the form records whether the participant is eligible for run-in and whether they will proceed. Variable VISIT = SCR for this form.

Several variables on this form are not included or were modified in the data release to avoid re-identification. These include exact age, and all measures of race/ethnicity, which have been recoded as described in BASEDATA.

4.4.2 RUNSTART: Start Of Run-In Visit Inventory

RISE Form RUNSTART was used to record information collected at the beginning of the 3-week run-in period. This form collected current diabetes management, any SAEs since the screening visit, symptom history since the screening visit, and to record run-in medication dispensing. Variable VISIT = RST for this form.

4.4.3 RUNEND: End Of Run-In Visit Inventory

RISE Form RUNEND was used to record information collected at the end of the 3-week run-in period. This form was used to enter any SAEs and diabetes management changes that took place during the run-in and calculate run-in medication adherence. Variable VISIT = REN for this form.

4.4.4 SLPQ_ADU: Adult Sleep Questionnaire Results

The RISE Sleep questionnaires were assessed during screening, and coded at the RISE Sleep Study Center at the University of Chicago. The raw data is not available. RISE data SLPQ_ADU contains the summary results of sleep questionnaires completed at the Screening visit. Adult study participants completed the Berlin Questionnaire, Pittsburgh Sleep Quality Index, and the Epworth Sleepiness Scale. Variable VISIT=SCR for this form.

4.5 Baseline and Follow-up Forms

4.5.1 BASELINE: Baseline Visit Inventory

RISE Form BASELINE was used to record information collected at the randomization visit to establish a baseline set of measurements. At the randomization visit, participants signed the final study informed consent, were given their randomization code, and began their randomized intervention. The Baseline visit took place across two visit days. Variable VISIT = BAS for this form.

4.5.2 CLAMP: Hyperglycemic Clamp Procedure

RISE Form CLAMP was used throughout RISE to record information pertaining to the hyperglycemic clamp procedure. Hyperglycemic clamps were performed at baseline after 12 months of intervention, and after 3 months of medication washout. Variable VISIT is used to identify the visit completed (BAS, M12, M15).

4.5.3 EXITFORM: Participant Exit Interview

RISE Form EXITFORM was completed at the end of the participant's participation in RISE to gather information about participant experiences in RISE. The questionnaire was optional and self-administered. Variable VISIT is used to identify the visit completed.

4.5.4 HISTORY: Participant Survey And Medical History

RISE Form HISTORY was administered at the baseline and Month 12 visits. The form includes medical history, menstrual history for females, and socioeconomic information. It was completed through interview with the participant and/or other knowledgeable family member. Variable VISIT is used to identify the visit completed (BAS, M12).

4.5.5 LOCLAB: Local Lab Results

RISE form LOCLAB was completed any time a local laboratory test was performed after the Baseline visit (i.e. after randomization). Possible tests include hemoglobin, hematocrit, serum creatinine, ALT, and HbA1c. Note: Hemoglobin and/or hematocrit were collected at M06, M12, and M15 for safety. Serum creatinine and ALT were collected at M06 for safety. Variable VISIT is used to identify the visit completed (M06, M12, M15).

4.5.6 OGTT: Oral Glucose Tolerance Test Procedure

RISE Form OGTT was used throughout RISE to record information pertaining to the oral glucose tolerance test procedure. Variable VISIT is used to identify the visit completed (BAS, M06, M12, M15, M21).

4.5.7 SMBG: Self-Monitoring Blood Glucose Form

RISE Form SMBG was completed for all participants randomized to insulin glargine at the M03 visit only. The form was completed at the M03 visit based on the blood glucose meter download. Using the information provided from the download, clinic staff entered mean fasting blood glucose, standard deviation, and total number of days with at least one glucose <70mg/dl for each two-week period between randomization and the visit as well as the participants' monitoring compliance. Variable VISIT=M03 for this form.

4.5.8 STATUS: Participant Study Status

RISE Form STATUS was completed with each status change after the participant has been randomized. A participant is considered active until the status is changed (i.e. there was no need to enter an initial status form). Clinic staff were asked to complete the STATUS form for each participant at completion of the study. Variable VISIT identifies the final visit completed (e.g., M03, M06… M21).

4.5.9 VISIT: Clinical Visit Inventory

RISE Form VISIT was used throughout RISE to record information pertaining to each visit following the Baseline visit. The form recorded the results of blood pressure measurement, anthropometrics, medical history and medication adherence. Variable VISIT is used to identify the visit completed (e.g., M03, M06… M21).

4.5.10 UNSCHED: Unscheduled Visit Inventory

RISE Form UNSCHED was completed for any non-scheduled visits following the screening phase. This form was used to document the following: SAEs, illness, medication management, or collection of CBL specimens for visits that are not planned quarterly visits. Variable VISIT=UNS.

4.6 Laboratory Data

4.6.1 RISEADULT_CLAMPDATA: Centrally-Measured Laboratory Data: Hyperglycemic Clamp

Dataset RISEAdult_CLAMPData includes the laboratory results from the hyperglycemic clamp procedure. Variable names and labels also include the blood draw times. A hyperglycemic clamp was completed at the baseline (BAS), Month 12 (M12) and Month 15 (M15) visit.

Notes:

- -10 and -5 are fasting values taken 10 and 5 minutes prior to initial glucose bolus.

- Minutes 2, 4, 6, 8, 10 were collected following the initial glucose bolus and infusion. These were used to compute the first phase response above fasting (ACPRg, AIRg).
- Minutes 100, 110 and 120 were used to compute steady state values.
- Minutes 155 and 159 were used to compute hyperglycemic state >450 mg/dl; these are samples drawn at least 15 minutes after reaching hyperglycemia, at 1 and 5 minutes prior to arginine injection.
- Minutes 162, 163, 164 and 165 were used to compute maximal glycemic potentiation, e.g., these are samples drawn 2, 3, 4 and 5 minutes after arginine injection (ACPRmax, AIRmax).
- The major variables computed from this data are included.
- Merge with form data by RISE_REPOSITORY_ID and VISIT.

Variable name	Brief description	Details
RISE_REPOSITORY_ID	RISE ID for NIDDK release datasets	Character
VISIT	Study visit completed	BAS, M12, M15
GLUC# GLUC_#	Glucose (mg/dL)	Measurement times (minutes before and after initial glucose bolus): -10, -5, 2, 4, 6, 8, 10, 30, 60, 90, 100, 110, 120, 155, 159, 162, 63, 164, 165 _ in variable names refer to fasting values taken 10 and 5 minutes prior to initial glucose bolus.
CPEP# CPEP_#	C-peptide (ng/ml)	Measurement times (minutes before and after initial glucose bolus): -10, -5, 2, 4, 6, 8, 10, 30, 60, 90, 100, 110, 120, 155, 159, 162, 63, 164, 165 _ in variable names refer to fasting values taken 10 and 5 minutes prior to initial glucose bolus.
INS# INS_#	Insulin (uU/ml)	Measurement times (minutes before and after initial glucose bolus): -10, -5, 2, 4, 6, 8, 10, 30, 60, 90, 100, 110, 120, 155, 159, 162, 63, 164, 165 _ in variable names refer to fasting values taken 10 and 5 minutes prior to initial glucose bolus.
GLUCAGON# GLUCAGON_#	Glucagon (pM/L)	Measurement times (minutes before and after initial glucose bolus): -10, -5, 100, 110, 120, 155, 159, 162, 63, 164, 165 _ in variable names refer to fasting values taken 10 and 5 minutes prior to initial glucose bolus.
ACPRg	Acute (first-phase) C-peptide response to glucose (ACPRg) (ng/dL)	Mean incremental C-peptide response above baseline (average of -10 and -5 min) from samples drawn at 2, 4, 6, 8, and 10 min after intravenous dextrose administration
ACPRmax	Acute C-peptide response to arginine at maximal glycemic potentiation (>450 mg/dL) (ACPRmax) (ng/dL)	Mean incremental C-peptide above concentrations achieved with hyperglycemia prior to the arginine bolus (i.e. mean concentration in samples drawn 2, 3, 4, and 5 min after arginine injection minus the mean concentration of the samples drawn 1 and 5 min prior to arginine)

M_I	M/I * 1000 (mg/kg/min/pg/L)	Mean glucose infusion rate (M) at 100, 110, and 120 min of the clamp divided by the corresponding mean steady-state plasma insulin concentration (I), adjusted for urine glucose lost
GIR	Glucose infusion rate (M) (mg/min)	D20 Glucose infusion Rate
INSULIN_STEADY	Steady-state insulin (I) (uU/ml)	Mean insulin at 100, 110, and 120 min
CPEPTIDE_STEADY	C-Peptide at steady state (ng/dL)	Mean c-peptide at 100, 110, and 120 min
AIRg	AIRg (Insulin)	Mean incremental insulin response above baseline (average of -10 and -5 min) from samples drawn at 2, 4, 6, 8, and 10 min after intravenous dextrose administration
AIRmax	AIRmax incremental mean (Insulin)	Mean incremental insulin above concentrations achieved with hyperglycemia prior to the arginine bolus (i.e. mean concentration in samples drawn 2, 3, 4, and 5 min after arginine injection minus the mean concentration of the samples drawn 1 and 5 min prior to arginine)

4.6.2 RISEADULT_OGTTDATA: Centrally-Measured Laboratory Data: 3-Hour Oral Glucose Tolerance Test

Dataset RISEAdult_OGTTData includes the laboratory results from the 3-hour, 75g oral glucose tolerance test. Variable names and labels also include the blood draw times. The 3-hour oral glucose tolerance test was completed at the baseline (BAS), Month 6 (M06), Month 12 (M12), Month 15 (M15) and Month 21 (M21) visits.

Notes:

- -10 and -5 are fasting values taken 10 and 5 minutes prior to glucose ingestion.
- Merge with form data by RISE_REPOSITORY_ID and VISIT.

Variable	**Brief description**	**Details**
RISE_REPOSITORY_ID	RISE ID for NIDDK release datasets	Character
VISIT	Study visit completed	BAS, M12, M15
GLUC# GLUC_#	Glucose (mg/dL)	Measurement times: -10, -5, 10, 20, 30, 60, 90, 100, 120, 150, 180 _ in variable names refer to fasting values taken 10 and 5 minutes prior to initial glucose bolus.
CPEP# CPEP_#	C-peptide (ng/ml)	Measurement times: -10, -5, 10, 20, 30, 60, 90, 100, 120, 150, 180 _ in variable names refer to fasting values taken 10 and 5 minutes prior to initial glucose bolus.
INS#	Insulin (uU/ml)	Measurement times: -10, -5, 10, 20, 30, 60, 90, 100, 120, 150, 180

INS_#		_ in variable names refer to fasting values taken 10 and 5 minutes prior to initial glucose bolus.
GLUCAGON# GLUCAGON_#	Glucagon (pM/L)	Measurement times: -10, -5, 10, 20, 30, 60, 90, 100, 120, 150, 180 _ in variable names refer to fasting values taken 10 and 5 minutes prior to initial glucose bolus.

4.6.3 RISEADULT_OTHERLABDATA: All Other Centrally-Measured Laboratory Results

Dataset RISEAdult_OtherLabData includes all other laboratory results measured at the Central Biochemistry Laboratory. Merge with form data by RISE_REPOSITORY_ID and VISIT.

Variable name	Brief description	Details
RISE_REPOSITORY_ID	RISE ID for NIDDK release datasets	Character
VISIT	Study visit completed	All visits possible.
HBA1C	HbA1c (%)	Measured at all quarterly visits.
CHOL	Total cholesterol (mg/dL)	BAS, M12, M15
TRIG	Triglycerides (mg/dL)	BAS, M12, M15
HDL	HDL (mg/dL)	BAS, M12, M15
LDL	LDL (mg/dL)	BAS, M12, M15
VLDL	VLDL (mg/dL)	BAS, M12, M15

4.7 Other Created Datasets

4.7.1 RISEAdult_BASEDATA: Baseline Data

RISE data RISEAdult_BASEDATA includes one record for each participant in the released database. Age and race/ethnicity were collapsed to protect identities. Merge with form data by RISE_REPOSITORY_ID. This file includes the following variables:

Variable	Type	Coding	Details
RISE_REPOSITORY_ID	Character	9-characters beginning with "RISE"	RISE ID for NIDDK release datasets. Randomly assigned.
AGEGROUP	Character	20-49 50-59 60+	Age group (years) at randomization collapsed into three groups.
TREATMENT	Character	METFORMIN GLARGINE + METFORMIN LIRAGLUTIDE + METFORMIN	Randomized treatment assignment. Not available on any data

		PLACEBO	form.
RACE	Numeric	1 = Non-Hispanic White 2 = All other	Self-reported race/ethnicity collecting during screening on Form SCREEN.
SEX	Numeric	1 = Male 2 = Female	Collected during screening on form SCREEN.
RANDPER	Numeric	2 = August – December 2013 3 = January – March 2014 4 = April – June 2014 5 = July –September 2014 6 = October – December 2014 7 = January – March 2015 8 = April – June 2015 9 = July –September 2015 10 = October – December 2015 11 = January – March 2016 12 = April – June 2016 13 = July –September 2016 14 = October – December 2016 15 = January – March 2017 16 = April – June 2017 17 = July –September 2017 18 = October 2018	Period of randomization

5. References:

1. The RISE Consortium: Restoring Insulin Secretion (RISE): design of studies of ß-cell preservation in prediabetes and early type 2 diabetes across the life span. Diabetes Care 2014;37:780-788
2. https://en.wikipedia.org/wiki/Seemingly_unrelated_regressions
3. https://www.jstatsoft.org/article/view/v023i04/v23i04.pdf
4. Zellner, Arnold. An efficient method of estimating seemingly unrelated regression equations and tests for aggregation bias". Journal of the American Statistical Association. 1962; 57: 348–368. doi:10.2307/2281644.
5. Srivastava, Virendra K.; Giles, David E.A. (1987). Seemingly unrelated regression equations models: estimation and inference. New York: Marcel Dekker.
6. Henningsen Arne, Hamann Jeff. systemfit: A Package for Estimating Systems of Simultaneous