JAEB CENTER FOR HEALTH RESEARCH

The International Diabetes Closed Loop (iDCL) trial: Clinical Acceptance of the Artificial Pancreas

A Pivotal Study of t:slim X2 with Control-IQ Technology

PROCEDURE MANUAL
VERSION 5.0

MARCH 5, 2019

Developed by:

Tiffany Campos/John Lum
Jaeb Center for Health Research
15310 Amberly Dr., Suite 350
Tampa, FL 33647-1642

Telephone: (813) 975-8690
Fax: (813) 975-8761
http://www.jaeb.org/

John Lum
I am approving this document
2019-03-06 10:28-05:00

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Sue Brown

Digitally signed by Sue Brown
Date: 2019.03.06 13:09:07 -05'00'

RECORD OF CHANGES

VERSION NUMBER	BRIEF DESCRIPTION OF REVISION	AUTHOR/ APPROVER	SECTION/PAGE	DATE
1.0	Initial document	Tiffany Campos/ John Lum	N/A	June 12, 2018
2.0	• Minor updates to Source Data Requirement Table(section1.5.1) • Minor update to list of devices not requiring upload at screening (section 1.6) • Instructions added to provide iDCL Control-IQ Study Participant Instruction Sheet at Run-in (section 2.1) • Update to supplies given to subject at Run-in (2.1.2) • Clarification of Central Lab Blood Glucose Testing (3.1.4) • Clarification of Follow up Clinic Visit and Phone contact windows (3.3.2 and 3.5.3) • Control-IQ Troubleshooting Tips updated regarding management of Alert Code #16 and Tandem Contact information for Study staff (3.6.2.1) • Device Downloads and Data Transfer section updated with t:connect website access and uploading instructions (6.4.5) • Updated Site Certification and Personnel Certification Sample added to Appendix.(Appendix L and M)	John Lum	Various	July 5, 2018
3.0	• Updated Record of Changes v2.0 to include section reference • Updated section 2.1 to include use of “G4, G5 and G6”	John Lum	Various	July 24, 2018

VERSION NUMBER	BRIEF DESCRIPTION OF REVISION	AUTHOR/ APPROVER	SECTION/PAGE	DATE
	• Updated section 2.1 to include use of Dexcom G5 “or G6 “mobile app • Clarification of requirements for management of TDI for MDI subjects Section 2.1.2 • Minor changes to section 2.1.2 to add supplies dispensed to subject G6 Receiver “(if not using Mobile app)” • Updated section 6.3 Acceptable values for the [Visit] portion of the filename			
4.0	• Updated Version table Procedure Manual Dates for v2.0 and 3.0 • Updated section 3.6.2.1 Control IQ Troubleshooting Tips: #3 Directions for placing a pump in shelf/storage mode: Statement deleted “download the pump if possible prior to beginning”. • Added section 9.7.3 Returning Items from Subject to Manufacturer	John Lum	Various	September 5, 2018
5.0	• Section 2.4, 3.5.2 and Appendix A updated to remove reference to Extension phase. • Section 6.8 updated to include information regarding JCHR management of receipt of non-redacted materials. • Section 9.7.3 updated to include additional information regarding return of defective pumps to the manufacturer	John Lum	Various	March 5, 2019

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SECTION 1: SCREENING AND ENROLLMENT

Seven clinical sites in the United States will enroll subjects with the goal of randomizing 168 total subjects so that at least150 have sufficient data to include in the primary analysis. A maximum of 225 subjects may be enrolled in the study in order to achieve the goal of randomizing 168 subjects.

There is no restriction on the number of participants to be enrolled by each site toward the overall recruitment goal. The expectation is equal enrollment across sites such that each of the 7 participating sites randomizes 24 subjects unless instructed otherwise. Please contact the Coordinating Center if there are any questions about enrollment targets.

Potential subjects should be evaluated for study eligibility through the elicitation of a medical history, performance of a physical examination by study personnel and local laboratory testing if needed to screen for exclusionary medical conditions. Subject exclusion will be at the discretion of the investigator based on study inclusion/exclusion criteria.

Subjects who do not initially meet study eligibility requirements may be rescreened once at later date per investigator discretion.

1.1 Informed Consent and Assent Forms

1. Make sure that the current IRB/ethics-approved version of the consent and assent forms are used (usually will have IRB stamp).

2. Allow time for the participant/parent to read the form(s).

3. Either the Primary Investigator or a Sub-Investigator must be present to answer questions, to witness signatures(s), and to sign the form(s).

4. Verify that the Adult consent, assent, and Parental consent/agreement forms are fully signed and dated.

5. If a separate HIPAA document is used, make sure it is fully signed and dated.

6. After blacking out all subject identifiers (name, signature, initials), scan and upload all signed ICFs using the secure uploader on the study website. Uploaded consent forms should include the PtID in the file name (i.e. DCLP3-001-001_Screening_Consent_1Jan2014). The “Upload Files” link can be accessed via the “Clinical Sites” tab.

7. Provide a copy of the signed form(s) to the participant/parent or legal guardian.

1.2 Steps to Enroll a Subject

1. Verify eligibility

    - Refer to Protocol Section 2.2 and 2.3 for a complete list of eligibility and exclusion criteria

For detailed instructions on required documentation of inclusion and exclusion criteria, please refer to the content and the table in section 1.5 below

2. Have participant and, if applicable, parental informed consent forms and assent signed (and HIPAA if applicable).

3. Obtain a subject ID on the DCLP3 website.

4. Complete and submit the Screening form.

    - Submit Insulin CRF, and Current Insulin Therapy CRF. If applicable, submit the Medical Conditions and Medications CRFs as well.

1.3 Subject Study ID

The subject ID (e.g. DCLP3-001-001) is assigned automatically by the study website when you enroll a subject. All subject IDs (sometimes referred to as PtIDs) use the following format:

- Protocol designation letter – 'DCLP3' for this study
- Site number (###) – site number
- Subject number at site (###) – sequential starting with 001 for first subject

It consists of a prefix ("DCLP3") defining the study followed by the site ID # (three digits) and the subject # at the site (three digits), with the segments separated by hyphens.

Enter subject initials when obtaining a Study ID. If the subject does not have a middle initial, use "X" (e.g. NXN). If the subject has a hyphenated middle/last name, use the first name of the hyphenated name - i.e. Nelly Agnes-Muthoni Njeru = NAN OR Nelly Agnes Muthoni-Njeru = NAM.

1.3.1 Instructions for Obtaining a Subject Study ID

- Log into the study website.
- Under the **Clinical Sites** tab, click the **Obtain a Study ID for a New Participant** link *for each new study participant enrollment*.

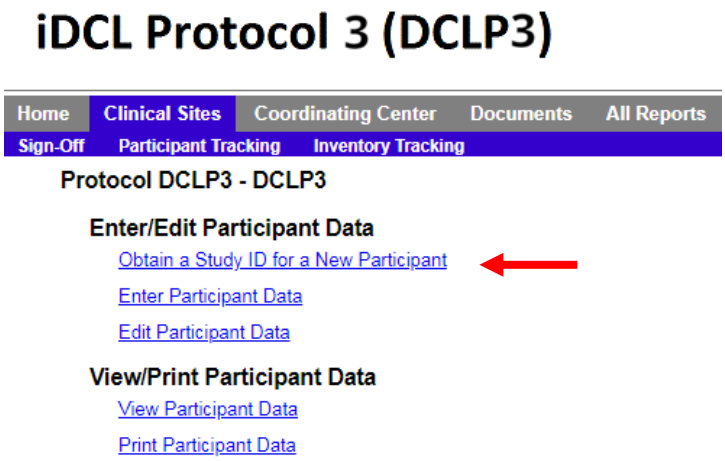


Figure 1-1. Obtain a Study ID for a New Participant

1.4 Issues Related to Completion of the Screening Form

For detailed instructions on required documentation of inclusion and exclusion criteria, please refer to the content and the table in section 1.5 below

1.4.1 Signed and Dated Informed Consent/Assent

- Eligible subjects will sign a formal informed consent form.

1.4.2 Age

- Only subjects ≥ 14.0 years of age are eligible.

1.4.3 Date of Diagnosis of Diabetes

- If exact month/year is not known, provide a best estimate.
- •Must be ≥12 months for eligibility.

1.4.4 Hemoglobin HbA1c

- This is measured at the screening visit, or is the value derived from a usual clinical care visit in the prior 2 weeks of enrollment.

1.4.5 Current Insulin Usage

- Determine total daily insulin using the average total daily insulin dose recorded on pump from the preceding 7 days (if a pumper) or by using an average over the last 3 days (if MDI).

1.4.6 Physical Exam

- The physical exam should be conducted by the center's usual routine
- Height and Weight
- Vital signs including blood pressure and Heart Rate

- Temperature and Fingerstick blood glucose result are part of Jaeb's global Physical Exam form, but is not required per protocol. Please mark these two exams as "not measured."

1.4.7 Pregnancy Assessment

- Urine or Serum Pregnancy test will be performed for all females of child-bearing potential, and if female and sexually active, subjects must agree to use a form of contraception to prevent pregnancy while participating in the study.

- If a subject becomes pregnant during the course of the study, a final status form will be completed.

1.4.8 Medical Conditions and Medications

- Complete as applicable. Complete the Medical Conditions Form before Medications as each medication has to be assigned to a condition previously entered.

- Do not include Type 1 diabetes on the Medical Conditions form.

- Do not include Insulin on the Medication list. It should entered on the Insulin eCRF

- If you are not able to find the medication name in the medication list, use the generic name. If you are still not able to find the medication, contact the Coordinating Center.

1.4.9 Exclusionary Medical Conditions

- Subjects with hemophilia or any other bleeding disorder are excluded from study participation. When considering other medical conditions that, in the opinion of the study investigator, would put the subject or the study at risk during the study, the following have been identified in prior similar studies; please consult with the study Clinical Chair if you have any questions:

    - Hemodialysis

1.5 Source Documentation Requirements

1.5.1 Source Data Requirements to Support Eligibility Assessment

An EMR progress note, visit summary, or equivalent record for at least the most recent and relevant clinical visit(s) for a participant must be obtained, printed out, and included in the participant binder prior to completing the screening visit.

Inclusion and exclusion criteria must be demonstrated by these printout(s) with annotations as needed to support the criteria listed below. Annotations should be accompanied by initials and dates of qualified personnel. Per clinical judgment, any medical conditions and medications listed on the EMR that do not appear to contraindicate eligibility do not require annotation.

Inclusion Criteria	Medical Records Verification Requirement
1. Clinical diagnosis, based on investigator assessment, of type 1 diabetes for at least one year and using insulin for at least 1 year	Show evidence on printed Medical Records that participant has had T1D with insulin use for at least 1 year. Annotate if needed.
2. Familiarity and use of a carbohydrate ratio for meal boluses.	Per clinical judgement. No verification needed on Medical Records printout.
3. Age ≥14.0 years old	Show evidence of date of birth on Medical Records printout. Annotate if needed.
4. For females, not currently known to be pregnant *If female and sexually active, must agree to use a form of contraception to prevent pregnancy while a participant in the study. A negative serum or urine pregnancy test will be required for all females of child-bearing potential. Participants who become pregnant will be discontinued from the study. Also, participants who during the study develop and express the intention to become pregnant within the timespan of the study will be discontinued.*	If female participant is of child-bearing potential and sexually active, show evidence female participant is on contraception. Annotate if needed. No verification needed on EMR printout for pregnancy test since it is captured on the eCRF.
5. For participants <18 years old, living with one or more parent/legal guardian knowledgeable about emergency procedures for severe hypoglycemia and able to contact the participant in case of an emergency.	Per clinical judgement. No verification needed in Medical Records printout.
6. Willingness to suspend use of any personal CGM for the duration of the clinical trial once the study CGM is in use	Per clinical judgement. No verification needed in Medical Records printout.
7. Investigator has confidence that the participant can successfully operate all study devices and is capable of adhering to the protocol	Per clinical judgement. No verification needed in Medical Records printout.
8. Willingness to switch to lispro (Humalog) or aspart (Novolog) if not using already, and to use no other insulin besides lispro (Humalog) or aspart (Novolog) during the study.	Per clinical judgement. No verification needed in Medical Records printout.
9. Total daily insulin dose (TDD) at least 10 U/day	Show evidence of insulin dosing on EMR printout. Annotate if needed.
10. Willingness not to start any new non-insulin glucose-lowering agent during the course of the trial (see section 2.3)	Per clinical judgement. No verification needed in Medical Records printout.
Exclusion Criteria	**Medical Records Source Verification Required**
1. Concurrent use of any non-insulin glucose-lowering agent other than metformin (including GLP-1 agonists, Symlin, DPP-4 inhibitors, SGLT-2 inhibitors, sulfonylureas).	Annotate on Medical Records printout whether any of these medications are being used. Annotate medications list if any appear to be contraindications.
2. Hemophilia or any other bleeding disorder	Annotate on Medical Records printout whether these conditions exist. Annotate medical conditions list if any appear to be contraindications.
3. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk	Annotate on Medical Records printout whether the investigator confirms no other conditions would put the participant or study at risk.
4. Participation in another pharmaceutical or device trial at the time of enrollment or during the study	Per clinical judgement. No verification needed in Medical Records printout.
5. Employed by, or having immediate family members employed by Tandem Diabetes Care, Inc. or TypeZero Technologies, LLC, or having a direct supervisor at place of employment who is also directly involved in conducting the clinical trial (as a study investigator, coordinator, etc.); or having a first-degree relative who is directly involved in conducting the clinical trial	Per clinical judgement. No verification needed in Medical Records printout.

1.5.2 Source Data Requirements Following Subject Enrollment

To ensure efforts are made to identify unreported adverse events, Medical records (if new records are available) must be obtained, reviewed, and included in each participant binder for the 13- and 26-week follow-up visits.

Include the records in the participant binder, ensuring an investigator has annotated them to indicate they have reviewed the printouts. If no records exist, make a note in the participant binder for the 13-week and 26-week follow-up visits indicating such.

1.6 Documents to be uploaded to the study website at screening

Once a subject has completed the required screening exams, the following documents should be uploaded to the study website within 3 business days of the visit.

- De-identified Signed Informed Consent Forms: Adult or Parental and Assent, and local HIPAA form, state bill of rights, or other local components (if applicable)
    - All pages of these documents must be included in the uploaded PDF
- Baseline CGM data (from personal CGM) for subjects who are not required to complete the run-in Phase and proceed directly to Randomization.

<u>Do NOT upload the following items at screening</u>:

1. Accu-Chek Guide BG Meter data file – defer until home use data has been obtained; each export should include all data obtained to date and will include any QC test records obtained by clinic staff prior to dispensing to the subject
2. Precision Xtra Ketone Meter data files – defer until home use data has been obtained; each export should include all data obtained to date and will include any QC test records obtained by clinic staff prior to dispensing to the subject
3. Participant's Personal Pump-defer until home use data has been obtained if randomized to SAP group
4. Trial Participant Tandem Training Checklist, CGM Training Checklist and patient specific information (i.e. lab reports, physical summaries, etc.) – these should be filed in the subject's study binder

SECTION 2: CGM RUN-IN PHASE

2.1 Introduction

Concurrent with the screening and enrollment visit, the subject will be assessed for the need for run-in activities prior to randomization. Subjects who use an insulin pump and a personal Dexcom G4, G5 or G6 CGM prior to the study for at least 11 of the prior 14 days will proceed directly to randomization. These subjects will have their personal CGM downloaded for capture of two-week baseline data:

For subjects that use an insulin pump and a Dexcom G4, G5 or G6 CGM and have used it for at least 11 of the prior 14 days and are currently using a CGM receiver, their data can be downloaded into their study subject Dexcom Clarity account as described in section 6.0 of the procedure manual. For those who are only using the Dexcom G5 or G6 Mobile app on their phone to record data prior to study participation, their information will be downloaded from the Clarity account to which the app had been sending data, and the file will need to be re-named based on the file naming convention as described in section 6.0. (i.e. DCLP3-010-007_Screening_2017-10-24+175922.csv) and then uploaded to the study website accordingly.

All other subjects will participate in the following run-in phase requiring additional clinic visits as shown in Table 1 of the protocol:

- Participants will use the study CGM for a minimum of 11 days with a goal of at least 14 days during the run-in phase.
- Participants who are on MDI at enrollment will receive a study pump to use and will receive training as detailed below. Note that this pump (the commercial t:slim X2 without the Control-IQ feature) does not integrate with the Dexcom G6 CGM, so that a separate CGM receiver will be required.
- All participants will receive training on the study CGM as detailed below. This will be an unblinded use of the study CGM.
- All participants will receive the iDCL Control-IQ Study Participant Instruction Sheet.

2.1.1 Initiation of CGM

The participant will be provided with sensors and instructed to use the study CGM on a daily basis. Training will be provided to participants not experienced with CGM use as to how to use the CGM in real-time to make management decisions and how to review the data after an upload for retrospective review. Participants using a personal CGM prior to the study will discontinue the personal CGM beginning in this period.

The participant will be observed placing the sensor. The study CGM user's guide will be provided for the participant to take home.

2.1.2 Initiation of Pump

Pump-naïve participants who are not using CGM at the time of enrollment will first complete a CGM-only Run-in period of approximately 14 days prior to initiating study pump use.

Participants who are pump-naïve will be provided with a study pump similar to the pump used with the closed-loop system, but with the closed-loop control feature either absent or deactivated, and will be instructed to use the pump on a daily basis. An initial basal insulin profile will be customized on a per-participant basis. Total daily insulin dose will be reduced by approximately 20% as a general rule using the procedure below; note that this is a general guide and that investigator discretion can be used to modify this approach on a per-subject basis:

- The basal rate should be determined by taking 80% of the participant's Total Daily Insulin Dose (TDD), dividing this by 2, and dividing again by 24.

  Example: [0.8 x TDD/2] x 1/24 = starting basal rate
  If TDD is 30 units, 0.8 x 30 = 24
  24/2 = 12
  12/24 = 0.5 units/hour

- Participants should continue using their usual insulin to carbohydrate ratio and correction factor.

Further adjustments to total daily dose and intraday basal rate profile may be made during the course of the run-in period.

Participants will complete training on the study pump as detailed below.

- The participant will be fully instructed on the study insulin pump. A qualified system trainer will conduct the training and in particular discuss differences from their home pump in important aspects such as calculation of insulin on board and correction boluses. Additional topics are not limited to but may include: infusion site initiation, cartridge/priming procedures, setting up the pump, charging the pump, navigation through menus, bolus procedures including stopping a bolus, etc.
- The study team will assist the participant in study pump infusion site initiation and will start the participant on the study pump. The study pump will be programmed with the participant's usual basal rates and pump parameters. The participant's personal pump will be removed.
- The participant will be supervised with the study pump during at least one meal or snack bolus to ensure participant understanding of the pump features.
- The participant will be encouraged to review the literature provided with the pump and infusion sets after the training is completed.

Subjects will be provided with a blood glucose meter Accu-Chek Guide, a blood ketone meter (Precision Xtra), test strips, lancets, and control solution to perform quality control (QC) testing at home per manufacturer guidelines.

All study meters will be QC tested with at least two different concentrations of control solution if available during all office visits. A tested meter will not be used in a study if it does not read within the target range at each concentration per manufacturer labeling. During all clinic visits, study meters should be tested with strips previously/currently dispensed to subject. If first test fails, repeat the test with a new strip from the same box (this is the procedure recommended in the Precision Xtra User Manual). If the test fails again, obtain a new box of test strips and re-test. If the test still fails with the new strips, assign the subject a new meter from ITA and return the defective meter as used and defective in ITA and dispense new strips. If the test passes with the new test strips, subject will continue with the same meter and new test strips. If subject is being assigned a new meter, it should be QC tested with the new test strips as well. Failure to complete QC testing of meters as clinic visits will be considered a deviation unless subjects failed to bring meter to their visit. Subjects are to be instructed to perform quality control testing of the BG meter at home with control solution in accordance with manufacturer guidelines and to contact study staff for a replacement of the meter, test strips, and control solution if a meter fails the testing.

If by accident the control solution for the Precision Xtra is used rather than the appropriate Accu Chek, the meter will read the solution as a fingerstick test rather than a QC test. When the appropriate solution is used, the meter will automatically recognize the solution as a QC test solution and will NOT save the test result in memory. QC tests performed during all office visits should be documented.

Throughout the study, participants will be instructed to calibrate the study CGM in accordance with manufacturer labelling. What this means in practice is that most participants may not do any calibrations at all, assuming they choose to use the factory calibration feature of the G6 system. Other participants may choose to start CGM sessions with required calibrations, and the system allows this. Please refer to the t:slim X2 with Control-IQ user guide or the Dexcom G6 user guide, both of which should contain the same information on this topic.

All fingersticks should be preceded by hand washing with warm water, soap, and a dry towel. Subjects should not use alternate site testing. Additional fingersticks may be needed if the initial calibration fails. The times of the CGM receiver and meters should be synced prior to sending the devices home with the subject. Remind all subjects to use the same study glucometer for all finger sticks and calibrations.

For subject entering the CGM Run-In Phase, the listed supplies should be dispensed through the Inventory Tracking Application

- G6 Sensors-1 box (3 sensors/box)
- G6 transmitter-1
- Lancets
- G6 Receiver-(if not using mobile app)
- Accu-Chek Guide BG Meter-1
- Accu-Chek Guide Blood Glucose Test Strips-2 boxes
- Accu Chek Guide Control Solution-1 box
- Precision Xtra Blood Ketone Meter-1
- Precision Xtra Blood Ketone Test Strips-1 box
- Precision Xtra Mid-range Control Solution-1 box

The subject is responsible for providing his/her own Glucagon emergency kit. If the subject does not have a current Glucagon emergency kit, the investigator should provide the subject with a prescription for a kit. The Glucagon emergency kit will come with written instructions for reconstitution and administration.

2.2 Dexcom CLARITY Clinic and Subject Account Setup

Jaeb will provide each Clinical Site with an IDCL-Specific Dexcom CLARITY Clinical Account, Username and Password. Dexcom CLARITY Clinical Account Passwords expire every 60 days. Please update this password when requested and update the Dexcom Clarity Account Spreadsheet that was provided to you at the beginning of the study. Forward a copy of this updated spreadsheet with new Clinical Account Password to the Protocol Manager at the Coordinating Center.

Jaeb has created 30 subject-specific CLARITY home user accounts for each site, with each home account preconfigured to share data with the parent CLARITY Clinical account for the site. Jaeb will provide each clinical site an Excel spreadsheet with Usernames and Passwords for each CLARITY home user account, to be assigned to the subjects at training. Passwords for the CLARITY home user accounts do not expire.

Participants will be instructed to refer to the Dexcom Mobile App user guide for setting up the G6 Mobile App or Follow App if they wish do so. The participant will be instructed to use the username/password provided to them by the clinic staff and follow the procedure on the Dexcom web site.

2.3 Run-In Phase Training, Initiation, and Review

Training will be provided to all subjects on use of the Dexcom G6 system using a provided CGM Training Checklist document.

Pump training will be provided to all subjects except those who are both not pump users and not CGM users at the time of enrollment. These subjects will have an initial 2-week CGM-only run-in, as described in the study protocol.

For those who receive it, pump training will be performed using a provided t:slim X2 Pump Training Checklist document. Note that the Control-IQ portion of this checklist and the G6 integration portion are not applicable and should be marked as such. Subjects using a personal CGM prior to the study will discontinue the personal CGM beginning in this period.

The subject will be observed placing the sensor. The study CGM user's guide will be provided for the subject to take home. The insulin pump user guide will be provided if a participant is using a study-assigned pump. User guides will be provided for the study BG meter and study ketone meter. Participants should also be provided with the Dexcom G6 Mobile User Guide during the period of sensor use, if not already included in supplies.

Run-in participants will be instructed to use the CGM on a daily basis for 2 weeks and the insulin pump daily, if applicable. Enrolled subjects will return approximately 14 days after the initiation of the CGM visit to assess the CGM wear. The purpose of the visit will include the following:

- Assessment of compliance with the use of the CGM (and study pump if applicable)
- Assessment of skin reaction in areas where a CGM sensor was worn
- Assessment of eligibility to continue to the RCT phase of the study

The CGM data (and pump data if applicable) will again be uploaded to CLARITY and reviewed. To enter the randomized trial, subjects must have obtained CGM readings on at least 11 out of the first 14 days of the Run-In period and, if using a study-provided pump, must have used it every day during the period. If the subject is eligible to continue in the study, study staff will follow the procedure for insulin pump optimization described above.

<u>Repetition of CGM Run-In Periods</u>

One or more additional 2-week run-in periods may be required:

- Pump- and CGM-naïve subjects who began with a CGM-only period will receive pump training and will have a subsequent 2-week period of pump and CGM use
- Subjects who failed to meet the success criteria above may repeat the CGM+pump run-in period up to two more times
- Investigators may require an additional 2-week period at their discretion, for example to ensure that the subject is fully comfortable with the system components

Subjects who are unable to meet the success criteria above during their final run-in period will be withdrawn from the study.

Refer to the Dexcom CGM user manual available on the study website for initial use and training.

2.4 Optimization of Insulin Pump Settings

Data-driven optimization of pump settings will occur at the following times only:

- Prior to Randomization:
  - At the Run-in Review Visit
- Following Randomization:
  - At the 2-, 13- and 26- week visits for all stud participants (both the CLC and SAP Group).
  - If the study subject contacts the study physician due to concerns about their pump settings due to recurring hypo- or hyperglycemia.

Adjustments to pump settings (basal rates, correction factor, insulin-to-carbohydrate ratio, etc.) will be made in response to major trends observed in the CGM data, with flexibility for clinicians to adhere to guidelines and practices established at each individual practice rather than a fixed set of heuristics for all sites. If insulin adjustments are made during any of the visits mentioned above, record the changes on the Insulin Pump Settings form, on the study website.

If adjustments to pump settings are made for either the CLC or SAP group during visits other than those listed above and are not made to address a safety concern, this will be considered a protocol deviation.

SECTION 3: RANDOMIZED TRIAL

3.1 Randomization Visit

3.1.1 Timing of Visit

The randomization visit may occur concurrently with the Enrollment Visit for subjects who meet CGM use requirements described above. Otherwise, the visit will be concurrent with the Run-in Review Visit.

Subjects will receive supplies for blood glucose and ketone testing and associated user guidelines and a prescription for a glucagon emergency kit if needed, as described above. Subjects will be advised to contact the study site staff for technical support for technical issues with the study CGM and to call the study physician for any health related issues.

A urine pregnancy test will be repeated for all females of child-bearing potential who participated in the CGM run-in phase if the Randomization visit is not on the same day as the Screening Visit.

3.1.2 HbA1c

HbA1c will be measured using DCA Vantage or similar POC device or local lab if the Randomization visit is not on the same day as the Screening Visit. A blood sample will also be drawn to send to the central laboratory for baseline HbA1c determination to be used in outcome analyses. Refer to DCLP3 Central Lab Manual of Procedures on Study Website for Central Lab HbA1c Processing (Appendix M of procedure manual)

3.1.3 Baseline C-Peptide Assessment

A blood sample will be drawn to send to the central laboratory for a random, non-fasting C-peptide determination. Refer to DCLP3 Central Lab Manual of Procedures on Study Website for C-Peptide Processing (Appendix M of procedure manual).

3.1.4 Baseline Blood Glucose

A blood glucose will be measured using a blood sample drawn to send to the central laboratory for a blood glucose assessment.

3.1.5 Questionnaires

Subjects will complete a set of baseline questionnaires, described in Section 5.1 of the Protocol, prior to randomization including:

- Diabetes Specific Personality Questionnaire
- Clark's Hypoglycemia Awareness Scale
- Fear of Hypoglycemia Survey (HFS-II)
- Hyperglycemia Avoidance Scale

- Hypoglycemia Confidence Scale
- Diabetes Distress Scale
- INSPIRE Survey

These questionnaires will be administered electronically using the study web site by clicking on the "Study Questionnaires" link in the visit menu. The study participant (and guardian if <18 years old) will choose a password and then use the subject ID and chosen password to log into the questionnaire interface, and will complete the questionnaires presented there.

3.1.6 Randomization

Eligible subjects will be randomly assigned to one of two treatment groups in a 2:1 ratio:

1. Closed-Loop Group (CLC)
2. SAP Group

Once the randomization form is submitted, the participant's Treatment Group will be displayed on the next page: Treatment Group CLC or Treatment Group SAP. The treatment group will also display at the top of the data entry menu for the subject for the remainder of the study.

3.2 Procedures for the CLC Group

Subjects randomized to the CLC group will complete an additional Technology Expectations Survey via another Study Questionnaires link in the visit menu, requiring another login using the subject's subject ID and previously-chosen password. If the password has been forgotten, there is an interface on the login screen to reset the password.

3.2.1 Study System Training

Subjects randomized to the CLC group will receive study CGM training if they skipped the Run-In period, and study pump training on the t:slim X2 pump with Control-IQ. The DCLP3 Trial Participant Pump Training Checklist and CGM Training Checklist will be used as needed. These training sessions can occur on the same day, or the Control-IQ training may extend to up to one additional day if needed within 1-7 days from randomization; subjects will not take the Control-IQ pump home until training has been completed.

Future visits will be scheduled based on the date of Randomization for both the CLC and SAP groups. Subjects randomized to the CLC group may return for additional training within 1- 7 days of randomization. If this occurs, it is possible that the 1-week phone call would occur when the subject has used the Control-IQ system for less than 1 week.

For subjects <18 years old, the parent/legal guardian will be trained on severe hypoglycemia emergency procedures including removal of the study pump and administration of glucagon.

Pump Training will include:

- The subject and if applicable, the parent/legal guardian will be fully instructed on the study insulin pump. A qualified staff member will conduct the training and cover all the topics included in the Pump Training Checklist document.

- The study team will assist the subject in study pump infusion site initiation and will start the subject on the study pump. The study pump will be programmed with the subject's usual basal rates and pump parameters. The subject's personal pump will be removed.

  - Note that if the participant has a total daily dose >100 U, you should choose the maximum allowed setting of 100 U on the "Set Total Daily Insulin" screen. If the participant has a weight below or above the allowed range 25-140 kg, then you should choose the minimum 25 kg or the maximum 140 kg, respectively.

- The subject will be supervised with the study pump during at least one meal or snack bolus to ensure subject understanding of the pump features.

- The subject and if applicable, parent/legal guardian will be encouraged to review the literature provided with the pump, infusion sets, and meter remote after the training is completed.

Closed-Loop Transitional Training Procedures

The subject and if applicable, the parent/legal guardian, will be trained by a study staff member previously trained on the use of and its functions, including meal announcement, meal bolusing, exercise, and switching back and forth between all operational modes.

Training will include a series of practice challenges using the different operational modes of the study system, such as Sleep mode and Exercise mode. Prior to initial use, the system will be initialized by a study team member with the subject's individual parameters, including carbohydrate ratio, correction factor, and basal rate pattern.

3.2.2 Study Device Data Transmission

Subjects will be instructed to upload pump data at least every 4 weeks throughout the remainder of the study.

3.2.3 1-Week Phone Contact

Study staff will perform a phone call with the subject within 7 (±1) days following randomization.

The following will occur:

- Assessment of compliance with study device use by review of any available device data.

- Assessment of adverse events, adverse device effects, and device issues.

- Study staff will answer any questions related to device use.

- Study staff are not required to upload any data to the study website during this visit

- Unplanned contact via phone, email, and or office visit should be documented using a Non-Protocol Contact form. This includes documenting non-trivial clinical, safety or technical issues that were discussed with a subject.

- If there have been major changes to the subject's insulin parameters, then this information must be captured using the 'Current Insulin Therapy" CRF.

- The subject will continue for a second week, then return to the clinic 14 (±3) days from the date of randomization.

3.2.4 2-Week (Training Review and Insulin Pump Optimization)

The subject will be offered review training to address any questions on the use of the study device including meal announcement, meal bolusing, and strategies related to pump use and exercise.

The following will occur:

- Assessment of compliance with study device use by review of any available device data.

- Assessment of adverse events, adverse device effects, and device issues.

- Study staff will answer any questions related to device use and follow the procedure for insulin pump optimization described above using the study CGM available data from the previous two weeks.

- Tandem pump data will be uploaded to a study-specific t:connect website. A study-specific URL will be provided for this purpose, both to the subject and to clinical staff.

- The study blood glucose meter and study ketone meter will be downloaded and QC tested with at least two different concentrations of control solution if available.

3.3 Procedures for the SAP Group

Subjects in the SAP Group will either continue to use their personal insulin pumps in conjunction with the study CGM, blood glucose meter, and ketone meter (if using an insulin pump at enrollment), or will use the study-assigned t:slim X2 insulin pump without Control-IQ technology that was used during Run-In.

Subjects may use commercially available features of the study CGM system related to mobile data access or remote monitoring (i.e. the Dexcom G6 Mobile App), but will be instructed not to use any third-party components for this purpose.
Note that Dexcom customer support personnel are unable to provide G6 Mobile App support for study participants because the transmitters are marked for investigational use only. Use of the G6 Mobile App is not mandatory for the study. Clinical site personnel are encouraged to provide basic troubleshooting support for participant use of the app and to contact the Coordinating Center with any questions about possibly malfunctioning CGM transmitters.

3.3.1 Study Device Data Transmission

Subjects in the SAP group will be instructed to upload data from the study CGM receiver prior to the 1-week phone contact and 2-week clinic visit for clinician review.

SAP subjects using the G6 Mobile App on their cell phone (or other compatible smart device) instead of a CGM receiver will need to ensure that they have periodic network connectivity prior to the visit so that data are uploaded to CLARITY automatically.

SAP subjects using a CGM receiver will perform uploads using the Dexcom CLARITY Uploader software available on the Dexcom CLARITY website, as described in Section 6 below.

3.3.2 1-Week Phone Contact

Study staff will perform a phone call with the subject within 7 (±1) days following randomization.

The following will occur:

- Assessment of compliance with study device use by review of any available device data
- Assessment of adverse events, adverse device effects, and device issues
- Study staff will answer any questions related to device use

The subject will continue on SAP for a second week, then return to the clinic 14 (±3) days from the date of randomization.

3.3.3 2-Week Visit (Training Review and Insulin Pump Optimization)

The subject will be offered review training on the use of SAP during the remainder of the study, including meal bolus strategies and strategies related to pump use and exercise.

The following will occur:

- Assessment of compliance with study device use by review of any available device data
- Assessment of adverse events, adverse device effects, and device issues
- Study staff will review uploaded CGM data, answer any questions related to device use, and follow the procedure for insulin pump optimization described above and in section 3.2 of the protocol.
- The study blood glucose meter and study ketone meter will be downloaded and QC tested with at least two different concentrations of control solution if available.

If using a CGM receiver, the subject will be instructed to upload data from the receiver at least once every 4 weeks for the remainder of the study using the Dexcom CLARITY Uploader software. If the subject is using the G6 Mobile App, data will be uploaded automatically when there is network connectivity.

3.4 Randomization Visit Procedures for Both Groups

- The subject will be given a one-page Study Participation Instruction Sheet, to be reviewed with study staff before the subject leaves the clinic—refer to the study web site to obtain the latest version of this document.

    - This document includes the most important safety information for the participant, including mandatory thresholds for low- and high-glucose alerts, treatment guidelines for hypo- and hyperglycemia and ketosis, and guidance for when to contact study staff.

- The subject will be provided with the User Guides (official manufacturer copies or paper printouts of same OK) for the study-provided devices the subject is using, if not previously provided, including insulin pump, CGM system, BG meter, and ketone meter.

3.5 Follow-up Visits and Phone Contact for Both Groups

The schedule for remaining follow-up visits and phone contacts is the same for both treatment groups. Study staff will discuss with the subject that periodic contact is required and will make arrangements with the subject for the contacts. If the subject (or guardian, for subjects less than 18 years old) cannot be reached, the subject's other contact methods will be utilized, including the emergency contact.

3.5.1 Follow-up Visits

Follow-up visits will occur at:

- 6 weeks (±1 week)
- 13 weeks (±1 week)
- 26 weeks (±1 week)

3.5.2 Procedures at Follow-up Visits

<u>Procedures performed in both groups at each visit, unless otherwise specified below:</u>

- Assessment of compliance with study device use by review of any available device data
- Assessment of adverse events, adverse device effects, and device issues
- Download of device data (study system or personal pump and study CGM, study BG meter, study ketone meter)

<u>Procedures Specific to the 13- and 26- Week Visit</u>

- HbA1c determination using the DCA Vantage or similar point of care device.
- Collection of a blood sample to send to the central laboratory for HbA1c determination. Refer to Lab manual on study website for instructions on processing sample.
- Completion of questionnaires.

- Weight measurement will be repeated, in addition to height for subjects <21 years old.
- Insulin Pump Optimization as described above

3.5.3 Phone Contacts

In addition to the 1-week phone contact described above for the respective treatment groups, the following phone call will be made:

- 4 weeks (±3 days)
- 9 weeks (± 3 days)
- 17 weeks (±3 days)
- 21 weeks (±3 days)

At each phone contact the following procedures will be performed in both treatment groups:

- Review of available CGM and/or system data to identify any safety issues associated with insulin pump settings and current diabetes management approach
- Assessment of adverse events, adverse device effects, and device issues
- Study staff will answer any questions related to device use.

3.6 Study Support

3.6.1 Study Coordinating Center Support

Table 3-1 lists the study team members able to provide technical assistance regarding protocol and study procedures, device use including the CGM, Pump, Meters, and Consumables:

Table 3-1. Study Coordinating Center Team Members

CONTACT NAME	ROLE	PRIMARY PHONE (8 A.M. – 5 P.M. ET)	SECONDARY PHONE (AFTER 5 P.M. ET)	EMAIL
John Lum, Jaeb	Protocol Director	813-975-8690	813-951-2039	idcl@jaeb.org
Tiffany Campos, Jaeb	Protocol Monitor/ Manager 2	813-975-8690	813-850-1158	idcl@jaeb.org
Samantha Passman, Jaeb	Research Assistant	813-975-8690	N/A	idcl@jaeb.org

3.6.2 Tandem Support

3.6.2.1 Control-IQ Troubleshooting Tips

1. Maximum Insulin Delivery Alert

a. This alert is described in the Tandem User Manual. It will be triggered whenever the total requested insulin (not delivered insulin) over two hours is 50% of the default TDI.
b. When the alert triggers, the pump will not deliver insulin until the alert clears. We suggest that subjects be instructed to contact the study team if they do receive this alert. It is expected that this alert is infrequent.
c. If there is no evidence of a pump malfunction, the subject can be instructed to turn off Control-IQ to resume insulin delivery and allow the alert to clear over approximately two hours.

2. What to do when the subject reports a message on the screen that includes “Contact Tandem”?

a. If it is unclear: contact idcl@tandemdiabetes.com and copy Jaeb (idcl@jaeb.org) to describe the problem

b. If it is a CGM Sensor Failed Error Code 11, CGM Unavailable Error Code 48: subject can be instructed to place a new sensor. If it does not immediately resolve, then try another sensor from a different lot. Ensure that the transmitter does not require replacement.

c. If it is Cartridge Error Code 16: subjects can be instructed to place the Pump in Shelf mode and Restart the pump. If this does not work, try a new cartridge. Ensure the cartridge is not overfilled. If multiple attempts with no resolution the pump may need to be replaced.

d. If it is CGM Error Code 42, subjects can be instructed to place the Pump in Shelf Mode and Restart the pump (see below).

e. Once the issue is clarified, Tandem will notify Jaeb: idcl@jaeb.org

f. If a device issue has occurred, the site is required to complete a Device Issue CRF on the DCLP3 Study website.

3. Directions for placing a pump in shelf/storage mode:
THIS SHOULD BE VERY INFREQUENT AND SHOULD ONLY BE FOLLOWED IF IT IS CLEAR IT IS A PROBLEM IDENTIFIED BY TANDEM AS REMEDIED BY PLACING THE PUMP IN SHELF MODE.-You will need to access the "Wake Button" for an extended period of time, so it may be easier if you take the pump out of the case.

-Just before you begin the process below, disconnect the tubing from your infusion site so that the pump is not connected to your body.

How do I place my pump in storage mode?

1. Plug a USB cable into the micro-USB port of your Tandem pump and connect it to a power source.

2. If properly connected, you should hear an audible alert and a charge symbol (lightning bolt) will appear on the battery level indicator.

3. Press and hold the Wake Button for approximately 30-40 seconds.

4. When the pump beeps/vibrates three times, release the button.

5. To confirm the pump is in Storage Mode, unplug the pump from the power source and press the Wake Button. The screen should not illuminate.

6. If the screen illuminates, repeat steps 1-4.

To turn the pump back on:

1. Plug a USB cable into the micro-USB port of your Tandem pump and connect it to a power source.

2. Do NOT push any buttons.

3. Wait 30 seconds and it will automatically reboot. Follow the directions on the screen.

4. If it does not reboot, unplug the USB cable then repeat steps 1-3

5. Your settings should still be saved but please review your insulin delivery settings.

6. You will be prompted that you need a new cartridge before resuming insulin. If your cartridge is intact and not in need of changing, then you can navigate to "change cartridge". Follow the prompts (making sure the infusion set is NOT connected to your body). Do not change the cartridge but keep the same cartridge in there. You will need to fill the tubing with at least 10 units of insulin. You do not need to fill the cannula.

7. Once completed, reconnect your tubing to your infusion set.

8. Resume insulin delivery.

SECTION 4: ADVERSE EVENTS

4.1 Definitions

Adverse Event (AE): Any untoward medical occurrence in a study participant, irrespective of the relationship between the adverse event and the device(s) under investigation.

Serious Adverse Event (SAE): Any untoward medical occurrence that:

- Results in death.
- Is life-threatening; (a non-life-threatening event which, had it been more severe, might have become life-threatening, is not necessarily considered a serious adverse event).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions (sight threatening).
- Is a congenital anomaly or birth defect.
- Is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above).

Unanticipated Adverse Device Effect (UADE): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of participants (21 CFR 812.3(s)).

Adverse Device Effect (ADE): Any untoward medical occurrence in a study participant which the device may have caused or to which the device may have contributed. (Note that an Adverse Event Form is to be completed in addition to a Device Deficiency or Issue Form).

Device Complaints: A device complication or complaint is something that happens to a device or is related to device performance, whereas an adverse event happens to a participant. A device complaint may occur independently from an AE, or along with an AE. An AE may occur without a device complaint or there may be an AE related to a device complaint.

Device Malfunction: Any failure of a device to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device. The intended performance of a device refers to the intended use for which the device is labeled or marketed. (21 CFR 803.3).

4.2 Reportable Adverse Events

For this protocol, a reportable adverse event includes any untoward medical occurrence that meets one of the following criteria:

1. A serious adverse event
2. An Adverse Device Effect as defined in protocol section 8.1.1, unless excluded from reporting in protocol section 8.2.
3. An Adverse Event occurring in association with a study procedure
4. Hypoglycemia meeting the definition of severe hypoglycemia as defined below
5. Diabetic ketoacidosis (DKA) as defined below or in the absence of DKA, a hyperglycemic or ketosis event meeting the criteria defined below

Hypoglycemia and hyperglycemia not meeting the criteria below will not be recorded as adverse events unless associated with an Adverse Device Effect. Skin reactions from sensor placement are only reportable if severe and/or required treatment.

Pregnancy occurring during the study will be recorded.

4.2.1 Hypoglycemic Events

Hypoglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when the following definition for severe hypoglycemia is met: the event required assistance of another person due to altered consciousness, and required another person to actively administer carbohydrate, glucagon, or other resuscitative actions. This means that the participant was impaired cognitively to the point that he/she was unable to treat himself/herself, was unable to verbalize his/ her needs, was incoherent, disoriented, and/or combative, or experienced seizure or coma. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. If plasma glucose measurements are not available during such an event, neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.

4.2.2 Hyperglycemic Events/Diabetic Ketoacidosis

Hyperglycemia not associated with an Adverse Device Effect is only reportable as an adverse event when one of the following 4 criteria is met:

- the event involved DKA, as defined by the Diabetes Control and Complications Trial (DCCT) and described below
- evaluation or treatment was obtained at a health care provider facility for an acute event involving hyperglycemia or ketosis
- blood ketone level ≥1.0 mmol/L and communication occurred with a health care provider at the time of the event

- blood ketone level ≥3.0 mmol/L, even if there was no communication with a health care provider

Hyperglycemic events are classified as DKA if the following are present:

- Symptoms such as polyuria, polydipsia, nausea, or vomiting;
- Serum ketones >1.5 mmol/L or large/moderate urine ketones;
- Either arterial blood pH <7.30 or venous pH <7.24 or serum bicarbonate <15; and
- Treatment provided in a health care facility.

All reportable Adverse Events whether volunteered by the participant, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported on an adverse event form online. Each adverse event form is reviewed by the Medical Monitor to verify the coding and the reporting that is required.

4.2.3 Relationship of Adverse Event to Study Device

The study investigator will assess the relationship of any adverse event to be related or unrelated by determining if there is a reasonable possibility that the adverse event may have been caused by the study device.

To ensure consistency of adverse event causality assessments, investigators should apply the following general guideline when determining whether an adverse event is related:

Yes

There is a plausible temporal relationship between the onset of the adverse event and the study intervention, and the adverse event cannot be readily explained by the participant's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study intervention; and/or the adverse event abates or resolves upon discontinuation of the study intervention or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the adverse event has an etiology other than the study intervention (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to study intervention.

4.2.4 Intensity of Adverse Event

The intensity of an adverse event will be rated on a three point scale: (1) mild, (2) moderate, or (3) severe. It is emphasized that the term severe is a measure of intensity: thus a severe adverse event is not necessarily serious. For example, itching for several days may be rated as severe, but may not be clinically serious.

- **MILD:** Usually transient, requires no special treatment, and does not interfere with the participant's daily activities.

- **MODERATE:** Usually causes a low level of inconvenience or concern to the participant and may interfere with daily activities, but is usually ameliorated by simple therapeutic measures.

- **SEVERE:** Interrupts a participant's usual daily activities and generally requires systemic drug therapy or other treatment.

4.2.5 Coding of Adverse Events

Adverse events will be coded using the MedDRA dictionary. The Medical Monitor will review the investigator's assessment of causality and may agree or disagree. Both the investigator's and Medical Monitor's assessments will be recorded. The Medical Monitor will have the final say in determining the causality.

Adverse events that continue after the participant's discontinuation or completion of the study will be followed until their medical outcome is determined or until no further change in the condition is expected.

4.2.6 Outcome of Adverse Event

The outcome of each reportable adverse event will be classified by the investigator as follows:

- **RESOLVED:** The participant recovered from the AE/SAE without sequelae. Record the AE/SAE stop date.

- **RESOLVED WITH SEQUELAE:** – The event persisted and had stabilized without change in the event anticipated. Record the AE/SAE stop date.

- **FATAL:** A fatal outcome is defined as the SAE that resulted in death. Only the event that was the cause of death should be reported as fatal. AEs/SAEs that were ongoing at the time of death; however, were not the cause of death, will be recorded as "resolved" at the time of death.

- **UNKNOWN:** An unknown outcome is defined as an inability to access the participant or the participant's records to determine the outcome (for example, a participant that was lost to follow-up).

- **ONGOING:** An ongoing AE/SAE is defined as the event was ongoing with an undetermined outcome.

    - An ongoing outcome will require follow-up by the site in order to determine the final outcome of the AE/SAE.

    - The outcome of an ongoing event at the time of death that was not the cause of death, will be updated and recorded as "resolved" with the date of death recorded as the stop date.

All clinically significant abnormalities of clinical laboratory measurements or adverse events occurring during the study and continuing at study termination should be followed by the participant's physician and evaluated with additional tests (if necessary) until diagnosis of the underlying cause, or resolution. Follow-up information should be recorded on source documents.

If any reported adverse events are present when a participant completes the study, or if a participant is withdrawn from the study due to an adverse event, the participant will be contacted for re-evaluation within 2 weeks. If the adverse event has not resolved, additional follow-up will be performed as appropriate. Every effort should be made by the Investigator or delegate to contact the participant until the adverse event has resolved or stabilized.

4.3 Reportable Device Issues

All UADEs, ADEs, device complaints, and device malfunctions will be reported irrespective of whether an adverse event occurred, except in the following circumstances.

The following device issues are anticipated and will not be reported on a Device Issue Form but will reported as an Adverse Event if the criteria for AE reporting described above are met:

- Component disconnections
- CGM sensors lasting fewer than the number of days expected per CGM labeling.
- CGM tape adherence issues
- Pump infusion set occlusion not leading to ketosis
- Battery lifespan deficiency due to inadequate charging or extensive wireless communication
- Intermittent device component disconnections/communication failures not leading to system replacement
- Device issues clearly addressed in the user guide manual that do not require additional troubleshooting
- Skin reactions from CGM sensor placement or pump infusion set placement that don't meet criteria for AE reporting

4.4 Pregnancy Reporting

If pregnancy occurs, the participant will be discontinued from the study. The occurrence of pregnancy will be reported on an AE Form.

4.5 Timing of Event Reporting

Serious or unexpected device-related adverse events must be reported to the Coordinating Center **within 24 hours** via completion of the online serious adverse event form.

Other reportable adverse events and device malfunctions (with or without an adverse event) and device complaints should be reported promptly by completion of an electronic case report form, but there is no formal required reporting period.

All reportable adverse events whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be **reported on an Adverse Event eCRF**.

Other reportable adverse events, device malfunctions (with or without an adverse event), and device complaints should be reported promptly by completion a Device Issue electronic case report form, but there is no formal required reporting period.

The Coordinating Center will notify all participating investigators of any adverse event that is serious, related, and unexpected. Notification will be made within 10 days after the Coordinating Center becomes aware of the event.

Each principal investigator is responsible for reporting serious study-related adverse events and abiding by any other reporting requirements specific to his/her Institutional Review Board or Ethics Committee.

Upon receipt of a UADE report, the Sponsor will investigate the UADE and if indicated, report the results of the investigation to the sites' IRBs, and the FDA within ten working days of the Sponsor becoming aware of the UADE per 21CFR 812.46(b)(2). The Medical Monitor must determine if the UADE presents an unreasonable risk to participants. If so, the Medical Monitor must ensure that all investigations, or parts of investigations presenting that risk, are terminated as soon as possible but no later than 5 working days after the Medical Monitor makes this determination and no later than 15 working days after first receipt notice of the UADE.

In the case of a device system component malfunction (e.g. pump, CGM, control algorithm), information will be forwarded to the responsible company by the site personnel, to be handled by its complaint management system.

SECTION 5: PARTICIPANT WITHDRAWALS AND STUDY STOPPING

5.1 Criteria for Individual Participant Discontinuation of Study Device

Rules for discontinuing study device use are described below.

- The investigator believes it is unsafe for the participant to continue on the intervention. This could be due to the development of a new medical condition or worsening of an existing condition; or participant behavior contrary to the indications for use of the device that imposes on the participant's safety
- The participant requests that the treatment be stopped
- Participant pregnancy
- Two distinct episodes of DKA
- Two distinct severe hypoglycemia events as defined in protocol section 8.1.2.1

If pregnancy occurs, the participant will be discontinued from the study entirely. Otherwise, even if the study device system is discontinued, the participant will be encouraged to remain in the study through the final study visit

5.2 Criteria for Suspending/Stopping Overall Study

In the case of a system malfunction resulting in a severe hypoglycemia or severe hyperglycemia event (as defined in section 8.1.2.2), use of the study device system will be suspended while the problem is diagnosed.

In addition, study activities could be similarly suspended if the manufacturer of any constituent study device requires stoppage of device use for safety reasons (e.g. product recall). The affected study activities may resume if the underlying problem can be corrected by a protocol or system modification that will not invalidate the results obtained prior to suspension.

The DSMB will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study and will review compiled safety data at periodic intervals. The DSMB will request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

The study medical monitor will be informed of all serious adverse events and any unanticipated adverse device events that occur during the study and will review compiled safety data at periodic intervals. The medical monitor may request suspension of study activities or stoppage of the study if deemed necessary based on the totality of safety data available.

SECTION 6: DEVICE DOWNLOADS AND DATA TRANSFER

6.1 Overview

CGM data from the Control-IQ system will be included in uploads done by study participants or by clinic staff to a study-specific Tandem t:connect web site.

Dexcom CGM data must be uploaded from home periodically to the Dexcom CLARITY cloud by study participants either using G6 receiver or using the G6 mobile app.

The upload timing is described above, and the upload process for participants is detailed below.

Note that some participants in the CLC group may use a conventional CGM receiver at times during the study. This could happen, for example, if:

- The participant has persistent issues with a Control-IQ pump and decides to switch over to a study-provided CGM receiver for a few hours or several days while awaiting further troubleshooting or equipment replacement

- The participant decides to stop using the study system altogether but is still willing to wear the study CGM for the remainder of the study

If this occurs with a CLC participant, then that participant should be asked to follow the same process as SAP participants and upload data from the CGM receiver at least once every 4 weeks during the use period.

Prior to the subject leaving the clinic for any particular visit, any available downloadable device data must be downloaded from its source and then uploaded to the study website by the study coordinator using the *Upload Files* link under the protocol header, with a copy saved to the coordinator's computer. Procedures for individual devices are described below.

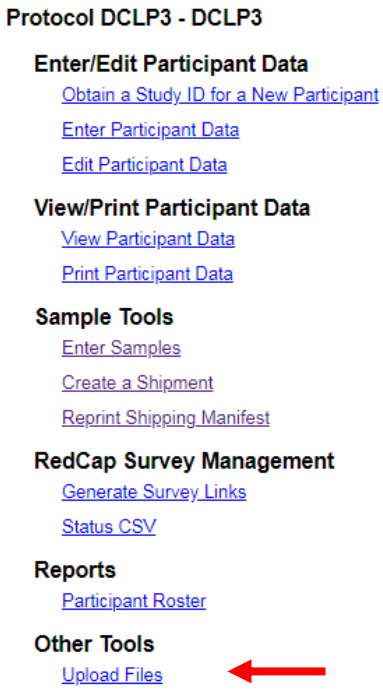


Figure 6-1. Upload Files Link

6.2 Sample Folder Structure for Storing Data

All downloaded data should be stored on a clinic computer or laptop in a study folder and kept until the end of the study. The following is an example of the appropriate folder structure, which is intended to be parallel with the structure you used on the study laptop to save an organized copy for each subject.

1. On the main drive (could be the C: drive or could be a network drive), the following main folder can be created: DCLP3 Study Data. Each subject should have a designated study data folder.

2. Each subject's folder should have subfolders for each study phase visit. Each study phase folder should contain subfolders for CGM, Pump, BG Meter and Ketone data files.

6.3 Device Filename Format Requirements

As detailed below for each device type, all datafiles uploaded to Jaeb using the Upload Files link on the study web site must have a filename that begins with the following pattern:

[PtID]_[Visit]_[remainder of filename].[extension]

For example, a valid filename for the exported Dexcom CLARITY file for the 2-Week visit of subject DCLP3-010-007 might look like this:

DCLP3-010-007_2-Week_2017-10-24+175922.csv

Acceptable values for the [Visit] portion of the filename are as follows:

- Screening
- Run-inInitiation
- Run-inReview
- Run-In24-HourCall
- Run-In72-HourCall
- Run-In1-WeekCall
- Randomization
- 1-WeekCall
- 2-Week
- 4-WeekCall
- 6-Week
- 9-WeekCall
- 13-Week
- 17-WeekCall
- 21-WeekCall
- 26-Week
- UnscheduledContact
- NoVisit
- Training

6.4 Transferring Dexcom CGM Data

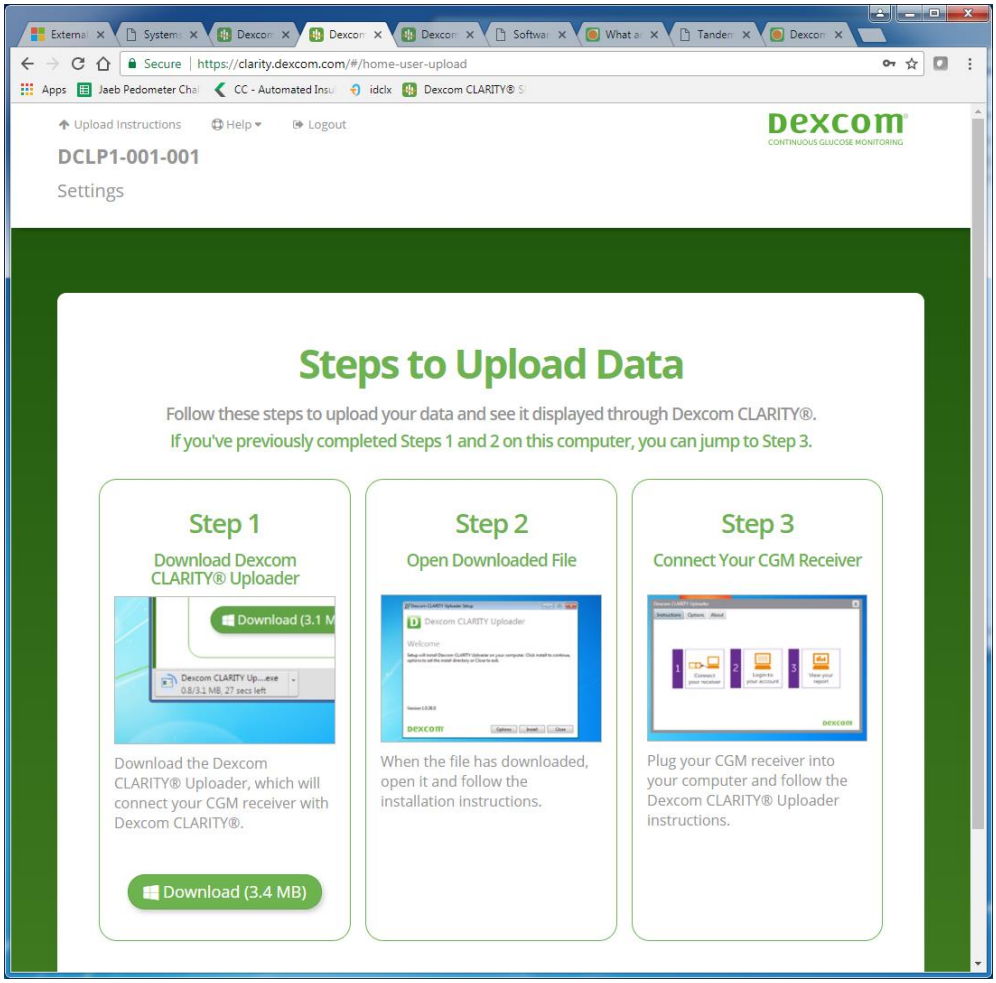
6.4.1 Study Subjects - Uploading CGM data to CLARITY from a Cell Phone

As noted above, CGM data will upload automatically on a continuous basis for subjects using the G6 Mobile App when their smart device has network connectivity.

6.4.2 Study Subjects - Uploading CGM Receiver Data to CLARITY from Home

When required to upload CGM receiver data from home per protocol, study participants will use the Dexcom CLARITY Uploader software installed either on their own computer (if available) or on a study-issued laptop computer.

This software can be installed by logging into a subject-specific CLARITY for Home Users account at clarity.dexcom.com, clicking the Upload Instructions link, and then following the steps shown on the screen for downloading and installing the software and for uploading data from the receiver:

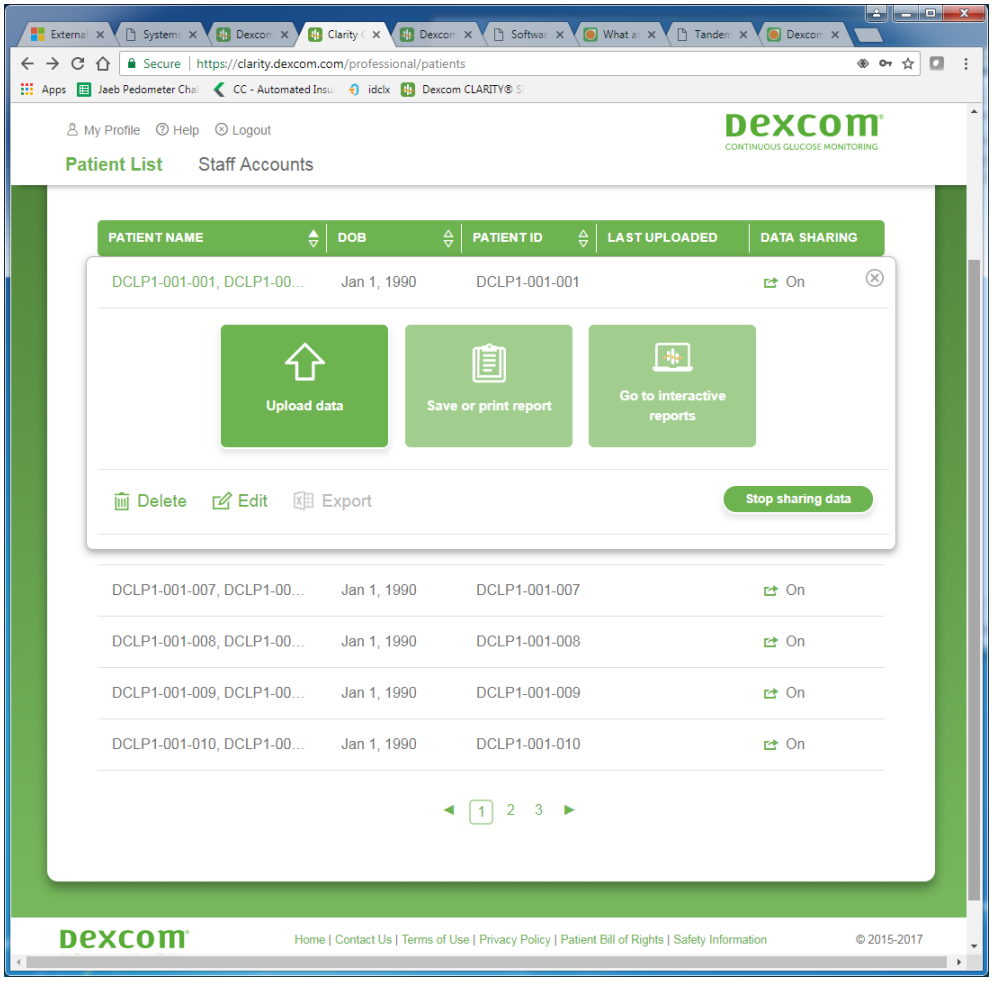


6.4.3 Clinic Staff - Uploading CGM Receiver Data at the Clinic

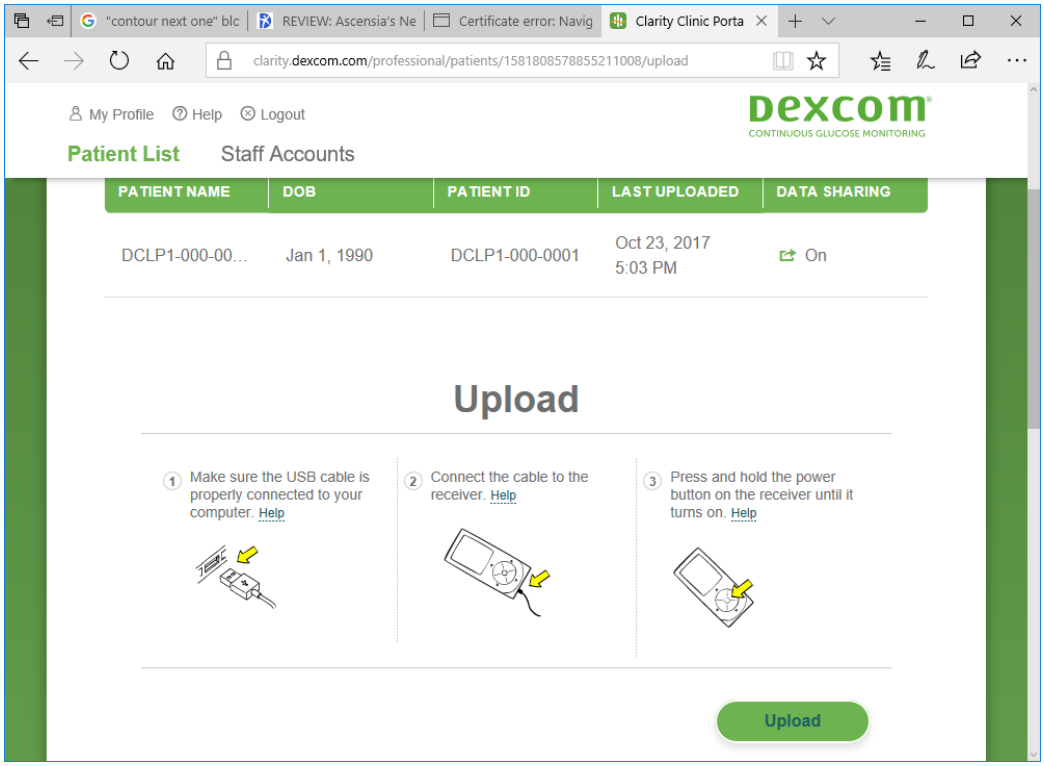
During each clinic visit, including the screening visit, for subjects using a Dexcom CGM receiver, the subject's receiver should be uploaded to the Dexcom CLARITY cloud to ensure that all available study data are saved.

At screening only, for those who are using the Dexcom G5 or G6 Mobile app on their phone to record data prior to study participation, their information will be downloaded from the Clarity account to which the app had been sending data, and the file will need to be re-named based on the file naming convention as described in section 6.0. (i.e. DCLP3-010-007_Screening_2017-10-24+175922.csv) and then uploaded to the study website accordingly.

To upload data for a subject, first log into your site's IDCL-specific CLARITY for Clinics account using the username and password provided by Jaeb. Then click on an individual linked subject to show the menu of actions for the subject, which will include "Upload data":

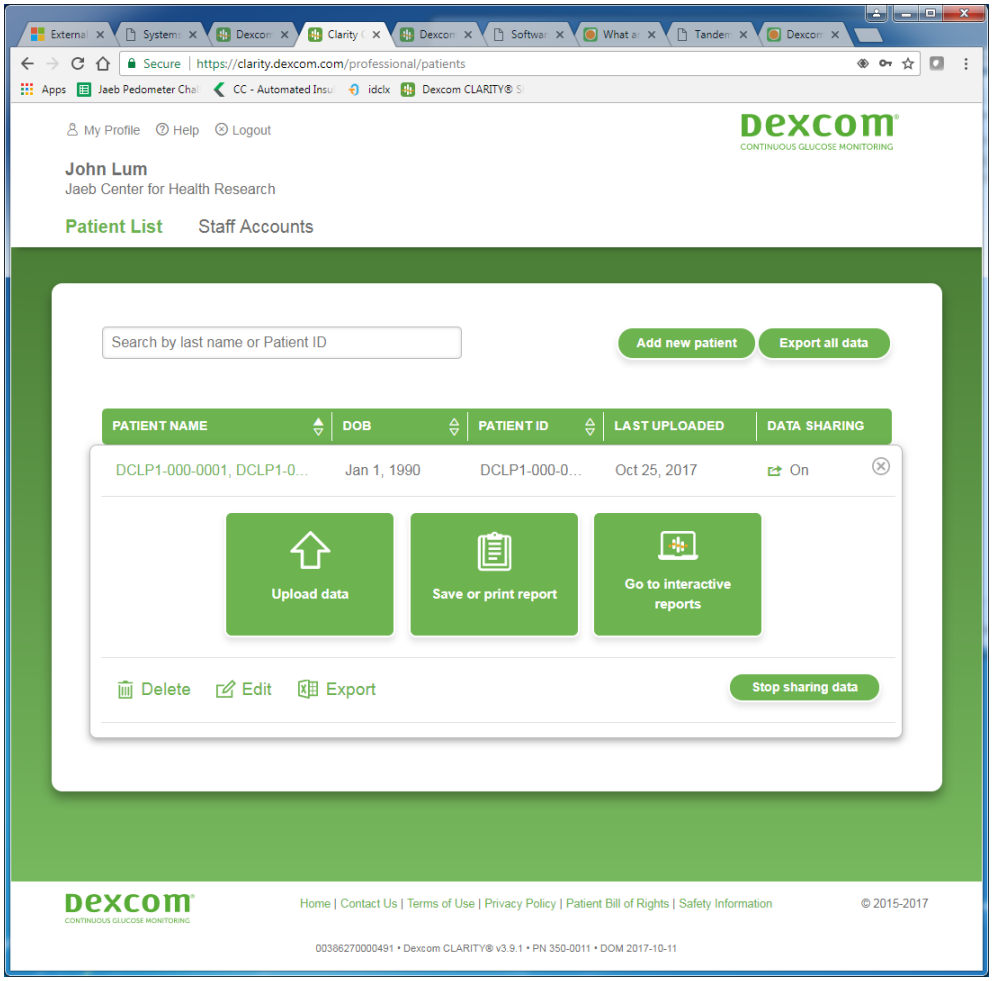


After clicking the “Upload data” link, you will be prompted to install the “dexcom-web-uploader-agent” software if it’s not already installed—note this is a different piece of software than study subjects will install on their computer at home to upload their data. After this software is installed, you will see directions for uploading data and an “Upload” button to begin the process with a subject’s receiver plugged in:



6.4.4 Clinic Staff - Downloading CGM Data for a Subject at the Clinic

When Dexcom CLARITY cloud data are available for a subject (having been uploaded either via the G5 or G6 Mobile App or from a CGM receiver), there will be an “Export” button for the subject within the CLARITY for Clinics account as shown below:



The exported datafile will by default have a name such as:

CLARITY_Export_DCLP3-010-001_DCLP3-010-001_DCLP3-010-001_2017-10-24+175922.csv

You will need to rename this file to remove the "CLARITY_Export_" portion at the beginning so that the filename begins with the PtID and an underscore, then includes the visit name and an underscore. The remainder of the filename aside from the .csv extension is not critical, but it is recommended to add the word "clarity" and retain the datestamp at the end of the filename as in the example shown below:

DCLP3-010-001_2-Week_clarity_2017-10-24+175922.csv

You will be able to upload properly-formatted files to the Jaeb study web site.

6.4.5 Clinic Staff or Participant - Uploading Study-Assigned Tandem Pump Data to Study-Specific t:connect Server

The same procedures apply both for study-provided t:slim X2 pumps with the Control-IQ feature and those without the feature.

6.4.5.1 Tandem t:connect web site for DCLP3 study

- Admin site (for JCHR staff to download study data): https://tconnectstudyadmindclp3.tandemdiabetes.com
- User Site (for site/participant use to upload data using t:connect accounts set up for each participant kind of like we do with CLARITY): https://tconnectstudydclp3.tandemdiabetes.com

6.4.5.1.1

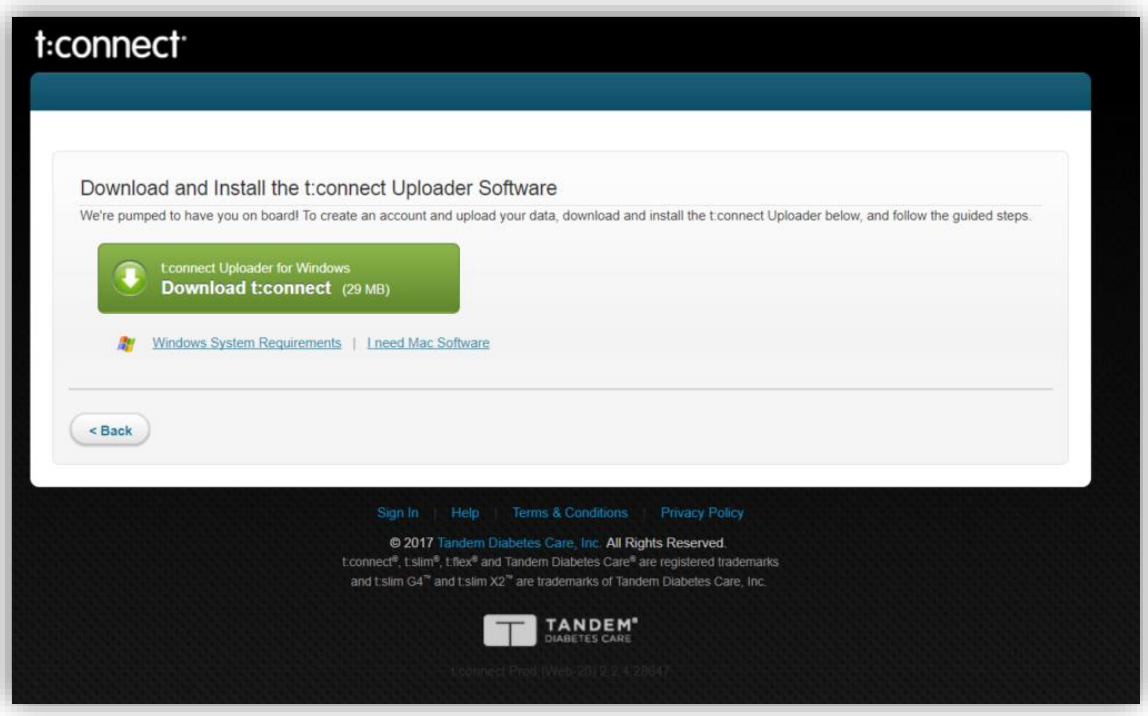
Similar to Dexcom Clarity accounts, each subject is given a t:connect account username. The password is the same for both the tconnect and clarity account for the participant. Please refer to the site specific CLARITY and tconnect Account excel spreadsheet provided to your site.

1. Introduction
   a. The following outlines the process to upload t:slim X2 pumps and login to the t:connect application for use during the iDCL Study. It is intended to be used by the clinical staff and study participants during the study period for t:slim X2 with Control-IQ. This document is not comprehensive, and is designed only as a support tool in conjunction with the other t:connect literature and user guide.

2. Installing the t:connect uploader *(may require local IT support for administrator access)*

3. Download the t:connect Uploader Software from this link, https://tconnect.tandemdiabetes.com/GettingStarted/

4. Run the “tconnect_Uploader_2.4.13_Setup” application appropriate for your operating system (MAC or Windows.)



a.

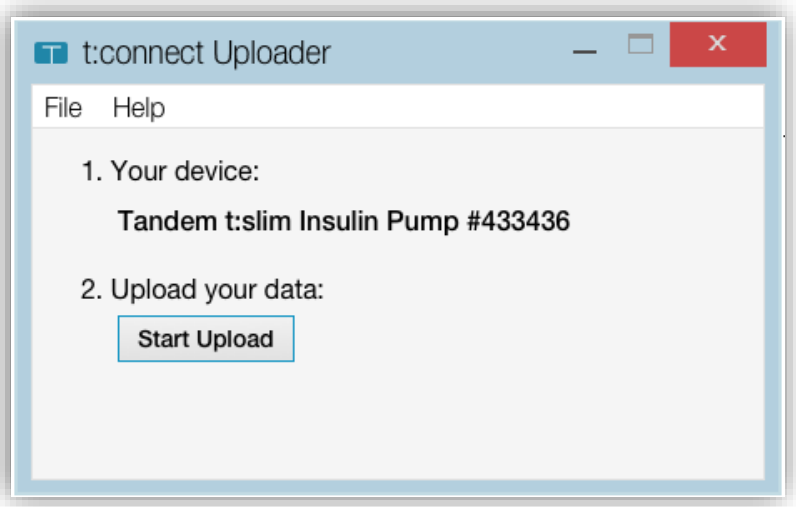
5. Follow the installation instructions on your computer.

Upload the Pump to t:connect:

6. Once installed, find and run the new application in your Windows Programs, or Mac Applications folder.

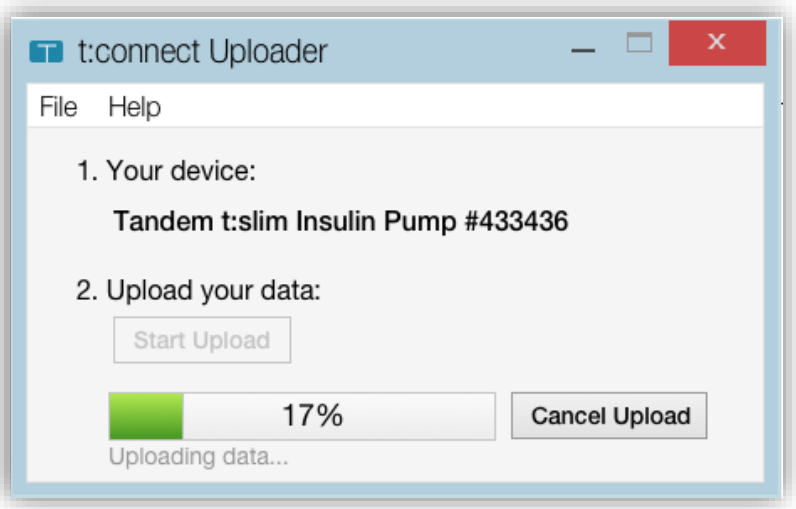
7. Plug your pump into your computer using the USB cable provided with the pump. When the uploader opens, you will see the screen below with your pump serial number.

8. Click on the “Start Upload” button to begin uploading your pump to t:connect.



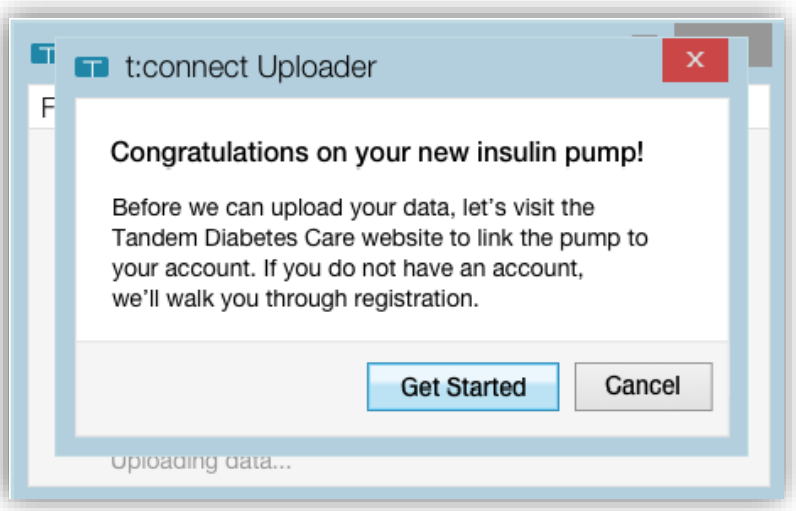
i.

9. The progress bar will give you an idea how long it will take to upload. Depending on how long it has been since your last upload, this process will take a bit shorter or longer. It may take up to a few minutes.



i.

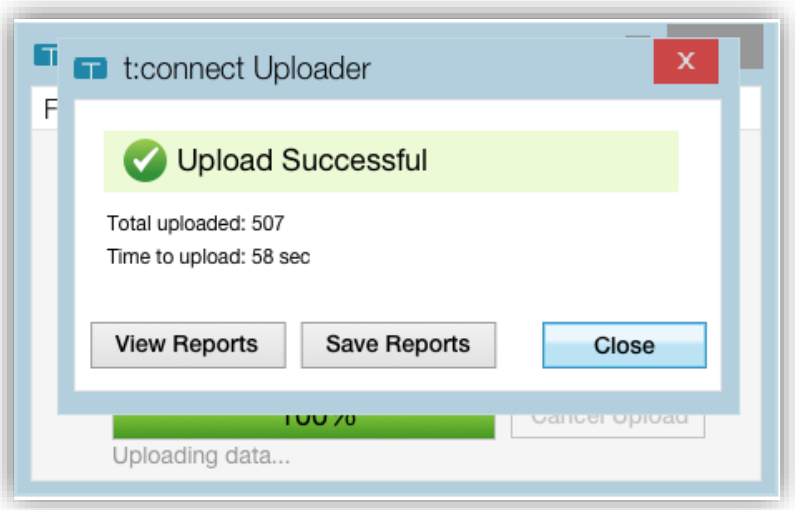
10. If this is the first time you have uploaded your pump, you will be presented with the following screen once the uploader completes.



i.

11. Click "Get Started" to open the t:connect sign in page on your browser and login with the account credentials that you have been provided (see the following section for more information).

12. For subsequent uploads, the following screen will be displayed. If you want to see your data on t:connect, click "View Reports."

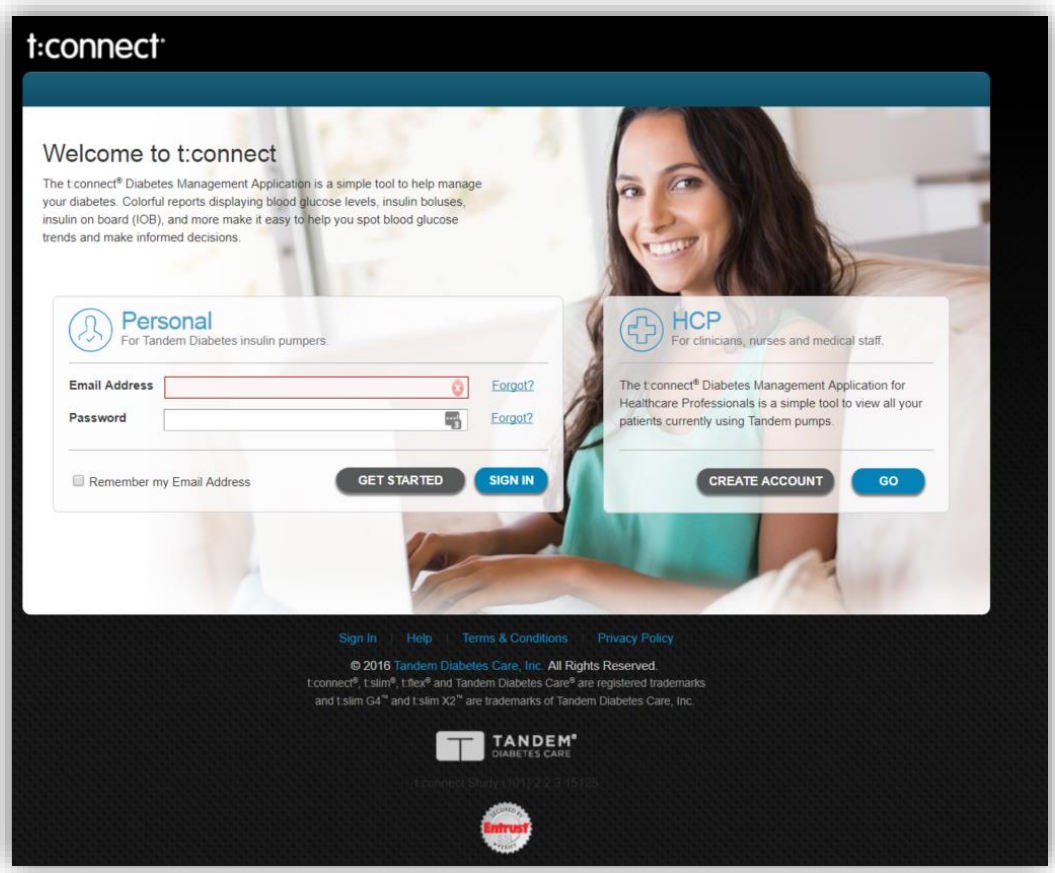


i.

13. View your data on t:connect

14. If you clicked "Get Started" or "View Reports" above you will be redirected to the following URL: https://tconnectstudydclp3.tandemdiabetes.com/Login.aspx.

15. You can also enter this URL into your browser at anytime to login to the study application after your first upload.

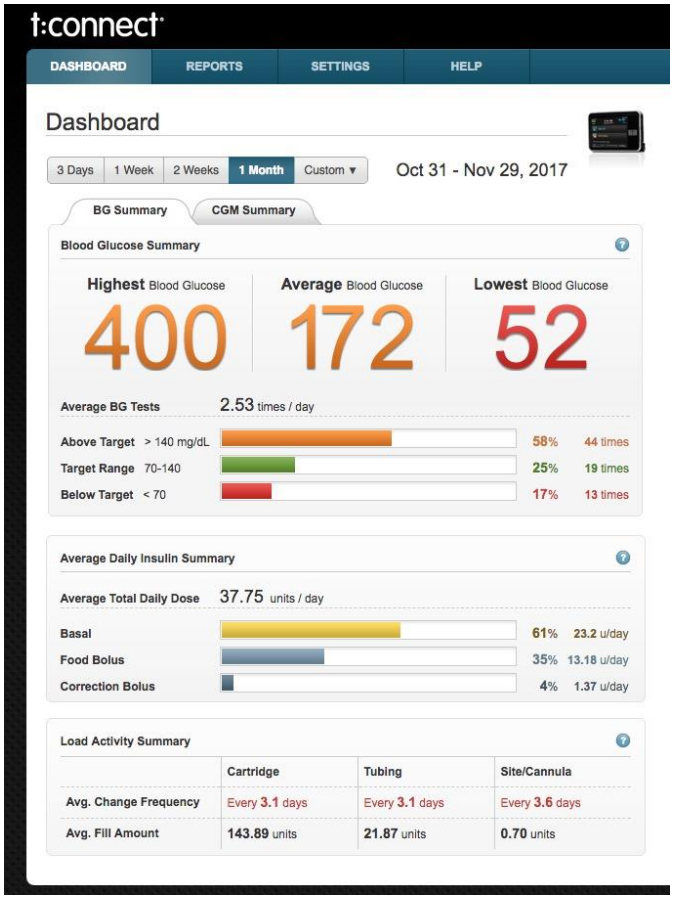


a.

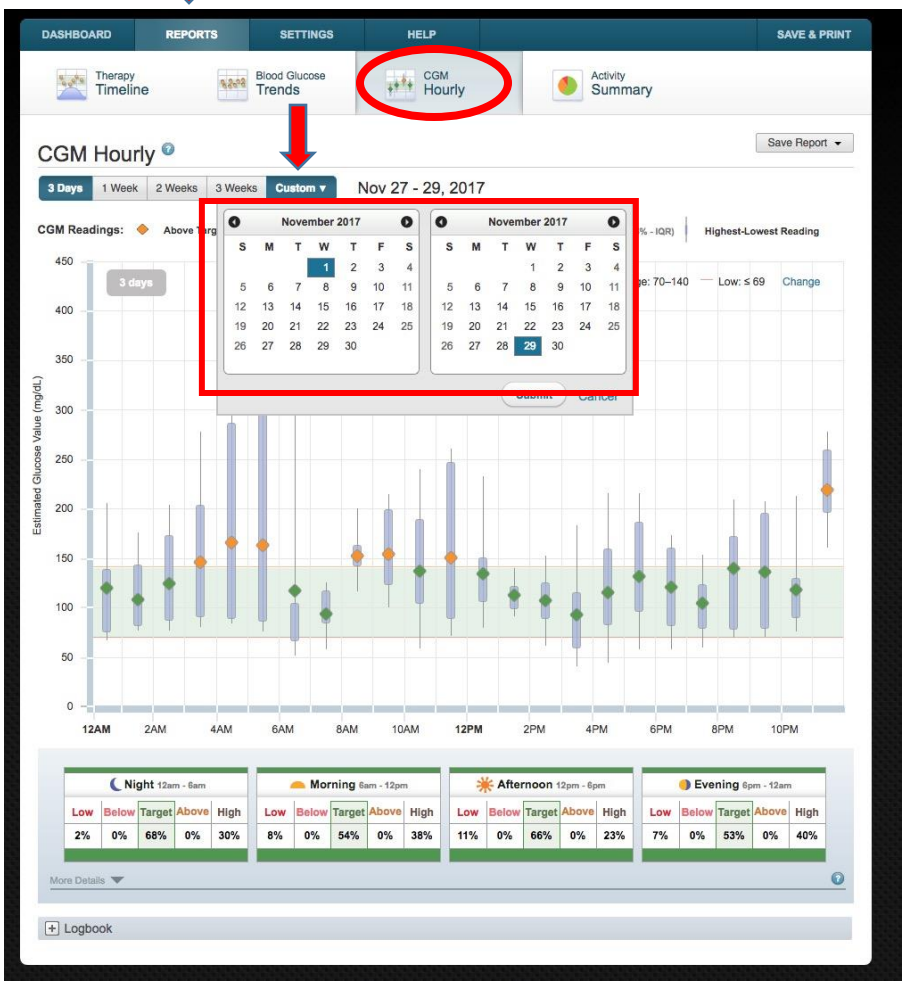
17. To sign in, enter your account credentials in the section titled "Personal" above (e.g. DCLP3-001-001@tandem-diabetes.com along with password provided in site-specific Excel sheet). The t:connect HCP application is not active for this study. Once logged in, you will be able to navigate throughout the t:connect application to see your previously uploaded insulin, blood glucose, and CGM data. Clinic Staff - Downloading CGM Data from a Tandem Pump for a subject at screening

For subjects who are using a Tandem pump with Dexcom CGM integration at screening, you will need to review their CGM data to determine if they will be required to participate in the Run-in Phase or whether they can proceed directly to Randomization. If they are eligible to proceed to Randomization, you will need to download their CGM data and upload it to the study website accordingly. In order to access this data see the following:

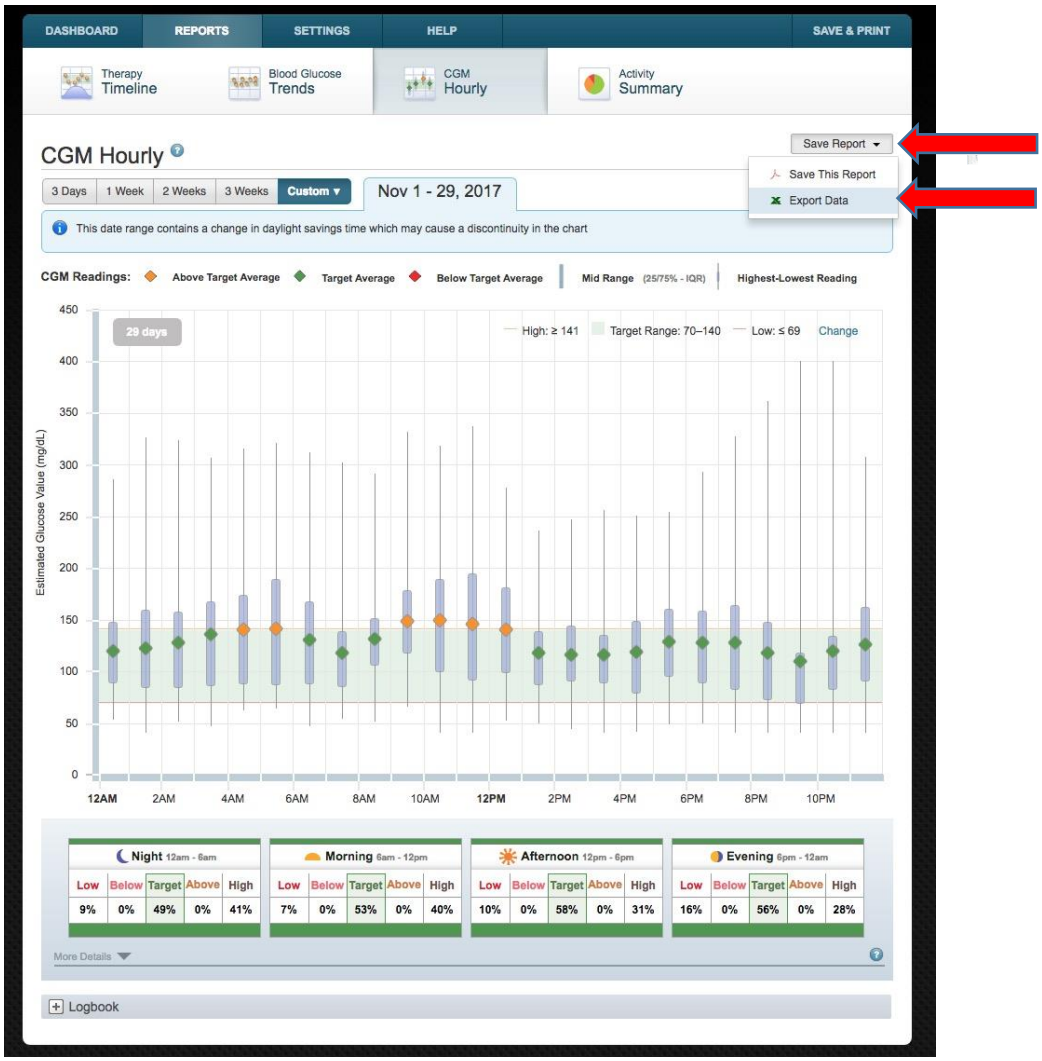
1. Log in to Tandem T-Connect for the patient's account. (e.g. DCLP3-001-001@tandem-diabetes.com along with password provided in site-specific Excel sheet)



2. Click on the Reports Tab
3. Click on the CGM Hourly Tab
4. Click on Custom Date and choose the last 30 days



5. Click on “Save Report”
6. Click on “Export Data” in the downbox to produce a CSV datafile



Once the data has been downloaded it will need to be renamed prior to uploading to the study website:

(i.e. DCLP3-001-006_Screening_CGM_TConnectExport_30NOV2017_cgm-30112017_102437_11302017163114841.csv)

6.5 Downloading Pumps Other Than the Tandem for SAP Subjects

If your clinic is configured to download data from the brand of pump that an SAP participant is using during the RCT, please go ahead and perform that download at each clinic visit. Make sure to include the PtID and Visit information at the beginning of the filename, as described above, and then upload the file to the study web site:

DCLP3-010-001_2-Week_pump.XXX
(where XXX is the pump brand-specific file extension)

Please see Appendix L for additional detailed instructions on downloading other pump types.

6.6 Downloading the Accu-Chek Guide Blood Glucose Meter

During each clinic visit, the participant's Accu-Chek Guide BG meter should be downloaded using the **Accu-Chek 360 Diabetes Management System version 2.2.3**.

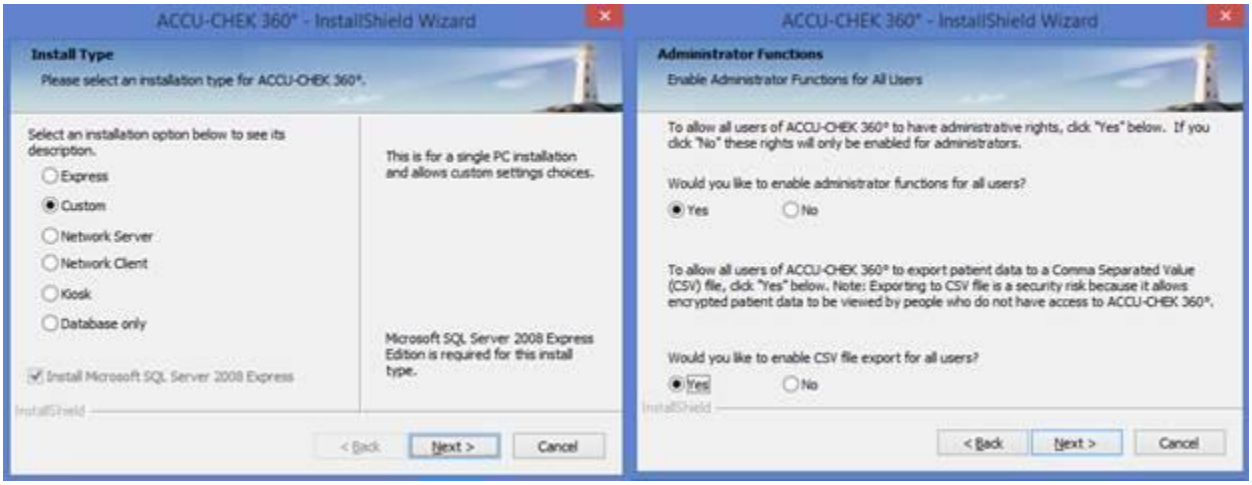
- If you do not have this version of the Accu-Chek 360 Diabetes Management System, contact Accu-Chek at 1-800-628-3346. Let them know which version you currently have. Customer Service will send you the new software and assist with installation.

- If you site does not currently have this software, it will need to be purchased from www.accuchek2.com Select "Shop" on the left margin. Go to page 2 to select the Accu-Chek 360 Diabetes Management System with Cable.

Set up a new profile for each study participant using DCLP3 as the First Name and the PtID as the Last Name. Do not include any participant names in the profile.

Export the .CSV file and upload this file to JCHR via the Upload Files link on the study website. **NOTE**: Make sure no participant names are included in the file.

Please NOTE during initial installation of ACCU-CHEK 360 Diabetes Management software, "Custom" must be selected under "Install Type" (see screenshot below) and "Yes" selected as the response to the second question of the "Administrator Functions" installation step (see screenshot below) in order to export CSV files.



DCLP3-010-001_2-Week_10242017232556.csv

6.7 Downloading the Precison Xtra Ketone Meter

You will use the Abbott CoPilot software (preinstalled on the study laptop) to download data from subjects' ketone meters.

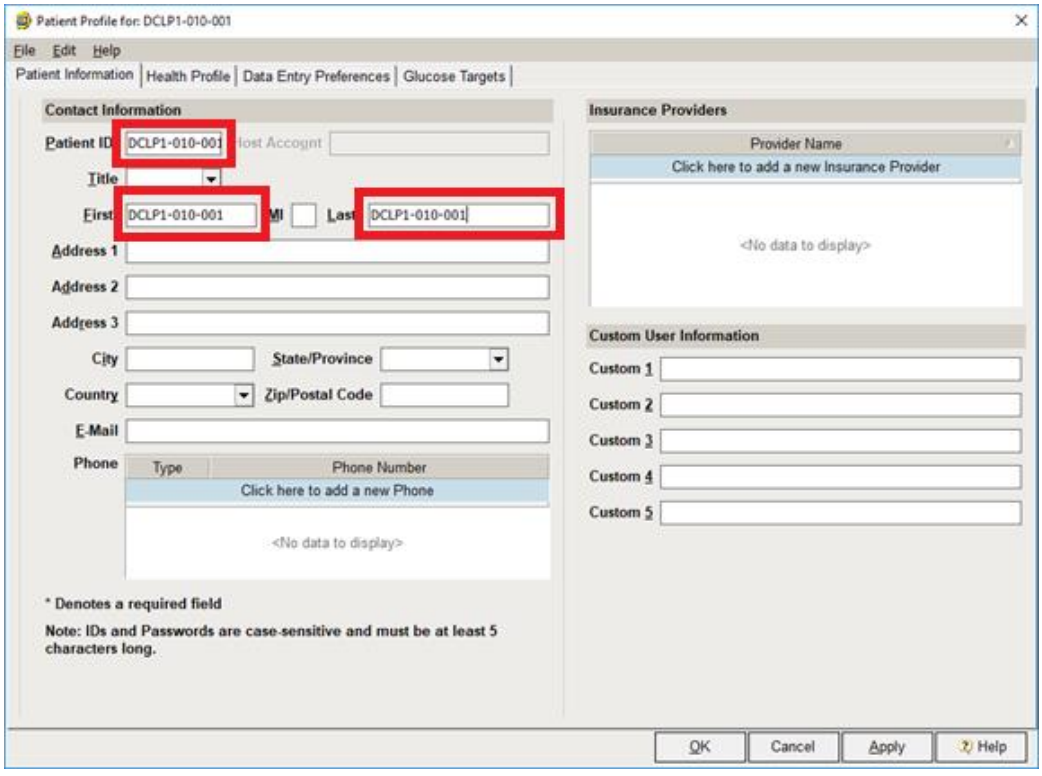
If you need to install the CoPilot software fresh or on a different computer, keep in mind that it is not compatible with Windows 8.1.

When configuring the software when you run it for the first time, you should accept the default settings except for the following:

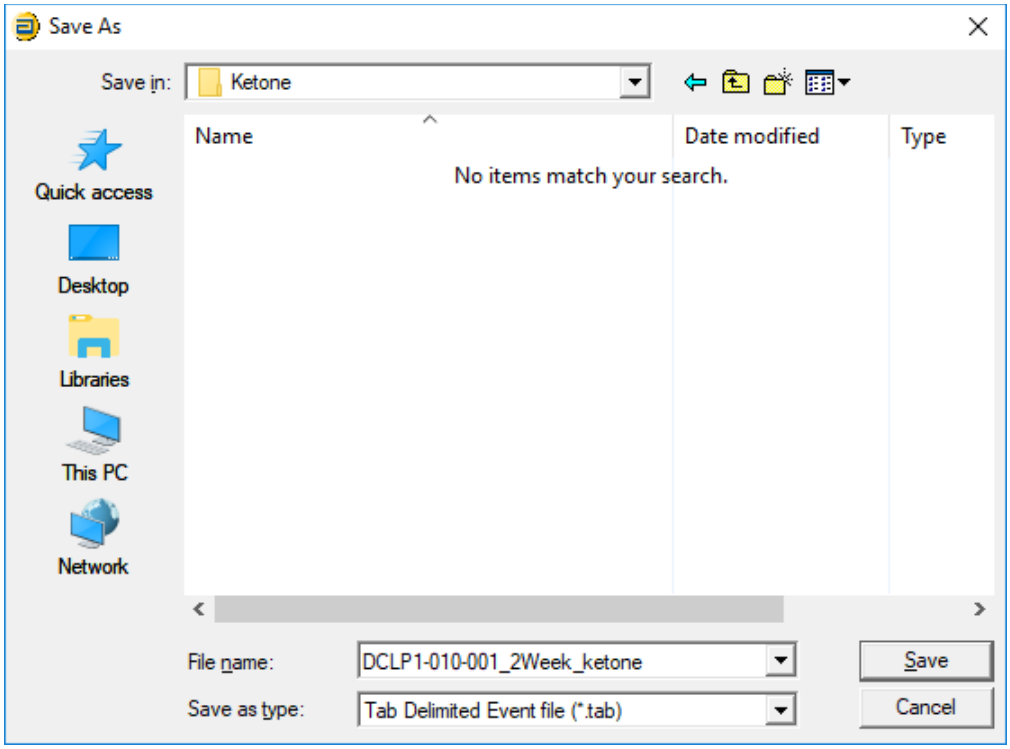
- On the Initial User Setup screen, choose "Health Care Professional," enter the PI's first and last name, then enter the username and password provided to your site for your Dexcom CLARITY Clinical Account. You can avoid entering any additional user info.

To download subject data, first connect the ketone meter to the computer using the special Precision Xtra download cable with one end that plugs directly into the strip port of the meter (cable not included with DCLP3 study materials; please contact the Coordinating Center if you need one). After launching the software, choose Data Entry >> Read Abbott BG Meter from the software menu (note there is no option to choose the Precision Xtra meter specifically).

The first time downloading a given meter, the software will recognize that the serial number isn't already associated with a user in its database and will prompt to create a new user. When creating a new user, enter the PtID for the required fields Patient ID, First Name, and Last Name as shown below:



To export and save the data, first choose a subject from the dropdown menu, then choose File >> Export from the software menu to open the “Save As” window. **Make sure to change the “Save as type” dropdown from XML to “Tab Delimited Event File (*.tab)” as shown below:**



In the “DCLP3 Study Data\DCLP3-00X-0XX\Visit” folder, save the file as [PtID]_[Visit]_ketone.tab, with a valid Visit string as described above. For example:

DCLP3-010-001_2-Week_ketone.tab

When all downloads and data exports are complete, upload the device data to the study website.

6.8 Transmitting Data to the Coordinating Center

Once all devices have been downloaded, the individual device files for that subject will be uploaded to the study website. **Device data should be uploaded to the study website within 3 business days from the date of the visit.**

Do not include any personal subject information or protected health information (PHI).

When JCHR receives source data from sites (e.g., uploads of local lab reports, informed consent forms, discharge summaries, etc.) JCHR must ensure that the sites have adequately redacted protected health information (PHI) prior to submission/upload. In the event that JCHR has received non-redacted materials, JCHR will immediately delete the material, notify the site to inform them of the sharing, prompt the site to report the sharing in accordance with local policies and procedures, and instruct the site to resubmit/re-upload the material once redacted.

SECTION 7: CERTIFICATION PROCEDURES

7.1 Clinical Site and Personnel Training and Certification

7.1.1 Site Certification:

Both the Primary Investigator and Primary Coordinator for the site must complete all study certification requirements before a site can be activated and begin enrolling participants. These requirements are listed on the DCLP3 Site Certification Checklist found in Appendix K

7.1.2 Site Personnel Certification:

Study personnel must complete all study certification requirements before a site can be activated and begin enrolling participants The site specific, Site Staff Delegation Log specifies which tasks personnel are certified to perform. The study personnel certification requirements are listed on the DCLP3 Personnel Certification Checklist found in Appendix L.

7.1.3 Site and Personnel Training

The JCHR Coordinating Center will hold a certification and training meeting/conference call (or a series of calls) for investigators, coordinators, and other staff involved in conducting the protocol.

- Separate calls may be held to review specific topics (i.e., device accountability, data entry, and/or central laboratory procedures).

The JCHR Protocol Monitor will track completion dates for each task for each site personnel or document on a site certification and training log located in the trial master file. Prior to being awarded certification, each site will be required to complete the following tasks and to submit supporting documents to the JCHR Coordinating Center.

7.1.3.1 Protocol Acknowledgment and Acceptance:

Each investigator and Coordinator is required to attest to having read the protocol and agree to abide by all provisions in the protocol by completing the Protocol Acknowledgement and Acceptance form on the study website.

7.1.3.2 Q&A Certification:

A certification Q & A quiz will be administered based on the content covered in the Protocol and the study procedures manual. All Investigators, Study Coordinators and other study staff that will have direct contact with the participants must complete the Q & A certification provided on the study website with a passing score of ≥80% prior to conducting any study related procedures. For those who score < 80% on the

Q & A quiz, their certification link will be re-set by the Coordinating Center, and they will be given the opportunity to review the protocol and re-take the quiz.

7.1.3.3 Protocol Training:

All study personnel including investigators, coordinators and any other staff participating in the DCLP3 study must participate in a protocol training teleconference including a detailed review of the study Protocol and study Procedure manual.

7.1.3.4 eCRF Taining:

Site personnel (including Investigators, if desired by the site) who will be entering data into electronic case report forms (eCRF) must complete a website training session and enter mock data on the study training website, including enrollment of a study participant and the subsequent CRFs required to successfully randomize the participant. Only study personnel who have completed the required data entry training will receive a website permission to enter or edit study protocol data (i.e., data collected specifically for the protocol).

- Note that a site's Primary Coordinator must specify a pump-naïve, CGM-naïve participant so that completion of Run-In-related CRFs is required prior to randomizing test subject
- Other personnel at a site may specify a participant who currently uses a pump and a Dexcom G4,G5 or G6 CGM at least 11 out of the prior 14 days, so that the Run-In CRFs may be skipped prior to randomizing test subjects.

7.1.3.5 Inventory Tracking (ITA) Training:

Any staff involved with device accountability must attend an ITA training teleconference prior to being granted access to this application via the study website. Only study personnel who have completed ITA training are given permission to access ITA on the study website.

7.1.3.6 Tandem System Training:

Site personnel including at minimum the PI and the primary coordinator will be trained by Tandem trainer personnel on the use of study pump and its integration with the study CGM. Trained personnel are subsequently eligible to provide this training to other site personnel or to study participants.

7.1.3.7 Study Procedure Required Training:

Coordinators responsible for collecting and shipping central lab samples must attend a Central Lab training teleconference.

Prior to engaging in any study related procedures, all study personnel are required to review the study procedure manuals, user guides and protocol.

SECTION 8: ADMINISTRATIVE

8.1 Maintaining Inventory for Study Materials

The coordinator must maintain a system for storage and accountability for all study supplies. Site online inventory should be kept updated as devices are received from the Coordinating Center, assigned to subjects, or returned to the clinical center. Coordinating Center will evaluate site inventory once a month.

Investigational device components may be used by study staff for the purpose of system training and troubleshooting as long as there is no insulin infusion.

For all re-usable durable equipment, such as insulin pumps, CGM receivers, CGM transmitters, laptops, and phones, the original box must be kept at your clinical center and stored appropriately.

8.2 Case Report Forms

Each subject may have a separate binder or folder for admission worksheets, checklists and printouts of the completed electronic case report forms. The electronic device files and electronic CRFs from the study website are considered the primary source documentation.

8.3 Guidelines for Worksheet Completion

1. Be sure to enter the subject's study ID on every page of every worksheet and checklist that is completed on paper. Store these complete worksheets in the subject's study binder.

2. Use a blue or black ballpoint pen.

3. To facilitate data entry and verification of data consistency, please utilize the following guidelines:

    a. Write clearly and legibly.

    b. If the test is not done, write ND. Do not leave blank.

    c. When the date is unknown, estimate dates to the best of your ability, and indicate an estimated date by placing an "E" next to the estimated date using dd/mmm/yyyy format.

    d. All forms should be checked for completeness and accuracy. This will help if the worksheet needs to be referenced at a later time for any reason.

    e. Write-in responses should be clearly legible.

8.4 Electronic Case Report Form Submission

Each subject may have a separate binder or folder for admission worksheets, checklists and printouts of the completed electronic case report forms. The

electronic device files and electronic CRFs from the study website are considered the primary source documentation.

All forms should be completed by the time of discharge for each subject. The following forms are data entered on the study website, and electronic data entry should always be completed within 3 business days from the date of the visit or contact:

- Obtain an ID for a new Participant (after consent is obtained)
- Screening Visit CGM Home Run-In Initiation
- Initiation of Run in Visit CGM
- End of Run-In Visit
- Randomization Visit
- Study CGM and Insulin Pump Training Visit
- Study Follow-up Phone Contact-1 week
- Study Follow-up Visit-2 weeks
- Study Follow up Phone Contact-4 weeks
- Study Follow up Visit-6 Weeks
- Study Follow up Phone Contact-9weeks
- Study Follow-up Visit-13 Weeks
- Study Follow up Phone Contact- 17 weeks
- Study Follow up Phone Contact-21 weeks
- Study Follow-up Visit-26 Weeks

Additional case report forms:

- Adverse Event
- Hypoglycemia Event Information
- Severe Hyperglycemia or DKA Event
- Device Issue
- Insulin Pump Settings
- Medical Condition

- Medications
- Unscheduled Contact
- Participant Final Status

A full packet containing all CRF worksheets will be available on the study website.

8.5 Investigator Review of Forms

Forms entered online must be reviewed by a study investigator. This procedure can be completed online at any time once a form has been submitted.

8.5.1 Electronic Sign-off

Investigators and Coordinators will be required to review and sign off on various aspects of data entered on the clinic website, which will serve as an electronic signature. Investigators will be required to sign off on forms in which they are listed as the examining/treating physician. Coordinators will be required to sign off on forms in which they are selected as the responsible party during a given visit.

It is expected that investigators and coordinators will review and approve forms within 7 days of completion. A weekly e-mail will be sent to investigators and coordinators as a reminder.

To approve each sign-off, the investigator and coordinator will need to log onto the clinic website with his/her User ID and password and navigate to the sign-off menu.

When they log onto the study website they may or may not see a counter listing how many sign-offs they have for all active Protocols:

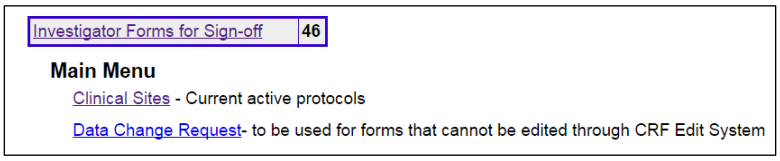


Figure 8-1. Sign-offs for Active Protocols

They will click on “Investigator Forms for Sign-off” or “to view and approve submitted eCRFs for the study.

To review and approve edits made to submitted/edited eCRFs or procedural/Protocol deviations, they can navigate to the sign-off menu by clicking on the links shown on the home tab or by clicking on the Clinical Sites tab > Sign-Off sub-tab.

Once in the Sign-off menu, click on the links under the header “Investigator Sign-off” to view one of the following:

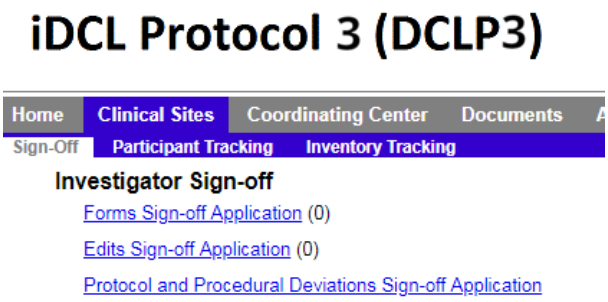


Figure 8-2. Investigator Sign-off

- **Form Sign-off Application:** Investigators can sign-off directly on forms prior to submission or subsequent to submission within the sign-off menu.

- **Edits Sign-off Application:** Investigators will be required to sign off on any edits made to a previously signed CRF.

- **Protocol and Procedural Deviations Sign-off Application:** The investigator responsible for the study visit at which a Protocol or procedural deviation occurred will be responsible for sign-off of the deviation. Additionally, the responsible PI will also be required to sign off on any deviations.

On that same menu, there is an option to view and print out the reports for pending sign-offs.

8.6 Coordinator Review of Forms

8.6.1 Coordinator Review of Deviations

Coordinators will only be required to review and sign-off on protocol deviations identified by the Coordinating Center during weekly reviews. To review and approve procedural/Protocol deviations, they can navigate to the sign-off menu by clicking on the links shown on the home tab or by clicking on the Clinical Sites tab > Sign-Off sub-tab.

8.6.2 Protocol Review Queries

Designated coordinators per visit will be required to review and sign-off on protocol review items identified by the Coordinating Center during weekly reviews. To review and approve procedural/Protocol review items, they can navigate to the sign-off menu by clicking on the links shown on the home tab or by clicking on the Clinical Sites tab > Sign-Off sub-tab.

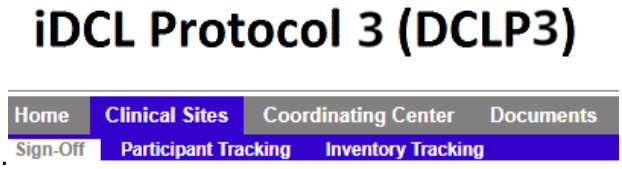


Figure 8-3. Sign-off Tab

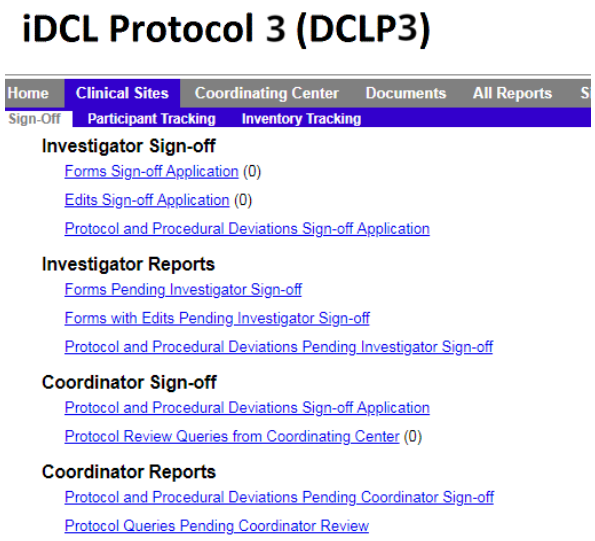


Figure 8-4. Sign-off Menu

Then select *Protocol Queries Pending Coordinator Review*.

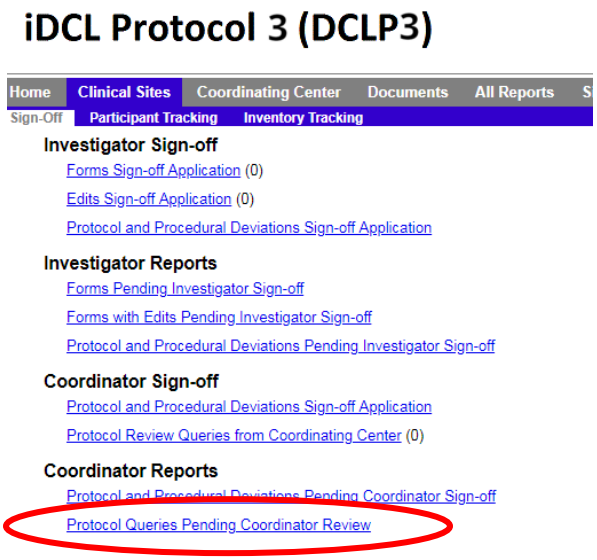


Figure 8-5. Sign-off Menu—Protocol Review Queries from Coordinating Center Link

A summary window will appear with issues that need to be addressed. Click “Select” under the Action header:

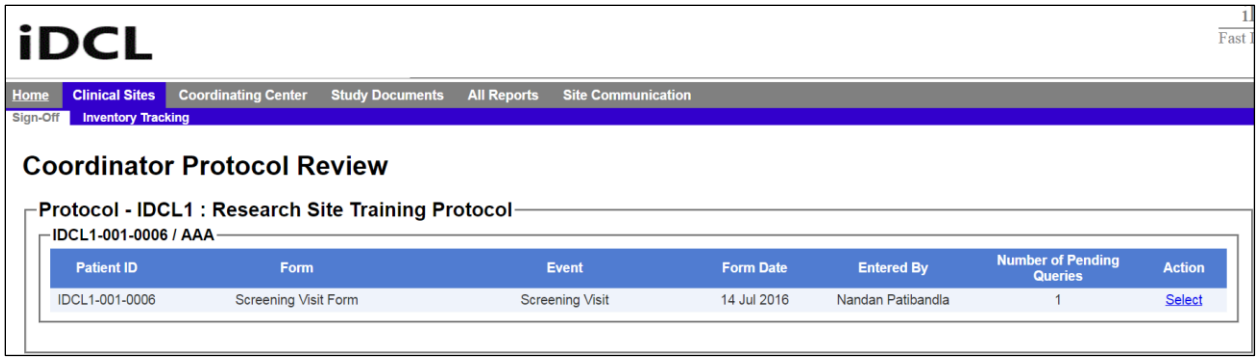


Figure 8-6. Coordinator Protocol Review

For each item identified for a given subject, comments from the Coordinating Center will display with a request to confirm the data reviewed. You can select from the following Comment Statuses:

1. **Query Completed:** Item has either been edited to reflect true data recorded during that particular visit or the item was edited to reflect transcription error.

2. **More information needed from Coordinating Center:** Further clarification from the Coordinating Center is required.

3. **Pending – Finish Later:** Completion pending.

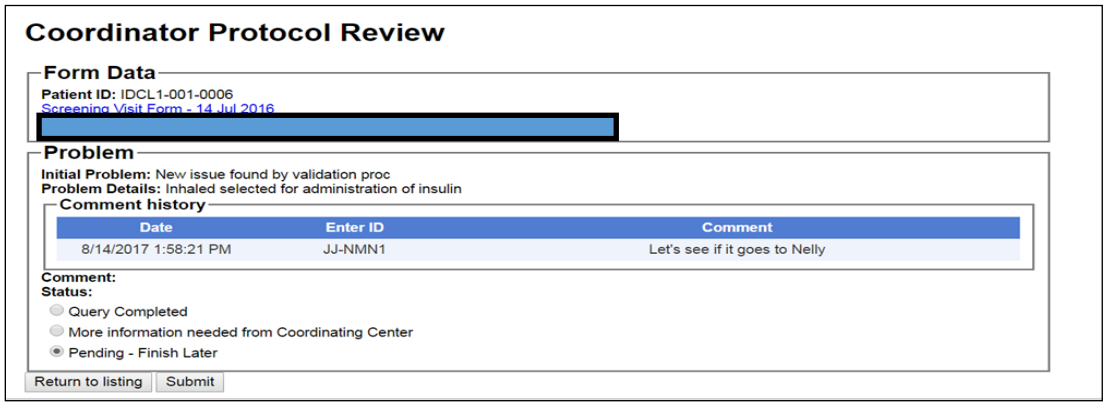


Figure 8-7. Coordinator Protocol Review—Comment Statuses

8.7 Communications with the Coordinating Center

1. Once a month a conference call will be held between CC staff and the clinic staff from all centers to discuss issues that may apply to all centers.

2. Once a week a conference call will be held between CC staff and the clinic coordinators from all centers to discuss issues related to the study procedures.

3. If a coordinator is going to be away, the CC should be informed so it can send necessary information by an alternate means.

4. After hour questions can be directed to idcl@jaeb.org. For emergency procedural events, issues can be directed to either Tiffany Campos (813-850-1158) or John Lum (813-951-2039).

8.8 Maintaining Study Records

1. In accordance with federal regulations, records relating to this study will not be destroyed until at least 3 years after the date that the investigation is terminated or completed, and until at least 2 years after the date that the records are no longer required for purposes of supporting a premarket approval application or a notice of completion of a product development protocol.

2. Institutional requirements for record retention apply as well.

SECTION 9: WEBSITE USER INFORMATION

9.1 Access to Website

All study personnel who will access the following website must have a study ID number and a password in order to log-in:

https://studies.jaeb.org/ndocs/idcl/Public/Login.aspx?ReturnUrl=%2fndocs%2fidcl%2fDefault.aspx

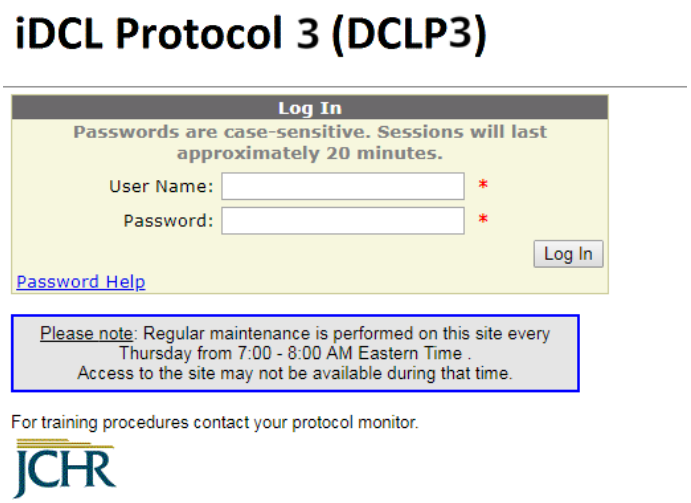


Figure 9-1. Study Log-in Screen

Permissions are set to restrict access to certain areas of the website to selected center personnel.

Only certain personnel will have the ability to enter data on the website.

If assistance is needed other than what is provided below in order to access the study website, personnel should contact the Coordinating Center for further assistance

Click “Password Help” on the log-in page:

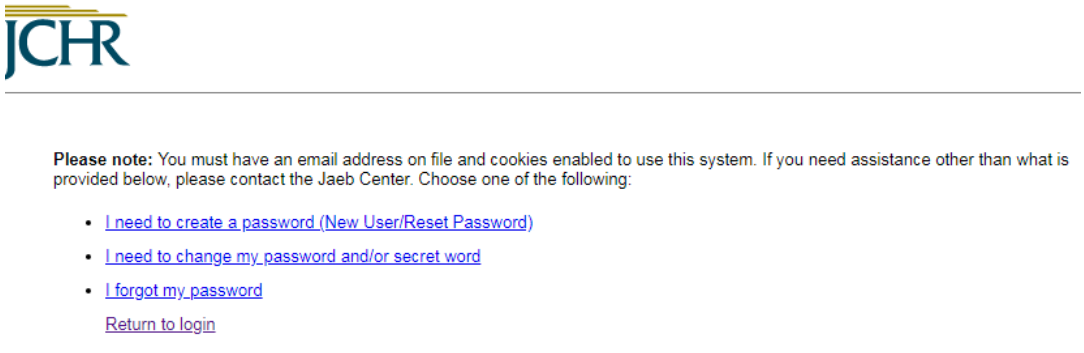


Figure 9-2. Password Help Screen

Once logged on, personnel can access the study protocol by clicking on “Clinical Sites” in the top gray header:

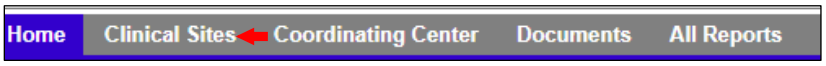


Figure 9-3. Clinical Sites Tab

To access the data entry links for the study, personnel should click under the header “Enter/Edit Participant Data”:

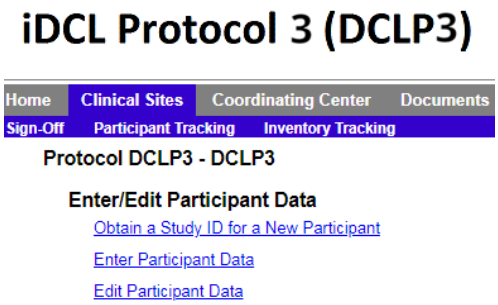


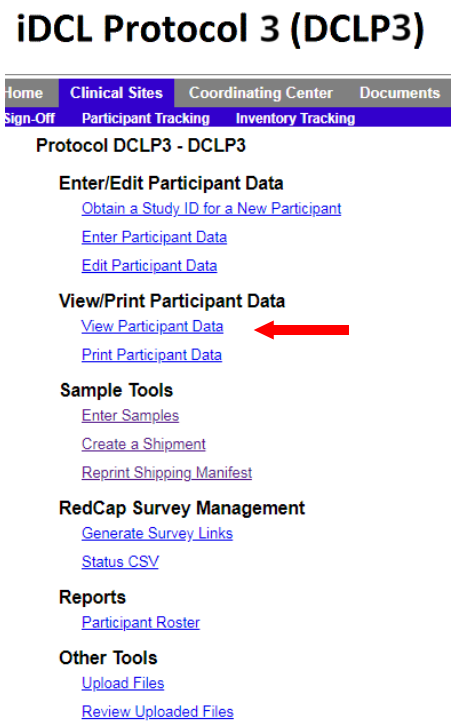
Figure 9-4. Enter/Edit Participant Data Screen

Study personnel can also access and download copies of the most recent DCLP3 protocol, procedure manual(s), and worksheet documents.

9.2 Data Entry Completion

Clinical trial data collection is for data to be completed directly onto the electronic case report forms (eCRFs) in real-time. Completing data entry directly on the clinic website in real time tends to improve data quality in preventing missing or invalid data. The website eCRFs will be considered the “source” whenever possible, thus use of paper worksheets is discouraged.

If direct data entry is not possible and worksheets are used, data entry should be completed within 3 business days from the time of the visit. Copies of the completed eCRFs from the study website can be printed using the “View/Print” menu mode located in the subject data entry menu.



View/Print Participant Data Links

Copies of completed paper worksheets should be signed and dated by the personnel responsible for the collection and added to the study regulatory binder. Sites that are pending data entry 3 business days after the visit will be contacted and encouraged to get the data submitted as soon as possible on a weekly basis.

The Enter/Edit Subject Data functions can be found on the subject data entry menu.

To enter in new data for a completed visit, personnel should click the link “Enter Participant Data”. The appropriate CRF for the next visit will already be up for personnel to complete for search subject.

To edit entered data on a submitted CRF, personnel should click the link “Edit Participant Data”. Select the subject you would like to correct and click “Continue to Subject Menu” to navigate to the CRF you would like to edit. Click the CRF link and complete your edits appropriately.

9.3 Miscellaneous Website Issues

1. All of the CRC data forms will be customized for printing after the subject is enrolled on the website.

2. At the conclusion of the final visit or during any time of the study for unexpected reasons, the Final Status Form must be completed.

9.4 Data Entry Tips

Generally it is faster to perform data entry with keystrokes rather than using the mouse. For dropdowns, here are tips about how to select the desired response with keystrokes:

1. Use the tab key to move from field to field.
2. Use the up or down arrow key or type the first letter of the desired response (you will also need to use the up or down arrow key if there is more than one response with the same first letter) to select the desired entry for each field.
3. For checkboxes, the space bar can be used to check or uncheck the field.
4. Use the tab key to move to the cancel or continue button and use the enter to key to select the appropriate button.

9.5 Instructions for Study Inventory Tracking

All study personnel will have access to an online “Inventory Tracking Application” (ITA) designed to help the Coordinating Center and individual research sites procure, track, and return supplies.

All official requests for study supplies will only be fulfilled if submitted through the online “Inventory Tracking” Application.

9.6 Guidelines for Non-Electronic Study Data Worksheet Completion

1. Be sure to enter the subject’s study ID on every page of every paper worksheet and checklist.
2. Use a blue or black ballpoint pen.
3. To facilitate data entry and verification of data consistency, please utilize the following guidelines:
    a. Write clearly and legibly.
    b. If the test is not done, write ND. Do not leave blank.
    c. When the date is unknown, estimate dates to the best of your ability, and indicate an estimated date by placing an "E" next to the estimated date using mmm/dd/yyyy format.
    d. All forms should be checked for completeness and accuracy. This will help if the worksheet needs to be referenced at a later time for any reason.
    e. Write-in responses should be clearly legible.

9.7 Instructions for Supply Reconciliation

Below are guidelines that are adapted from the site agreement for returning ALL supplies from the subject to the clinical center, and for reconciling items in the clinical center's inventory (adjusting for item quantities that are not reflected elsewhere).

9.7.1 Returning Items from Subject to Clinical Center

Open the Inventory Tracking Application (ITA) > Manage Site Inventory > Return Items as seen in Figure 9-5:

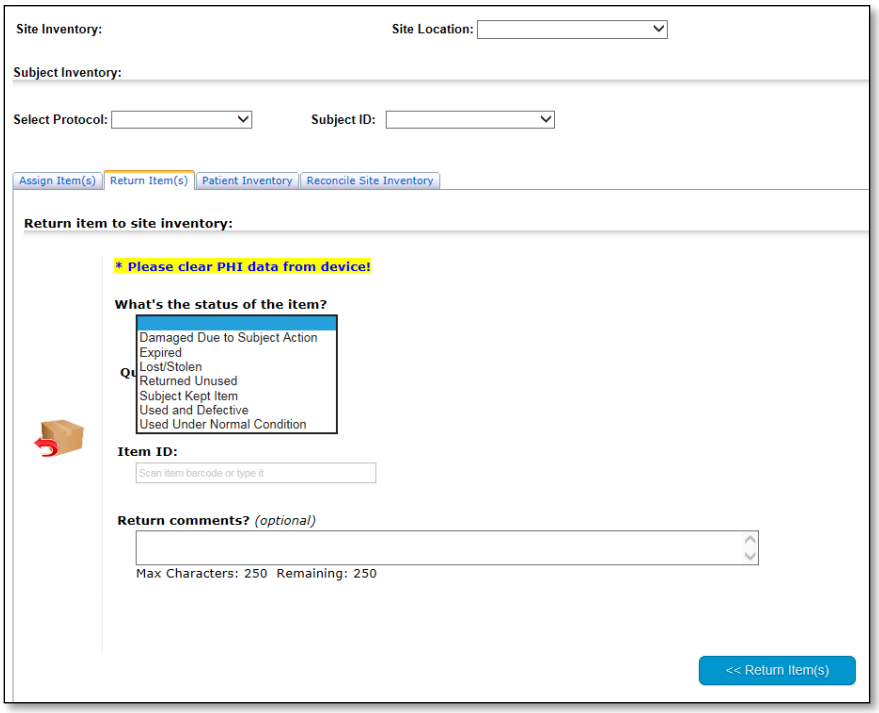


Figure 9-5. Inventory Tracking Application Return Items Screen

Ensure the site location, protocol, and subject ID are populated (not shown in this example). Then, use the guidelines listed below to select the applicable status of each item that subjects used in the study. For a full list of items that were sent to you, please generate applicable reports in the main ITA menu – note that you must select either Bulk or Individual items to view the applicable item (Bulk items refer to consumables such as cartridges and lancets whereas Individual items refer to non-consumables such as laptops and phones. If you are unsure about which category an item falls under or do not see an item in the list, please select the other option (Bulk or Individual) to ensure you can view the item).

As a general rule, select the most appropriate status from the dropdown menu. The system will automatically adjust the availability of each item in your inventory based on your selection, and based on the nature of the item (i.e. consumable or durable). For example, if you return a sensor, the system will remove this from your inventory because it cannot be re-used; if you return a pump, the system will keep it in or remove it from your inventory based on the status of item (i.e. defective vs used under normal condition).

After you return all items for a particular subject, go to Manage Site Inventory > Patient Inventory > Currently Assigned Items. This should be blank. If there are items still listed here, you need to keep returning the items until this list is blank.

9.7.2 Reconciling Items in Clinical Center's Inventory

This section in the ITA is used to adjust item quantities for supplies that are currently not assigned to a subject (items that exist at a clinical center). For example, if a site used a box of cartridges for benchtop testing, or if a box of strips were damaged or lost, then this section can be used to mark those items as such.

Open the Inventory Tracking Application (ITA) > Manage Site Inventory > Reconcile Site Inventory as seen in Figure 9-7.

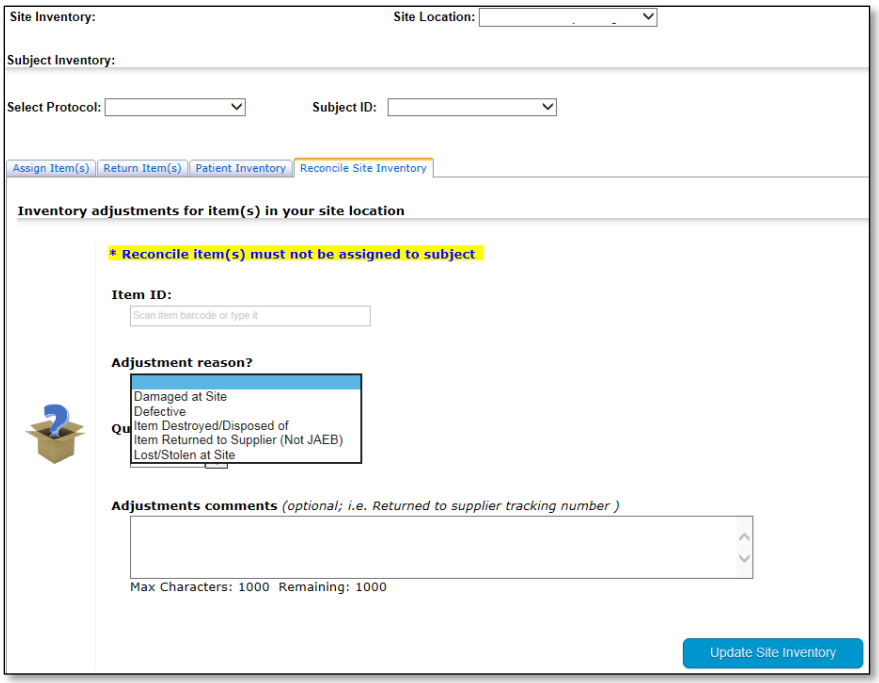


Figure 9-6. Inventory Tracking Application—Reconcile Site Inventory Screen

1. Ensure the site location, protocol, and subject ID are populated (not shown in this example).
2. Enter or scan the item lot # or serial number as it applies to either a bulk or individual item.
3. Select the adjustment reason.
4. Enter any applicable comments.

For items that were used for benchtop testing:

1. Bulk items, such as cartridges, sensors, etc. > select “Item Destroyed/Disposed of” for the Adjustment reason, then comment that the item(s) was used for local benchtop testing.

2. Individual items, such as pumps and CGM Receivers/Transmitters, DO NOT select an adjustment reason at this point. Instead, create a note-to-file about which items were used for benchtop testing and email idcl@jaeb.org with that information. Note this is a procedure specific to this protocol and will change for subsequent protocols.

APPENDIX A: FOR ADDITIONAL INFORMATION, PLEASE REFERENCE APPENDIX K: IDCL CONTROL-IQ INSTRUCTION SHEET

(Refer to study website located under Documents/Participant Handouts)

Inventory Tracking Application Site User Guide.

9.7.3 Returning Items from Subject to Manufacturer

1. After a defective pump is replaced, the defective pump should be returned to Tandem for troubleshooting.

    a) This instruction also applies if a pump was replaced because it was thought to possibly be defective, even if it was later concluded that the hardware was probably OK.

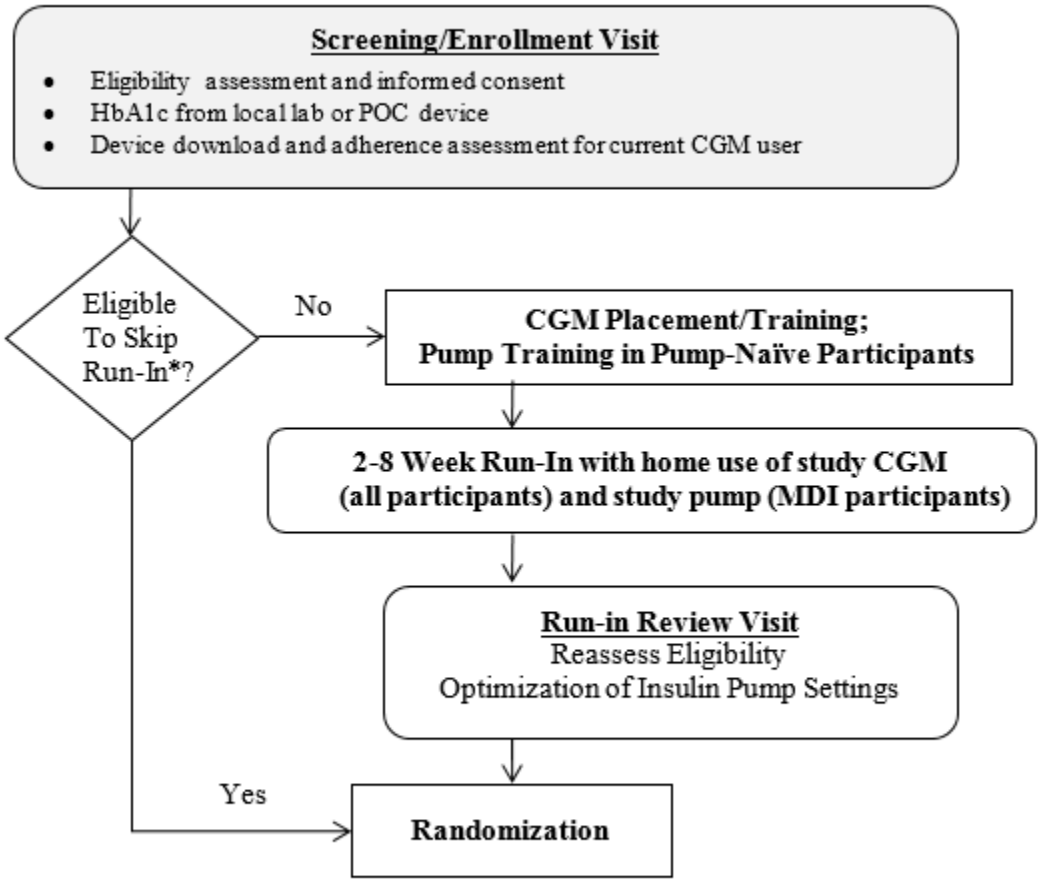
2. Open the Inventory Tracking Application (ITA) > Manage Site Inventory > Return Items as seen in Figure 9-5. Select “Used and Defective” for the status to remove the pump from the subjects current inventory and remove it from your site inventory. Include in the Return Comments that the pump is defective and being returned to Tandem.

3. Once the pump has been returned, open the Inventory Tracking Application (ITA) > Manage Site Inventory > Reconcile Site Inventory tab as seen in Figure 9-7. Select “Item Returned to Supplier (Not JAEB)” for the Adjustment Reason, then comment that the pump is defective and being returned to Tandem and include the device serial number.

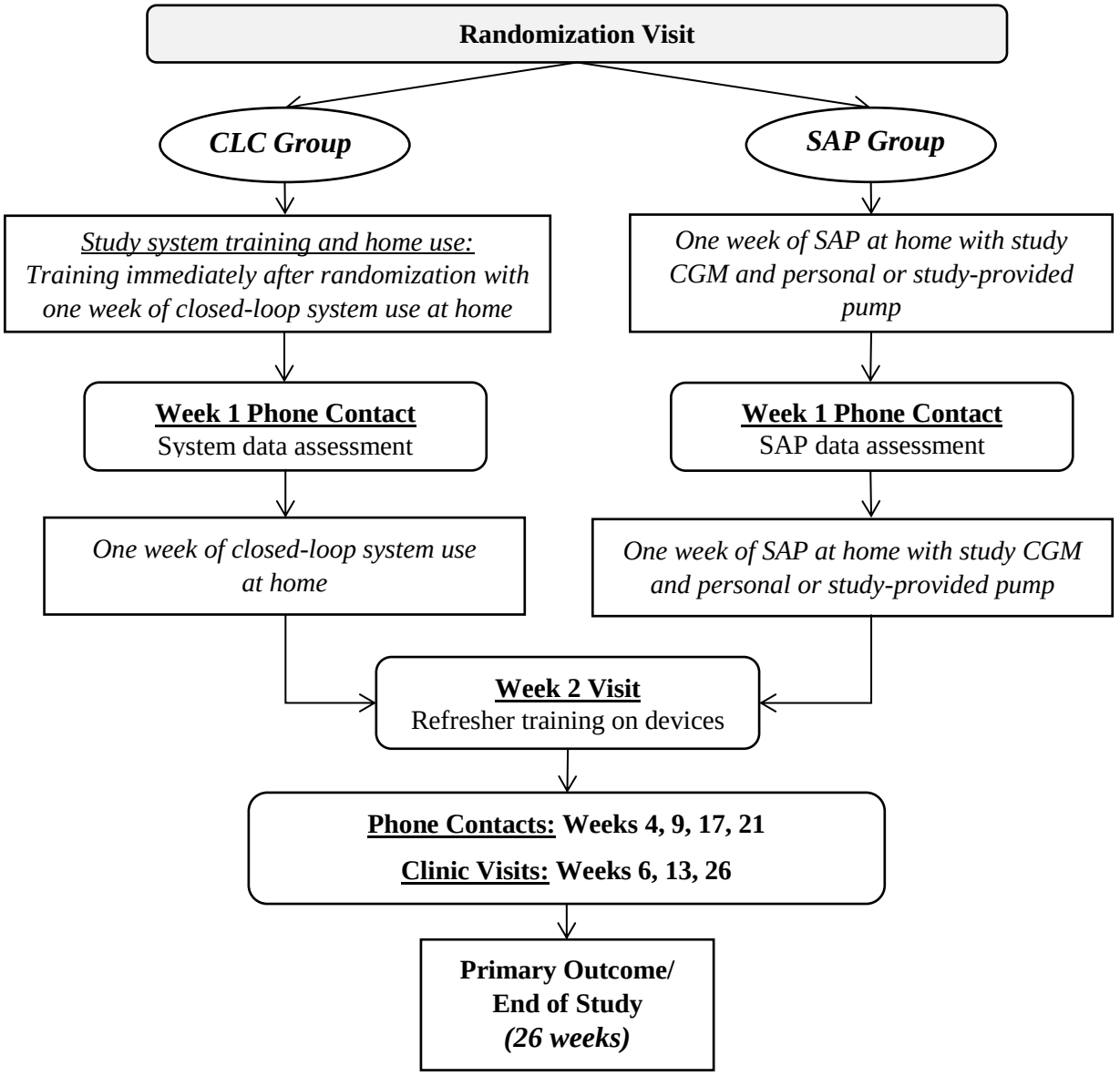
4. Once the pump has been reconciled in ITA, contact the Coordinating Center, include the serial number of the pump as well as the weight of the box that needs to be returned in the email. The Coordinating Center will provide all shipping documentation necessary for the site to ship the defective pump back to Tandem.

APPENDIX A: ENROLLMENT AND PRE-RANDOMIZATION FLOW DIAGRAM

SCHEMATIC OF STUDY DESIGN



*Current use of insulin pump and Dexcom G5 CGM with readings captured on at least 11 out of the previous 14 days


Randomization Visit
CLC Group
SAP Group
Study system training and home use:
Training immediately after randomization with one week of closed-loop system use at home
One week of SAP at home with study CGM and personal or study-provided pump
Week 1 Phone Contact
System data assessment
Week 1 Phone Contact
SAP data assessment
One week of closed-loop system use at home
One week of SAP at home with study CGM and personal or study-provided pump
Week 2 Visit
Refresher training on devices
Phone Contacts: Weeks 4, 9, 17, 21
Clinic Visits: Weeks 6, 13, 26
Primary Outcome/
End of Study
(26 weeks)

1754

APPENDIX B: T:SLIM X2 INSULIN PUMP WITH CONTROL-IQ TECHNOLOGY USER GUIDE

(Refer to Study Website Located under Documents/Manuals)

APPENDIX C: T:SLIM X2 INSULIN PUMP USER GUIDE

(Refer to Study Website Located under Documents/Manuals)

APPENDIX D: TANDEM PUMP TRAINING CHECKLIST

(Refer to study website located under Documents/Visit and Phone Call Instruction Sheets and checklists)

APPENDIX E: DCLP3 CGM TRAINING CHECKLIST

(Refer to study website located under Documents/Visit and Phone Call Instruction Sheets and checklists)

APPENDIX F: iDCL CONTROL-IQ INSTRUCTION SHEET

(Refer to study website located under Documents/Participant Handouts)

APPENDIX G: INVENTORY TRACKING APPLICATION SITE USER GUIDE

(Located in Inventory Tracking Application on study website)

APPENDIX H: SETTING UP SUBJECT LAPTOP

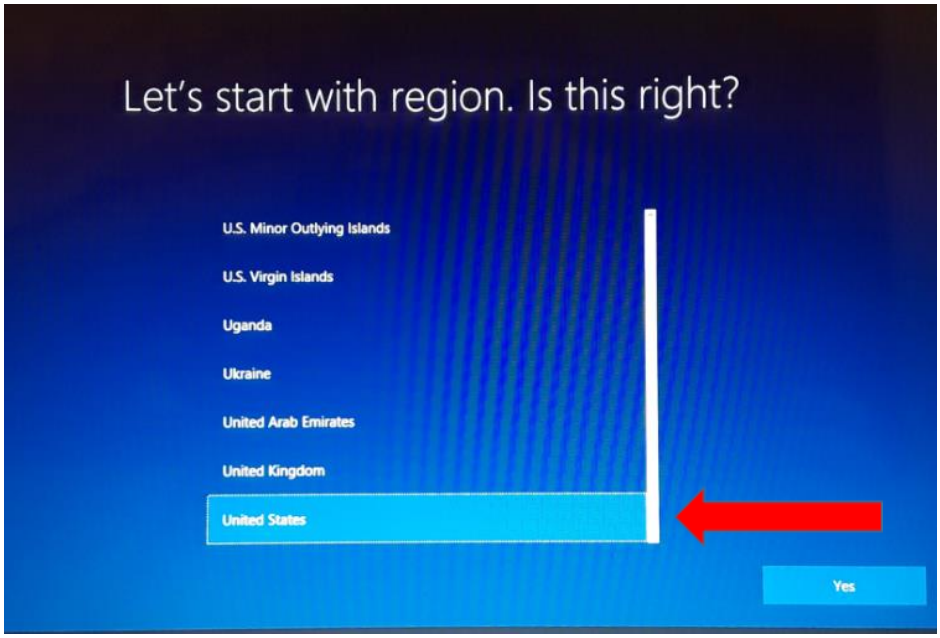
H.1 Setting Up Subject Laptop

For subjects participating in the study that are randomized to the **SAP** arm of treatment and do not have access to a computer at home to download their CGM device data, a subject laptop will be assigned to them through the Inventory Tracking Application to use during the study prior to proceeding with home use. No software has been downloaded onto the subject laptops.

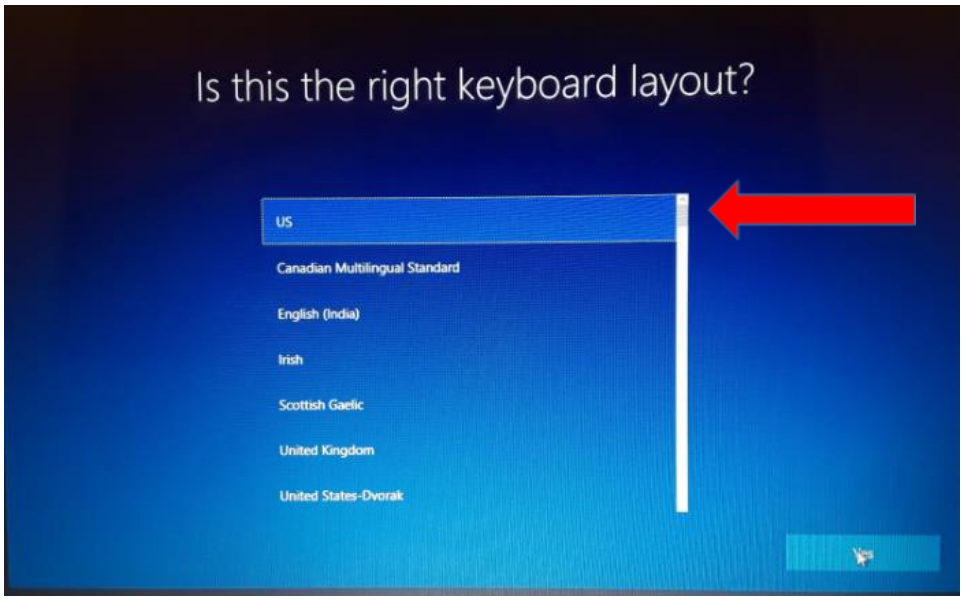
H.1.1 Instructions For Setting Up Subject Laptop

Setup for the laptop will need to occur in clinic and prior to the patient going home. Refer to the following to assist with setting up the subject laptop.

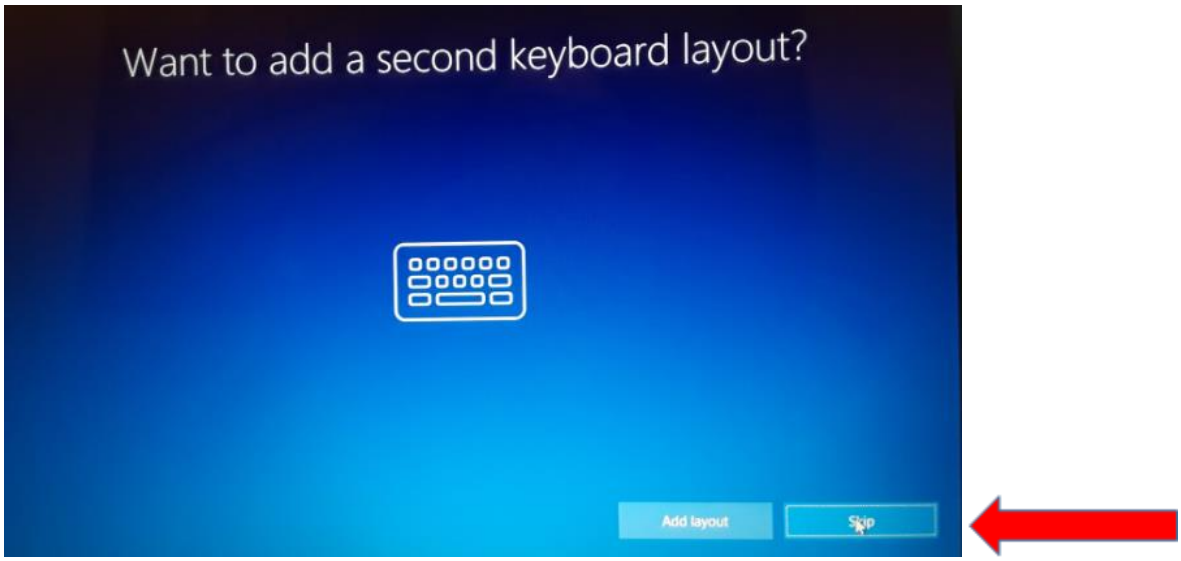
1) Once you turn on the laptop you will see the following screen, Select the "**United States" and click "Yes".**



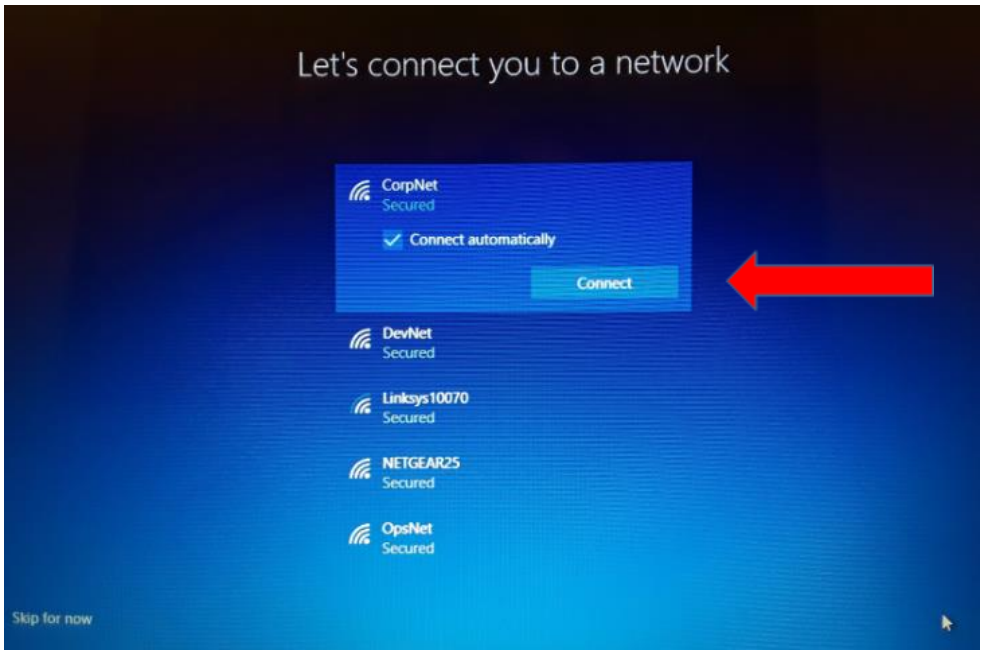
2) Select **"US"** and click on **"Yes"**



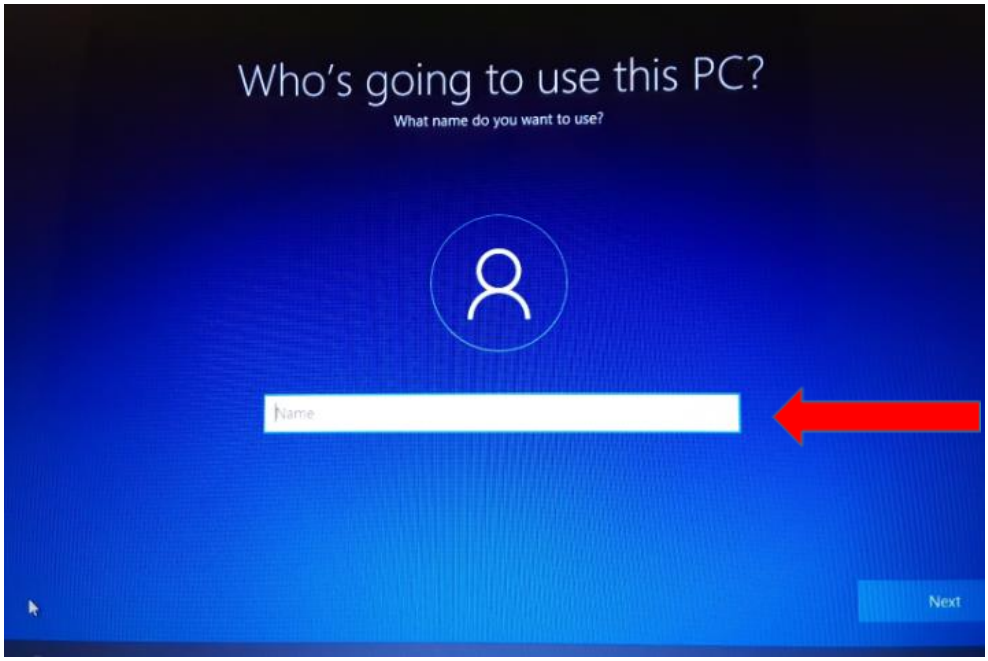
3) Next Click "Skip"

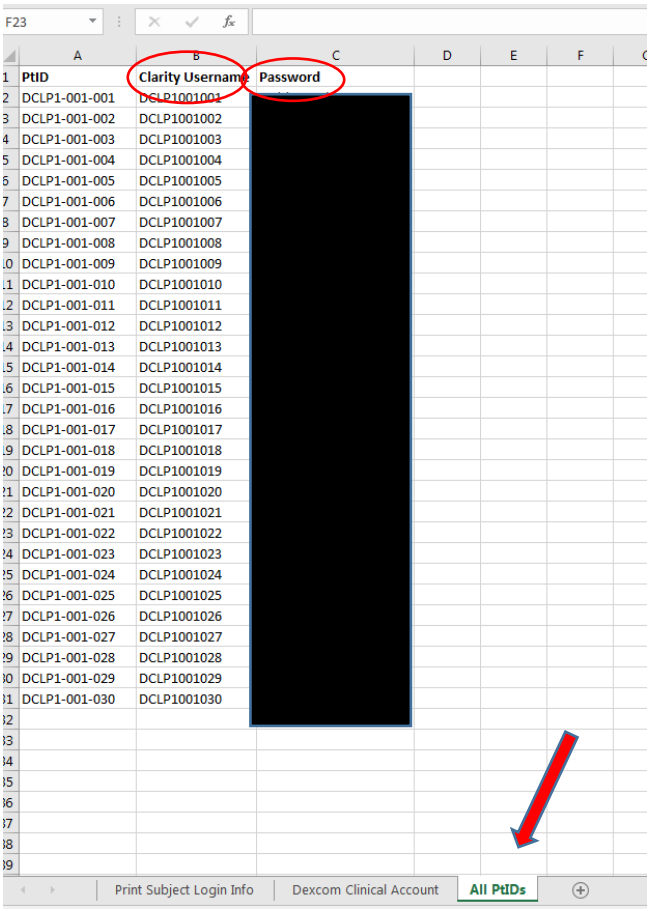


4) Select Network. Subject will have to select their personal network at home.



5) "Who is going to use this PC?": The Username on this screen is the subject's "Clarity Username" that has been assigned to the subject and is available for your reference on the "PtIDs" tab on the Dexcom Clarity Spreadsheet Provided to your site. (i.e. DCLP3-001-001)

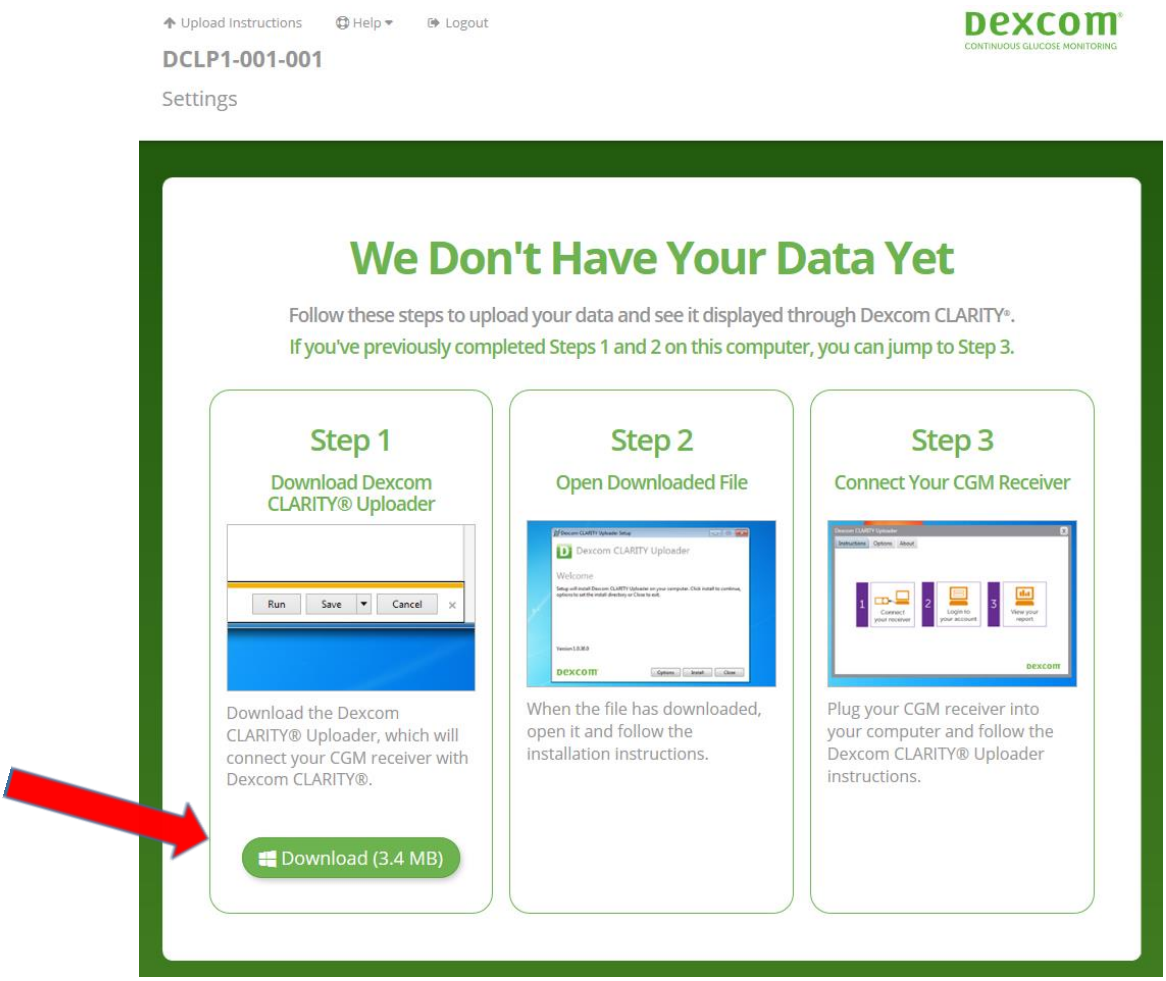




6) The Password for the laptop is the subject's "Clarity Password" that is located on the "All PtIDs" tab on the Dexcom Clarity Spreadsheet provided to your site.

7) Once the User name and Password have been established, you will be able to proceed with access to the Dexcom Clarity website at https://**clarity**.**dexcom**.com and establish the "Home Users" account for the subject.

8) You will use the same Username and Password for entry into the Dexclom Clarity "Home Users" account as was used in setting up the computer. Next, Follow the instructions on the screen to install the "Dexcom Clarity Uploader"as seen below.



9) Once the software has been downloaded onto the laptop, the subject will return to this site periodically to download CGM device data per protocol.

APPENDIX I: RESETTING SUBJECT LAPTOP

I.1 Resetting Subject Laptop

For subjects participating in the study that are randomized to the SAP arm of treatment and do not have access to a computer at home to download their CGM device data, a subject laptop will be assigned to them to use during the study prior to proceeding with home use. Once the subject has completed the study and returned the laptop to the site, the site staff will be responsible for resetting the laptop prior to assigning it to another participant.

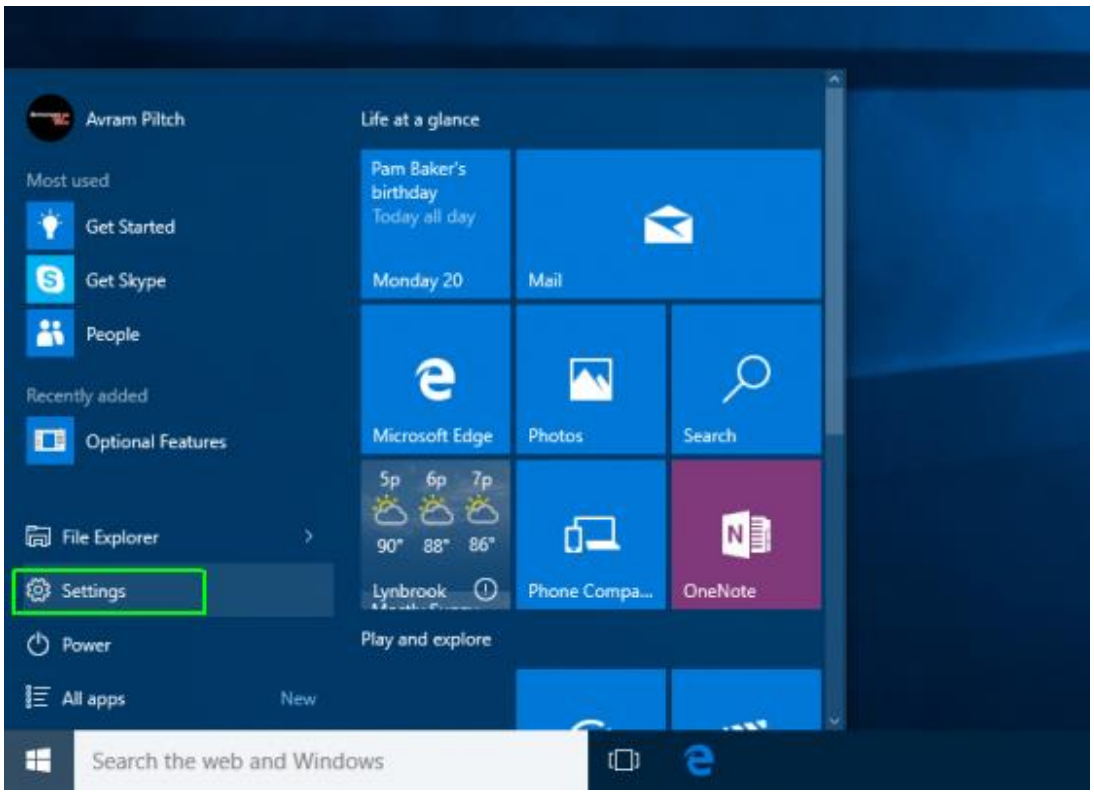
I.1.1 Instructions for Resetting Subject Laptop

Click on the Following Link:

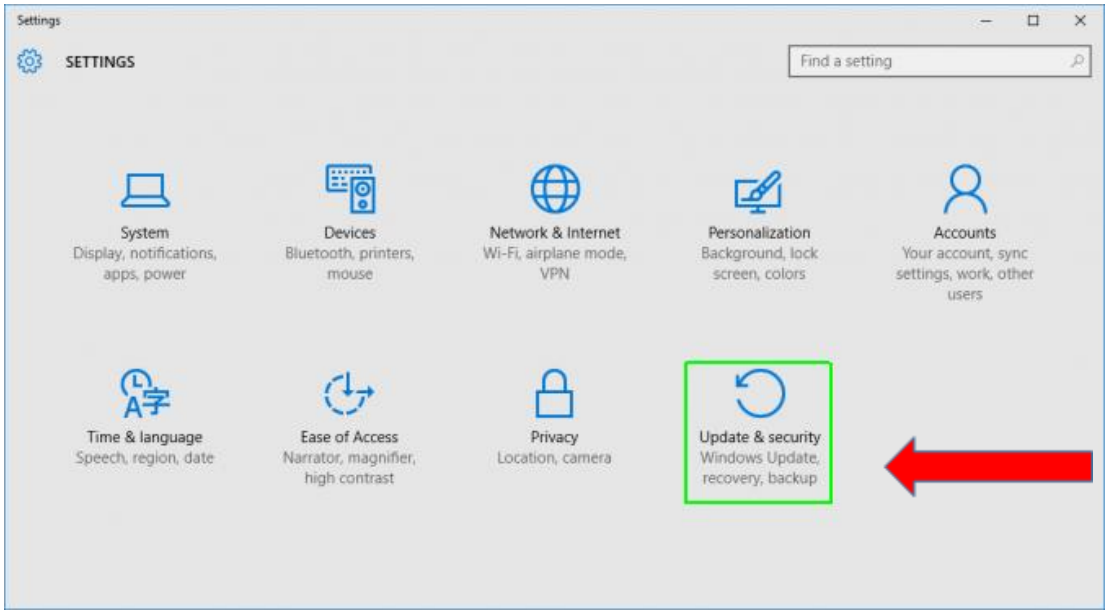
https://www.laptopmag.com/articles/reset-windows-10-pc

Once you click on the link, follow the screens as shown below.

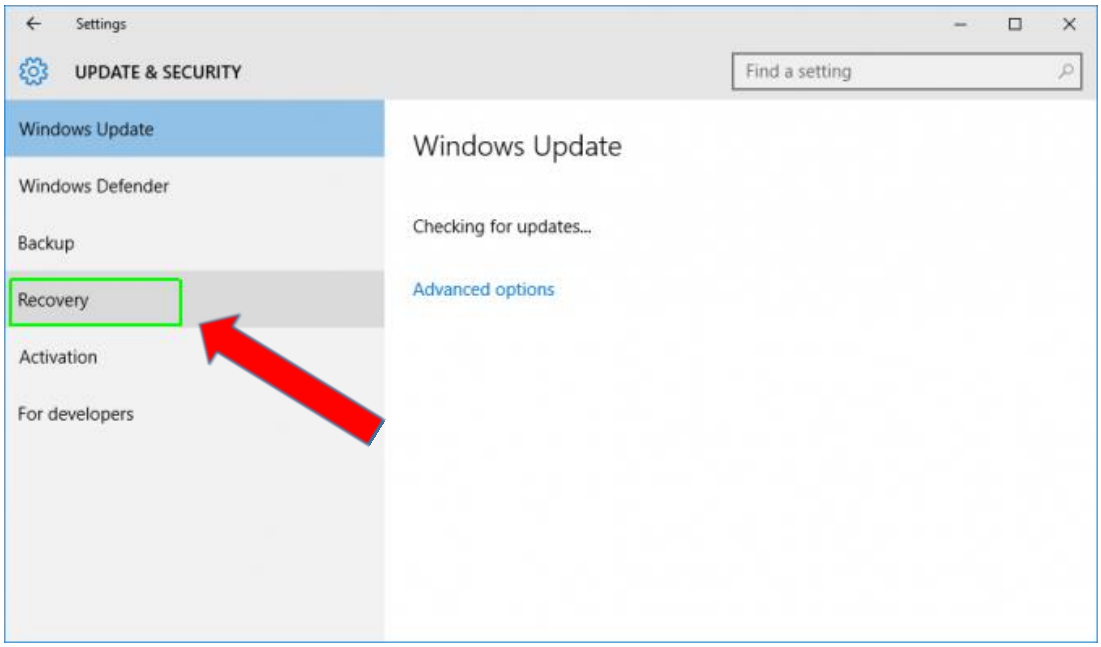
1. **Navigate to Settings.** You can get there by clicking the gear icon on the Start menu.



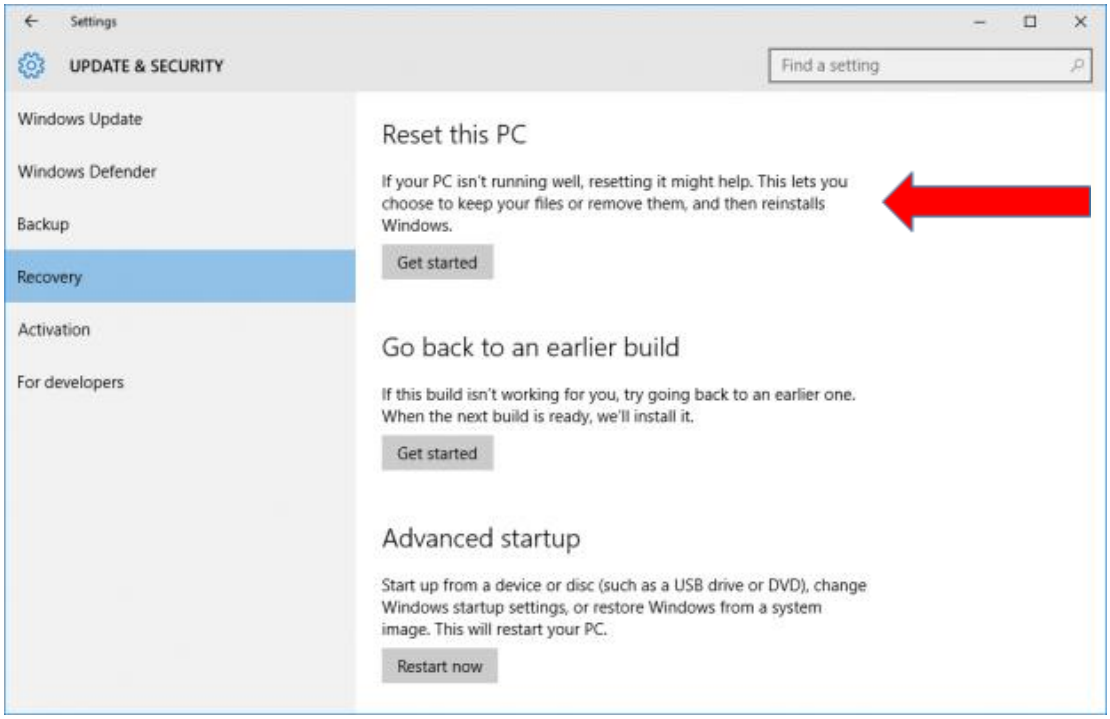
2. **Select "Update & security"**



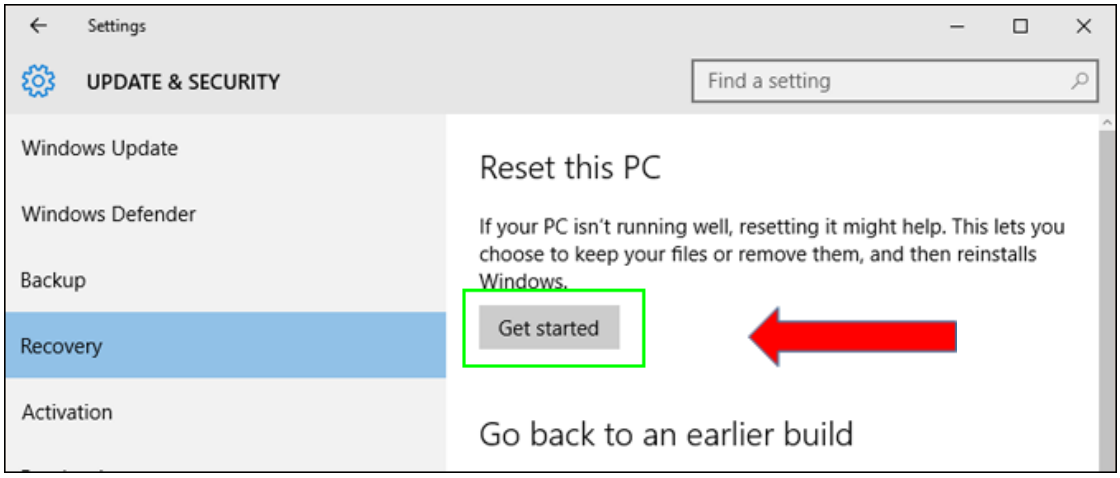
3. **Click Recovery** in the left pane.



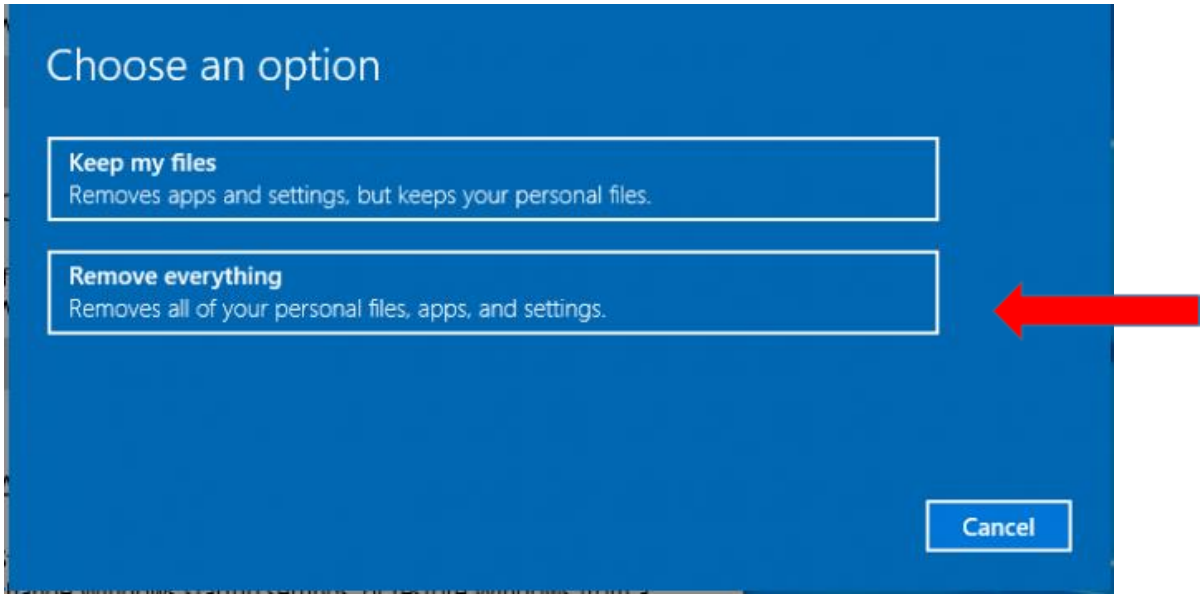
Click "Reset this PC"



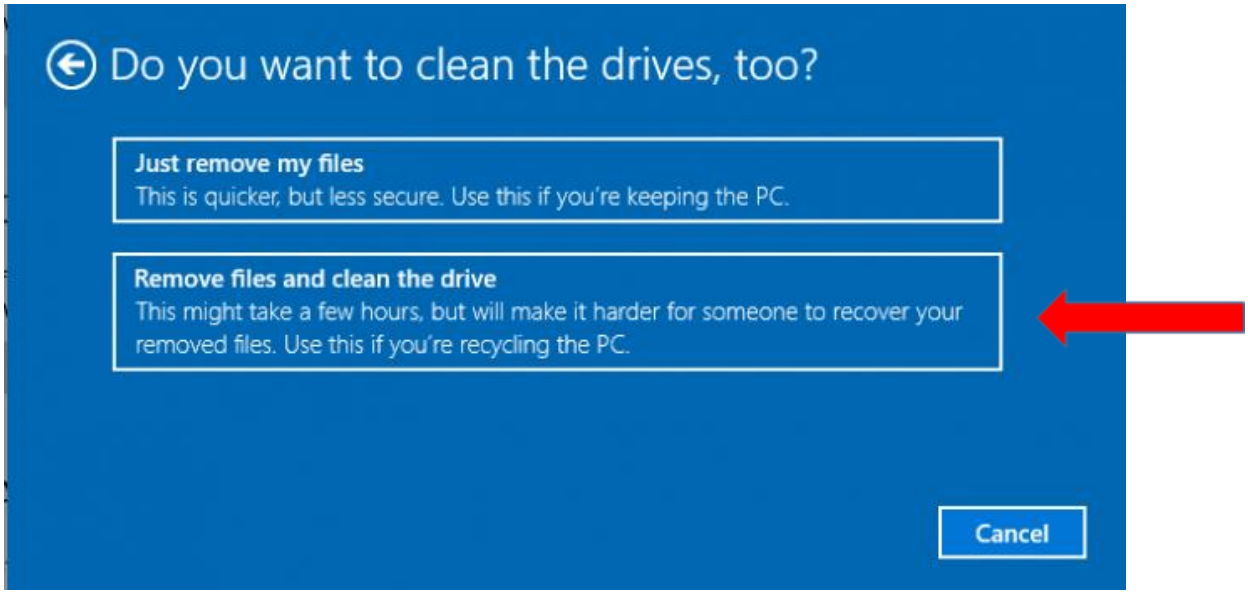
4. **Click Get started under Reset this PC.**



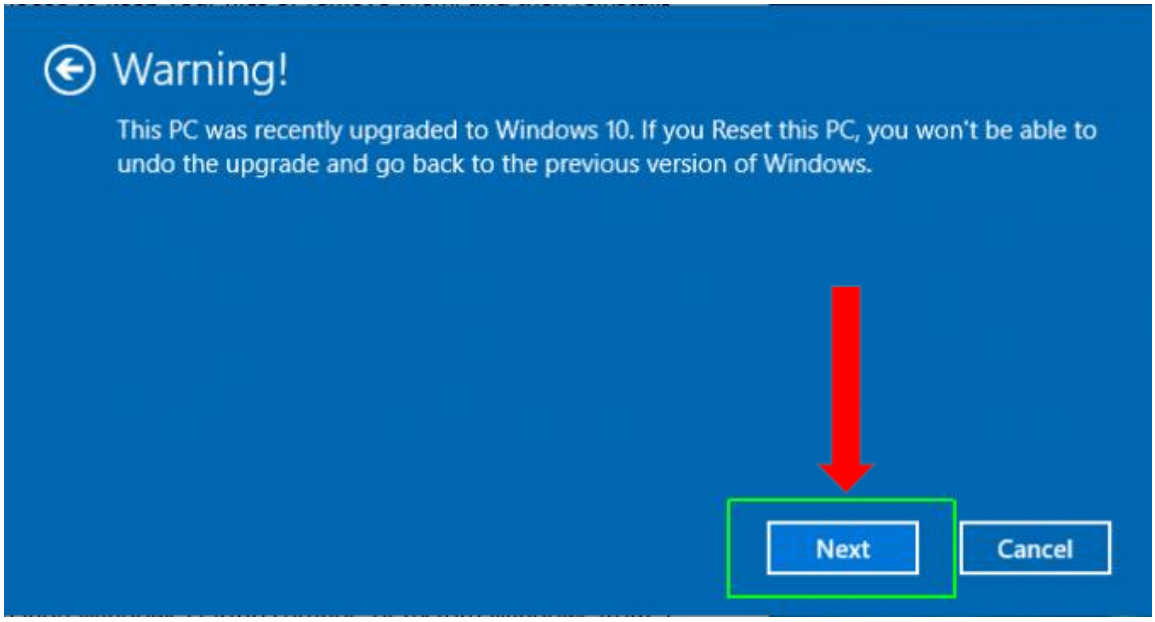
5. **Click "Remove everything,"** All of your settings will return to their defaults and apps will be uninstalled.



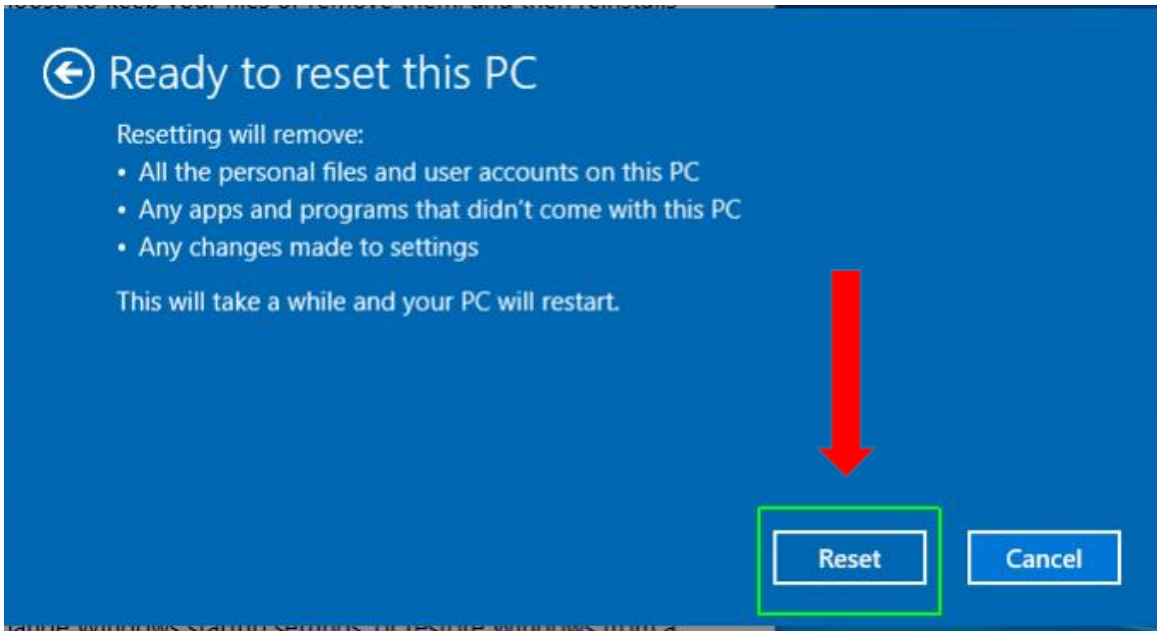
6. **Select "Remove files and clean the drive**



7. **Click Next** if Windows warns you that you won't be able to roll back to a prior version of the OS.

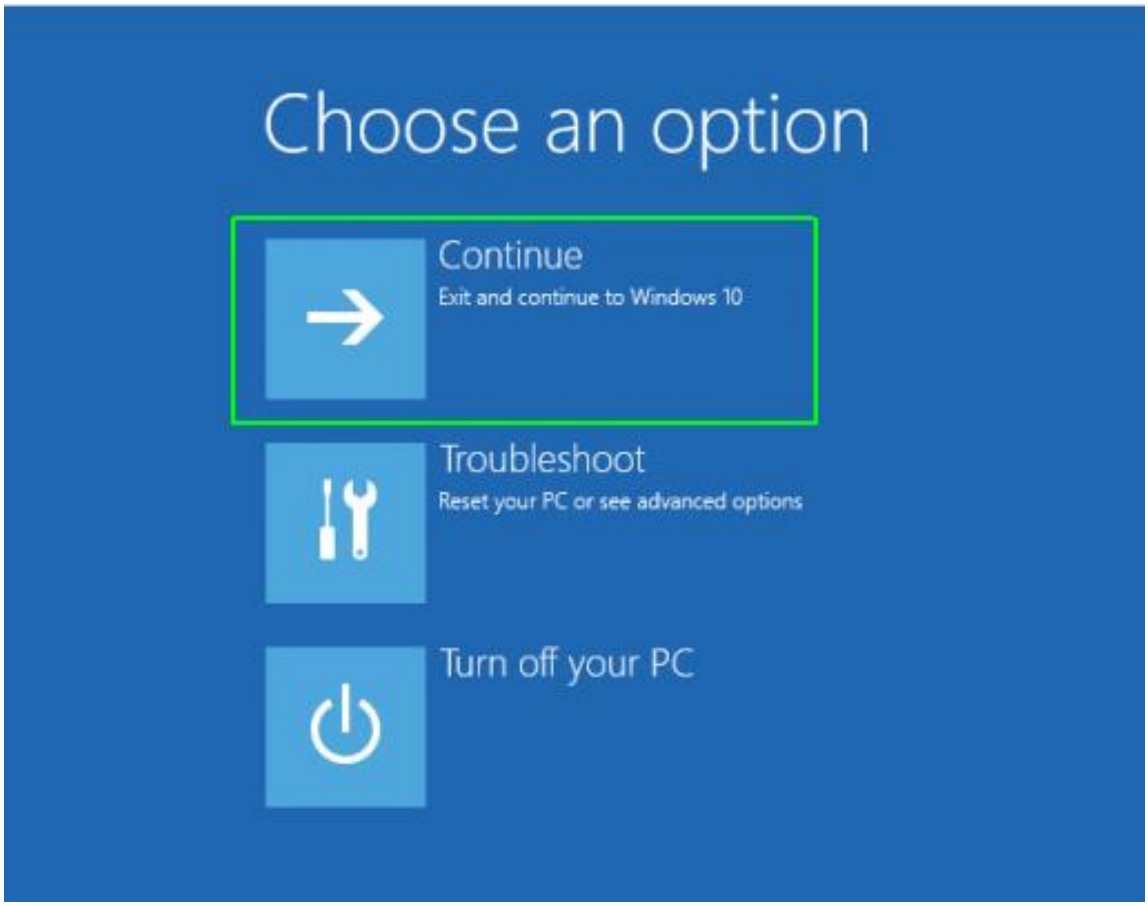


8. **Click Reset** when prompted.



Windows will then restart and take several minutes to reset itself.

9. **Click Continue** when prompted.


Choose an option
Continue
Exit and continue to Windows 10
Troubleshoot
Reset your PC or see advanced options
Turn off your PC

APPENDIX J: PARTICIPANT BINDER CHECKLIST

The following documents should be maintained in the participant's study binder and available for review during on-site monitoring visits.

Participant Binder Checklist – DCLP3 Study

Include Originals

Please include each of the following items, and include originals when possible:

1. Original informed consent/assent/HIPAA/Bill of Rights Documents
2. Print Obtain an ID printout from DCLP3 study website when ID created (not able to return to that screen and print once you leave that screen)
3. HbA1c/Pregnancy test results: include Pt. Identifier on results: Note: making a copy of the HbA1c results and attaching the original HbA1c for source as the original is suggested as the original often fades.
4. Copy of relevant EMR to confirm eligibility source for review of adverse events as described in section 1.5.1 of the Procedure Manual "Source Data Requirements to Support Eligibility Assessment"
5. Copies of relevant EMR source to ensure efforts are made to identify unreported adverse events, EMR records (if new records are available) must be obtained, reviewed, and included in each participant binder for the 13- and 26-week follow-up visits. Include the records in the participant binder, ensuring an investigator has annotated them to indicate they have reviewed the printouts. If no records exist, make a note in the participant binder for the 13-week and 26-week follow-up visits indicating such as described in section 1.5.2 "Source Data Requirements Following Subject Enrollment".
6. Original Tandem pump Training checklist (if applicable)
7. CGM Training Checklists
8. CRF paper worksheets: All handwritten originals
9. Other: additional signed training tools

APPENDIX K: SITE CERTIFICATION CHECKLIST SAMPLE

Jaeb Center for Health Research
15310 Amberly Drive, Suite 350
Tampa, FL 33647
Tel: (813) 975-8690
Fax: (813) 975-8761
jlum@jaeb.org

Site Certification

Confirms the site, principal investigator, and person acting as primary coordinator have met JCHR requirements for participation in the indicated study. Other study personnel may not participate in study activities until a separate certification document is provided to site staff. Enrollment may commence on the certification date below.

Study Name	**The International Diabetes Closed Loop (iDCL) trial: Clinical Acceptance of the Artificial Pancreas - A Pivotal Study of t:slim X2 with Control-IQ Technology**
Site Name	
Site Number	
Principal Investigator (PI)	
Primary Coordinator (PC)	

Is the site under JCHR Central IRB?

☒ Yes – Complete Sections A and C
☐ No – Complete Sections B and C

Section A – Complete if site is using reliance agreement with JCHR IRB

Requirements for Site Certification		
Name of Requirement	**Date of Document or Completion Date**	**Check if Not Applicable**
JCHR Protocol Approval Letter		-
JCHR IRB-Approved Protocol		-
JCHR IRB-Approved Adult Consent Form, Stamped		☐
JCHR IRB-Approved Customized Adult Consent Form, Stamped		☐
JCHR IRB-Approved Parental Consent Form, Stamped		☐
JCHR IRB-Approved Customized Parental Consent Form, Stamped		☐
JCHR IRB-Approved Assent Form, Stamped		☐
JCHR IRB-Approved Customized Assent Form, Stamped		☐
JCHR IRB-Approved HIPAA Authorization Form		☐
Site Approval by JCHR IRB for Study Participation		-

PI Approval by JCHR IRB for Study Participation		-
Local IRB Approval/Acknowledgment of Protocol & Consent/Assent		☐
Signed Task Delegation Log		-
Site Qualification Checklist		-
Clinical Site Contract(s) Completed		-

Section B – Complete if site is not using reliance agreement with JCHR IRB

Requirements for Site Certification		
Name of Requirement	**Date of Document or Completion Date**	**Check if Not Applicable**
JCHR Protocol Approval Letter	-	-
JCHR IRB-Approved Protocol	-	-
Local IRB Protocol Approval Letter	-	-
Local IRB Membership Roster and FWA number	-	-
Local IRB-Approved Adult Consent Form	-	☐
Local IRB-Approved Parental Consent Form	-	☐
Local IRB-Approved Assent Form	-	☐
Clinical Site Contract(s) Completed	-	-
Signed Task Delegation Log	-	-
Site Feasibility Questionnaire	-	-

Section C

Certification Requirements for: Principal Investigator (PI) and Primary Coordinator (PC)		
Name of Requirement	**Date Complete/Expire - PI**	**Date Complete/Expire - PC**
Protocol Training		
eCRF Training		
Mock Data Entry Using Test Participant		
Inventory Tracking Application (ITA) Training		
Good Clinical Practice (GCP) Training		
Site Principal Investigator Statement of Compliance (protocol signature page)		
Principal Investigator Agreement (incorporated into protocol signature page)		
Medical/Professional License		
Protocol Acknowledgement		
Protocol Certification Quiz		
Most recent JCHR-IRB Handbook Attestation		
Financial Disclosure		
CV or Biosketch		
Central Lab Processing Training		
Tandem System Training		

In addition to the required documents listed above, the following items have been reviewed with the site PI and PC prior to certification:

- ❑ Confirm study role of all site personnel participating on call
- ❑ Establish site and coordinating center support contacts
- ❑ Explain that the Protocol and Procedures documents are considered authoritative for reference and are expected to be 100% correct and self-consistent
- ❑ Review the high-level structure of the study protocol and procedures manual
- ❑ Review Study Device and answer questions regarding use of the study system
- ❑ Device data download expectations
- ❑ Set weekly monitoring expectations
- ❑ Scheduling and handling of safety monitoring alerts
- ❑ Review of study website and Inventory Tracking
- ❑ Review Central Lab Procedures
- ❑ Set expectations that presiding investigator sign-off will be required for each CRF after an visit is complete
- ❑ Review what supplies the site can expect to receive and procedures for tracking and requesting additional supplies on the study website (with ITA call)
- ❑ Device deficiencies/issues reporting
- ❑ Review subject enrollment timelines
- ❑ Ask what additional questions the site personnel have regarding the study

I attest to the best of my knowledge that the aforementioned site and personnel have met all the requirements for study participation in the indicated study, and are able to commence participant enrollment beginning on the date indicated below.

Date of Certification: _____

JCHR Protocol Director Name, Signature and Date:

_____

APPENDIX L: PERSONNEL CERTIFICATION CHECKLIST SAMPLE

Jaeb Center for Health Research
15310 Amberly Drive, Suite 350
Tampa, FL 33647
Tel: (813) 975-8690
Fax: (813) 975-8761
jlum@jaeb.org

Personnel Certification

Confirms the following personnel have met JCHR requirements for participation in the indicated study and may participate in study-related activities beginning on the certification date below.

Study Name	
Site Name	
Site Number	
Principal Investigator (PI)	

Certified Site Personnel	**Role**

Certification Requirements for Site Personnel

Name of Requirement	**Date Complete or Expire**	
Protocol Training		
eCRF Training		
Mock Data Entry Using Test Participant		
Inventory Tracking Application (ITA) Training		
Good Clinical Practice (GCP) Training		
Medical/Professional License		
Protocol Acknowledgement		
Protocol Certification Quiz		
Financial Disclosure (FCOI)		
Most recent JCHR-IRB Handbook Attestation		
CV or Biosketch		
Central Lab Processing Training		
Tandem System Training		

Certification requirements marked with "NA" are not applicable due to the personnel's role or to the study tasks that are assigned as indicated in the site-specific delegation log.

In addition to the required documents listed above, the following items have been reviewed with the site personnel prior to certification:

- ❑ Confirm study role of all site personnel participating on call
- ❑ Establish site and coordinating center support contacts
- ❑ Explain that the Protocol and Procedures documents are considered authoritative for reference and are expected to be 100% correct and self-consistent
- ❑ Review the high-level structure of the study protocol and procedures manual
- ❑ Review Study Device and answer questions regarding use of the study system
- ❑ Device data download expectations
- ❑ Set weekly monitoring expectations
- ❑ Scheduling and handling of safety monitoring alerts
- ❑ Review of study website and Inventory Tracking
- ❑ Review Central Lab Procedures
- ❑ Set expectations that presiding investigator sign-off will be required for each CRF after an visit is complete
- ❑ Review what supplies the site can expect to receive and procedures for tracking and requesting additional supplies on the study website (with ITA call)
- ❑ Device deficiencies/issues reporting
- ❑ Review subject enrollment timelines
- ❑ Ask what additional questions the site personnel have regarding the study

I attest to the best of my knowledge that the aforementioned personnel have met all the requirements for study participation in the indicated study, and are able to participate in study-related activities beginning on the certification date below.

Date of Certification: _____

JCHR Protocol Director Name, Signature and Date:

_____

APPENDIX M: DCLP3 CENTRAL LAB MANUAL OF PROCEDURES

(Refer to study website located under Documents/Manuals)