Manual of Operations

KIDCARE
(**K**awasak**i** **D**isease
Comp**ar**ative **E**ffectiveness Trial)

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Jane C. Burns, MD (Co-PI)
Katherine Kim, PhD (Co-PI)
Adriana H. Tremoulet, MD, MAS (Safety Officer)
Samantha Roberts, MS (Program Coordinator)
Sonia Jain, PhD (Biostatistician)

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1. List of investigators

Jane C. Burns, MD
Role: Co-PI
Professor
Director, Kawasaki Disease Research Center
Division of Allergy, Immunology, and Rheumatology
Department of Pediatrics
University of California San Diego
Rady Children's Hospital San Diego
jcburns@ucsd.edu
Page: 858-576-1700, ext. 0
(w) 858-246-0155
(m) 858-775-6805
FAX: 858-246-0156

Katherine Kim, PhD, MBA, MPH
Role: Co-PI
Assistant Professor
Bette Irene Moore School of Nursing
University of California Davis
kathykim@ucdavis.edu
(w): 510-761-5406

Adriana H. Tremoulet, MD, MAS
Role: Safety Officer
Associate Professor
Associate Director, Kawasaki Disease Research Center
Division of Pharmacology and Drug Discovery
Department of Pediatrics
University of California San Diego
Rady Children's Hospital San Diego
atremoulet@ucsd.eduj
Pager: 858-616-3856
(w): 858-246-0012
(m): 858-245-1347
FAX: 858-246-0156

Sonia Jain, PhD
Role: Study Biostatistician
Professor
Director, Biostatistics Research Center
Division of Biostatistics and Bioinformatics
Department of Family and Preventive Medicine
University of California San Diego

2. Study Overview

2A. Overall Objective

The goal of this study is to determine whether infliximab or a second IVIG infusion abrogates fever faster and is associated with fewer adverse events in IVIG-resistant Kawasaki disease (KD) patients.

2B. Study Type

This is a Phase III, two-arm, randomized, multi-center, treatment study.

2C. Study Population

Infants and children with acute KD who are IVIG-resistant (fever T ≥38°C orally or rectally or 37.5°C axillary/ T ≥100.4°F orally or rectally or ≥ 99.5°F axillary) between 36 hours and 7 days after the end of the first IVIG infusion without other likely cause.

2D. Study Duration

4 years

2E. Primary Outcome

1) Afebrile at 24h after initiation of study treatment and remains afebrile with no recurrence of fever related to KD in the first 7 days after discharge.

2F. Secondary Outcomes

1) Afebrile at 24h following completion of infusion of study treatment (i.e., infliximab or IVIG) and remains afebrile until discharge with no recurrence of fever related to KD in first 7 days after discharge.
2) Number and severity of therapy-related adverse events according to treatment arm as adjudicated by the Adverse Events Committee.
3) Change in white blood cell count (WBC), absolute neutrophil count (ANC), hemoglobin (Hgb), platelet count, and C-reactive protein (CRP, mg/dl) concentration between baseline (pre-IVIG at diagnosis), 24 hours (± 2 hours) post-end of study treatment and 5-18 days following completion of study treatment
4) Change in erythrocyte sedimentation rate (ESR) between pre-IVIG at diagnosis and 5-18 days following completion of study treatment
5) Change in Z_{Max} score (defined as the largest internal diameter of either the right coronary or left anterior descending arteries normalized for body surface area and expressed as standard deviation units from the mean) between baseline (first echocardiogram on admission) and 5-18 days following completion of study treatment echocardiograms
6) Total number of fever days (24 hour period with a T≥38.0°C orally or rectally or ≥37.5°C axillary/ T ≥100.4°F orally or rectally or ≥ 99.5°F axillary) from enrollment
7) Duration of hospitalization
8) Number and severity of study treatment infusion reactions
9) Requirement for additional anti-inflammatory therapies after crossover failure
10) Comparison of patient/parent-reported outcomes (PROs) by study arm through the use of a parent observation tool to record discomfort, psychosocial concerns, and other experiences of treatment during the child's in-hospital stay and outpatient course.

3. Background, Significance, and Rationale

3A. Significance

Kawasaki disease (KD) is a self-limited vasculitis of unknown etiology that is the most common cause of acquired heart disease in children (Newburger et al. 2016). Intravenous immunoglobulin (IVIG) reduces the incidence of coronary artery aneurysms (CAA) from 25% to approximately 5% (Newburger et al. 1986). However, for the 10-20% of IVIG-resistant patients (defined as having T≥ 38.0°C at least 36h following the end of the IVIG infusion), there is no evidence-base to guide treatment and this group has an increased risk of coronary artery aneurysms. In our study of 362 consecutive KD patients, 9 of 60 IVIG-resistant patients (15%) versus 9 of 302 (3%) developed CAA (Tremoulet, Best et al. 2008). Recent data from Japan suggests that the rates of IVIG-resistance have risen from 7% in 2003 to 23% in 2014 with a concomitant increase in CAA (Kibata, Suzuki et al. 2016).

3B. Rationale

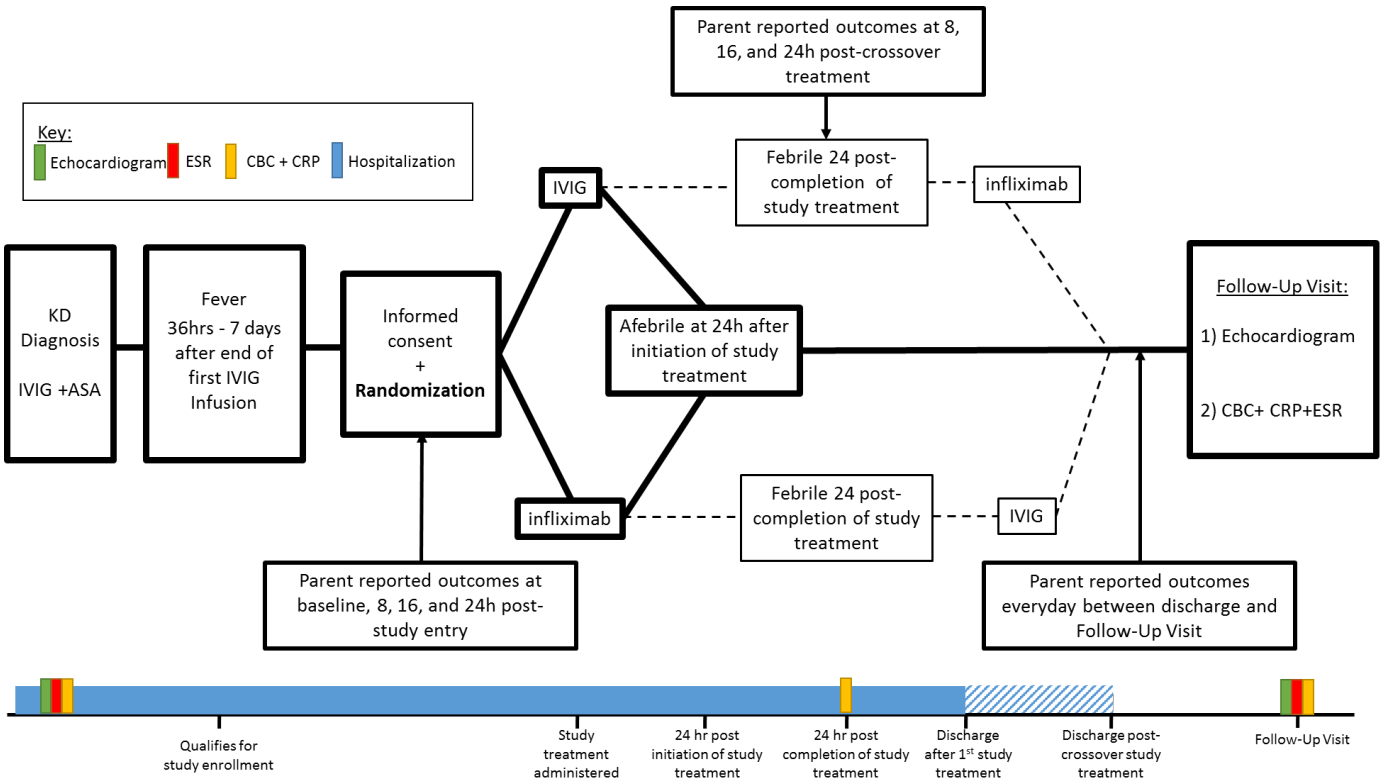
There is clinical equipoise regarding the best treatment for IVIG-resistant patients and either a second infusion of IVIG or infliximab (a monoclonal antibody that blocks the pro-inflammatory cytokine tumor necrosis factor (TNFα) is the most common second treatment (Sundel, Burns et al. 1993, Burns, Capparelli et al. 1998, Burns, Best et al. 2008, Son, Gauvreau et al. 2011). Some centers also treat with steroids (Yang, Liu et al. 2015). The American Heart Association (AHA) KD guidelines assign an Evidence level of C (Consensus opinion of experts) to re-treatment with either second IVIG or infliximab (Newburger, Takahashi et al. 2004). However, the stakes are high for this subgroup of patients as CAA due to persistent inflammation constitutes permanent damage to the arterial wall with an associated risk of myocardial infarction, arrhythmias, or sudden cardiac death (Kato, Sugimura et al. 1996, Gordon, Daniels et al. 2016).

For this trial, the dose of infliximab will be 10 mg/kg IV. A Phase III clinical trial of adjunctive primary therapy with infliximab at 5 mg/kg demonstrated that infliximab is safe and well-tolerated even in infants less than 6 months of age (Tremoulet, Jain et al. 2014). Further study of KD patients enrolled in this trial demonstrated that pre-treatment soluble TNFα receptor 1 (sTNFR1) levels are elevated in acute KD and are higher in KD patients with CAA compared to those with normal CA. At 24 hours following infusion of infliximab 5 mg/kg, KD patients with CAA had lower levels of free (unbound) infliximab compared to those with normal CA. These data suggest that 5 mg/kg of infliximab may be insufficient for many KD patients and thus a single dose of 10 mg/kg of infliximab is warranted for this study. Infliximab at a dose of 10 mg/kg has been used at RCHSD for the treatment of 88 acute KD patients with either CAA or IVIG-resistance with no adverse events related to this therapy.

4. Study design

4A. Research Design Overview

KIDCARE is a 4-year (3.75-years of enrollment), Phase III, two-arm, randomized, multi-center, treatment study to compare infliximab to a second intravenous immunoglobulin (IVIG) infusion for treatment of persistent or recrudescent fever in children with KD who fail to become afebrile after the first IVIG infusion at collaborating clinical sites (see Appendix A).

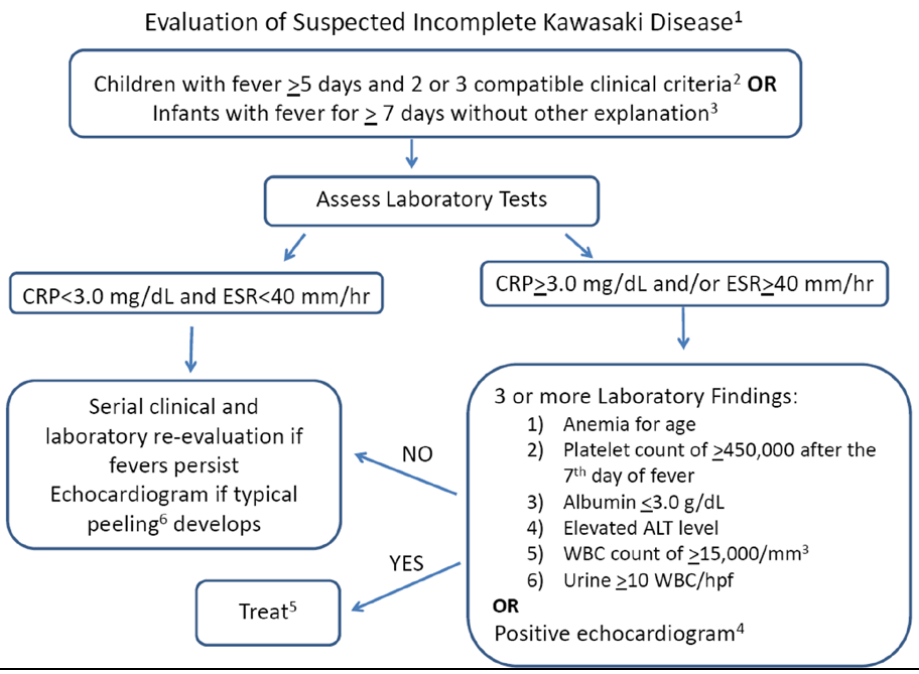


4B. Inclusion

1) 4 weeks to < 18 years of age,
2) Meets American Heart Association (AHA) criteria for KD by one of the following:
    a. Four of five clinical KD criteria (see Table 1)
    b. Meets 2017 AHA criteria for incomplete KD (see Table 2)
3) Fever by parental history for 3 to 10 days prior to initial IVIG treatment
4) Fever (T ≥38°C orally or rectally or ≥37.5°C axillary/ T ≥100.4°F orally or rectally or ≥ 99.5°F axillary) between 36 hours and 7 days after end of the first IVIG infusion <u>that is more likely than not related to KD in the opinion of the Site PI or Co-investigator</u>

Table 1. Diagnostic criteria for KD with CAA (Adapted from American Heart Association 2017 guidelines)
KD standard clinical criteria: • Bilateral conjunctival injection • Changes of the mucous membranes of the upper respiratory tract: injected pharynx, injected, fissured lips, strawberry tongue • Changes of the peripheral extremities: peripheral edema, peripheral erythema, periungual desquamation • Polymorphous rash • Cervical adenopathy >1.5 cm

Table 2. AHA Criteria for incomplete KD (McCrindle et al., Circulation, 2017)



(1) In the absence of a "gold standard" for diagnosis, this algorithm cannot be evidence based but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought any time assistance is needed. (2) Clinical findings of Kawasaki disease are listed in Table 3. Characteristics suggesting that another diagnosis should be considered include exudative conjunctivitis, exudative pharyngitis, ulcerative intraoral lesions, bullous or vesicular rash, generalized adenopathy, or splenomegaly. (3) Infants ≤6 months of age are the most likely to develop prolonged fever without other clinical criteria for Kawasaki disease; these infants are at particularly high risk of developing coronary artery abnormalities. (4) Echocardiography is considered positive for purposes of this algorithm if any of 3 conditions are met: Z-score of left anterior descending coronary artery or right coronary artery ≥2.5; coronary artery aneurysm is observed; or ≥3 other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion, or Z scores in left anterior descending coronary artery or right coronary artery of 2 to 2.5. (5) If the echocardiogram is positive, treatment should be given within 10 days of fever onset or after the tenth day of fever in the presence of clinical and laboratory signs (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) of ongoing inflammation. (6) Typical peeling begins under the nail beds of fingers and toes. ALT indicates alanine transaminase; and WBC, white blood cells

4C. Exclusion

1) Patient treated with infliximab or steroids for present illness (e.g. RAISE protocol) (NB. patients who received oral steroids as outpatients prior to KD diagnosis (e.g. for suspected allergic reaction) but who otherwise qualify for the study will not be excluded)
2) Known prior infection with tuberculosis, coccidiomycosis, or histoplasmosis.
3) Household member with active TB.
4) Use of a TNF-α blocker within the 3 months prior to enrollment
5) Have any chronic disease, except asthma, atopic dermatitis, autism or controlled seizure disorder
6) Patient has a history of hypersensitivity to infliximab or antibodies derived from murine cells

4D. Study Sites and Target Enrollment

Subjects will be enrolled at participating sites over 3.75 years and randomized to infliximab or 2nd IVIG. Target enrollment will be 112 subjects (56 subjects/arm). We anticipate an enrollment of 0-15 subjects/year per participating site.

4E. Dosing Protocols

1. Second IVIG

All subjects randomized to receive a second dose of IVIG as their first study treatment will receive **2g/kg IV over 8-12 hours.** The start and stop times, as well as the brand of IVIG administered, will be recorded on the **Study Drug Administration** form on REDCap. Premedication is not recommended but its use will be at the discretion of the site PI. If premedication is used, this drug name, dose, route, and time administration must be recorded on the **Concomitant Medication** form on REDCap.

2. Infliximab

All subjects randomized to receive infliximab will receive **10 mg/kg intravenously over a minimum of 2 hours.** The start and stop times will be recorded on the **Study Drug Administration** form on REDCap. Premedication is not recommended but its use will be at the discretion of the site PI. If premedication is used, this drug name, dose, route, and time of administration must be recorded on the Con Med CRF. The FDA does not require a PPD or Quantiferon® testing prior to single dose administration of infliximab to KD patients given that the majority are anergic during the acute illness. A CXR is no longer a requirement prior to single dose infliximab administration for treatment of KD.
N.B. Documentation of a concomitant viral infection by PCR or other methods should not be considered a contraindication to receiving infliximab.

3. Aspirin

All subjects should receive **30-50 mg/kg/day divided every 6 hours** following randomization until the time of discharge. Centers may use 80-100 mg/kg/day but are encouraged to adopt the more moderate ASA dosing of 30-50 mg/kg/day. Upon discharge or in the event of initiation of dual anti-platelet therapy in a subject with aneurysms, the dose of aspirin (ASA) will be lowered to 3-5 mg/kg/day and administered as either 40.5 mg or 81 mg aspirin once daily. ASA will be continued at least until the end of the study (follow-up visit) and discontinued thereafter at the center PI's discretion. This medication will be recorded on the **Concomitant Medication** form on REDCap. It will also be recorded on the Temperature Measurement form. You will need to record the date and time of the Aspirin given before the temperature was taken.

4F. Discharge from the Hospital

A subject who is afebrile at 24h after the completion of study drug administration may be discharged from the hospital as long as 24 hours have elapsed from the completion of the study treatment to ensure that outcome measures and laboratory studies are obtained.

4G. Temperature measurement by parents during first 7 days after discharge

Sites will receive thermometers to give to the parents at the time of discharge for at home measurement of axillary temperatures once/day for the first 7 days following discharge. The daily Twilio contact will ask the parent for the first 7 days only if their child had a fever and the answer will be recorded. The parent will be prompted each day for the first 7 days to contact their study doctor if a fever is documented ($T \geq 37.5°C$ / $T \geq 99.5°F$ axillary). Causality of any recurrent fever will be adjudicated by the site PI and will be designated as related (more likely than not) or unrelated to KD.

5. Data Collection

*****All data from hospitalization must be entered into REDCap within a week of patient discharge and all data from follow-up visit no later than one week after the visit*****

All Forms are located in Appendix C.

5A. Tracking Total Number of KD Patients at each Site

Each site will be responsible for maintaining a log of the total number of KD patients seen at their site during the study period. For each site, this log will need to be maintained from the time the site was opened for enrollment in KIDCARE until the closure of enrollment. It will include the date of KD onset for each patient seen at your site. This information will **NOT** be entered into the REDCap database but will be requested by the Program Manager at Coordinating Center, Samantha Roberts (sroberts@ucsd.edu), via email every month.

5B. Obtaining a REDCap account

Each approved site's research team needs to get access to the KIDCARE REDCap database. Once you have been IRB approved, Samantha will set up a call with each member of your team to start the process of access. Below are the steps that need to be taken:

University of California San Diego (UCSD) Active Directory (AD) Account:

Samantha will need to set up a call with each individual member of the research team. To get an AD account with UCSD, each member will have to give Samantha the following information: the last 4 of their Social Security Number, month of birth, and day of birth. This information is submitted securely to UCSD. Each member will then receive an email from UC Health Service Management that will include their AD account username and their temporary password. All passwords much be changed immediately.

How to change your UCSD AD account password

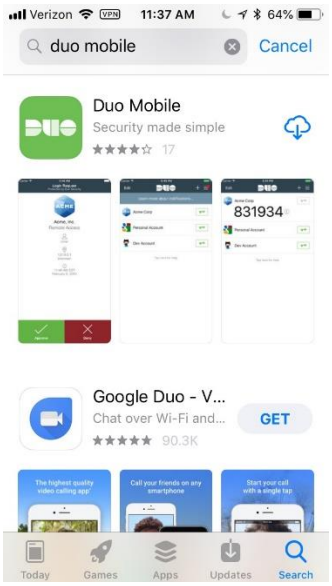
1. Go to -> https://password.ucsd.edu/
2. Choose "I know my current AD password and would like to change it"
3. Your password needs to be:
    a. At least 7 characters long
    b. Have characters from at least 3 of the following 4 categories: uppercase, lowercase, numbers, and symbols
    c. Cannot contain any part of your username
    d. Cannot resemble any single work or name

Two-Step Authorization with DUO:

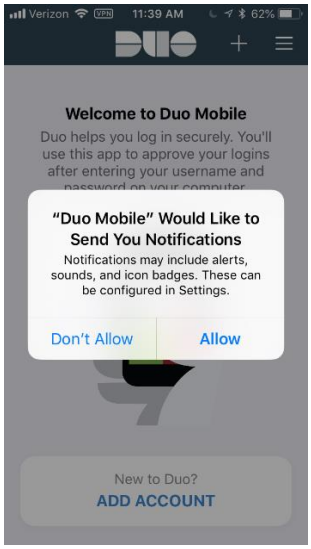
Access to the KIDCARE REDCap database requires two-step authorization using DUO. It is recommended that the DUO App is downloaded onto the user's phone. You do not have to use DUO mobile app for two-step authorization, it is just recommended.

Install DUO App on a Mobile Phone:
Before starting, note that for Apple you'll need to be running iOS 10.0 or greater, and for Android, you'll need to be on Android 6.0 or greater.

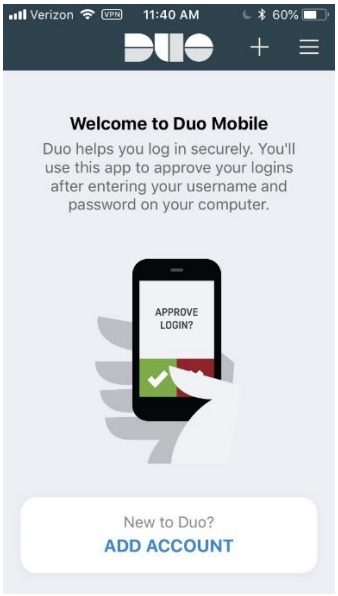
1. Find the Duo Mobile app. Note that other apps may appear, so be sure you're installing Duo Mobile with the green logo.



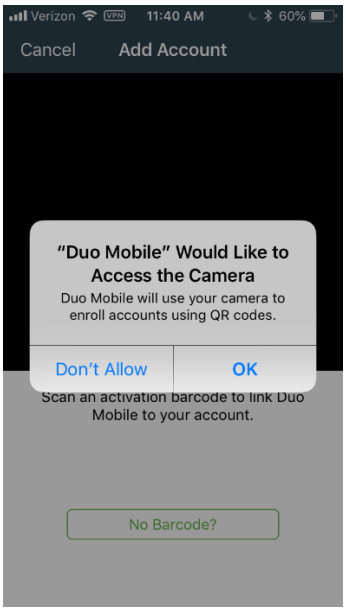
2. When you open the app, you'll probably want to allow Duo to send notifications. This will lead to the most seamless experience using two-step login. Otherwise, each time you log in you'll have to open the app to approve.



3. Get ready to add your account in the Duo app. You can either tap "ADD ACCOUNT" or tap the plus symbol in the upper right corner.

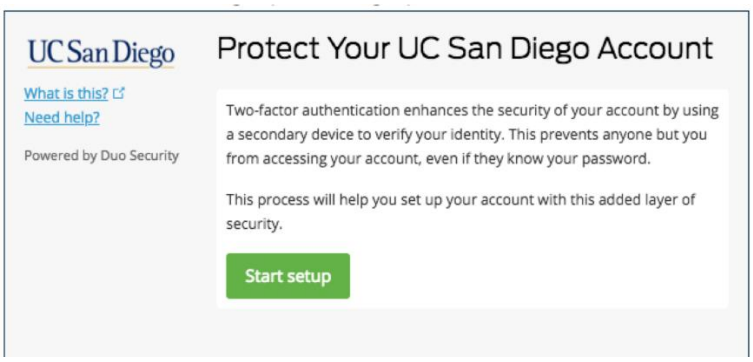


4. The Duo app will need to access your camera to complete the registration process (see below). Allow the access, then put the phone down momentarily to continue to the device registration interface.

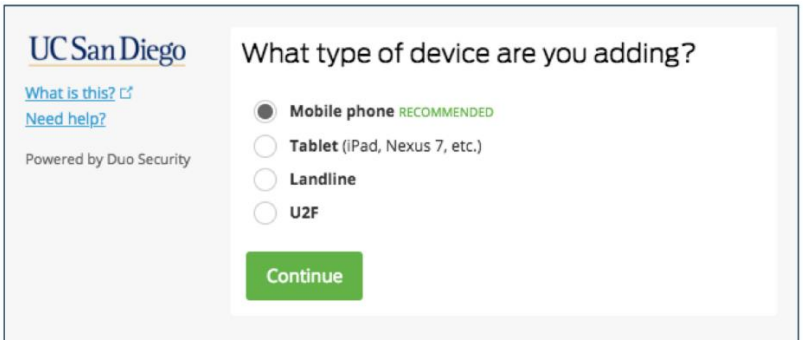


Register a Mobile Phone for Two-Step Login

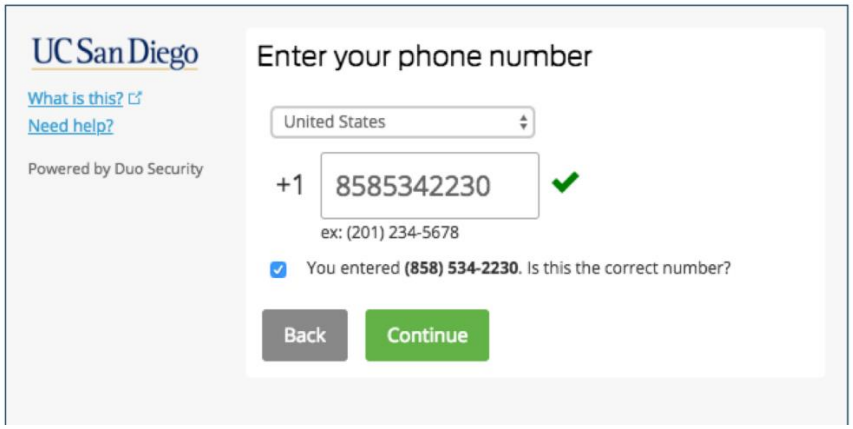
1. You will need to complete the registration page: https://healthapps.ucsd.edu/duo/duo-app.asp using your AD username login and password. When you see the screen below, click "Start setup" to get going.



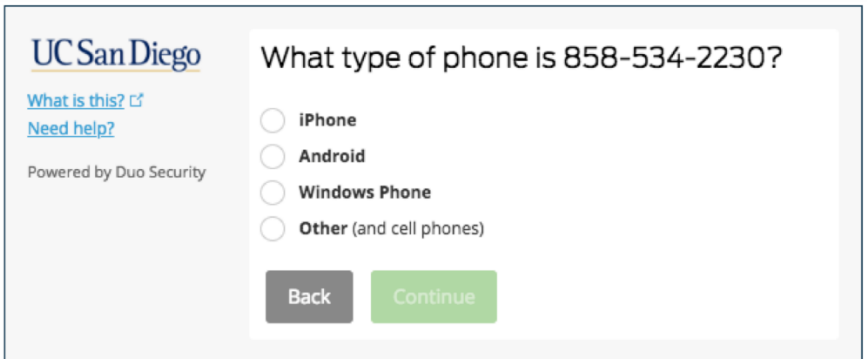
2. Choose the type of device to add. Using a mobile phone as your primary device is highly recommend. Select the radio button and click "Continue."



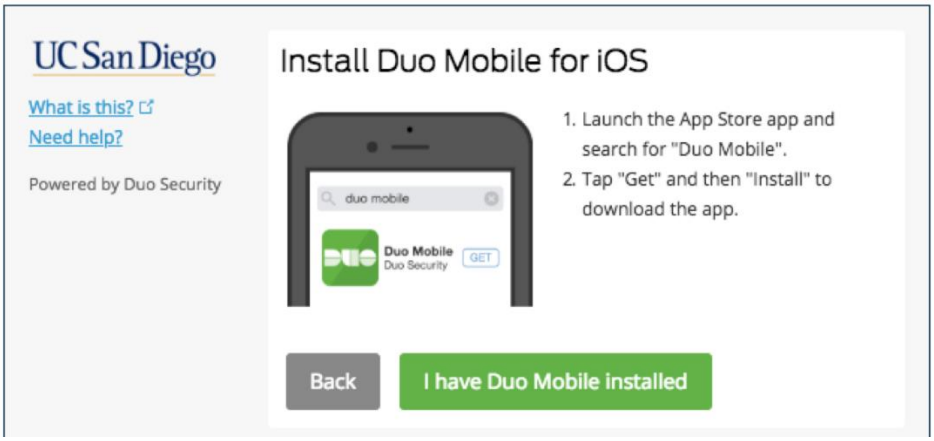
3. Enter the mobile phone's number, click the check box to confirm, and click "Continue."

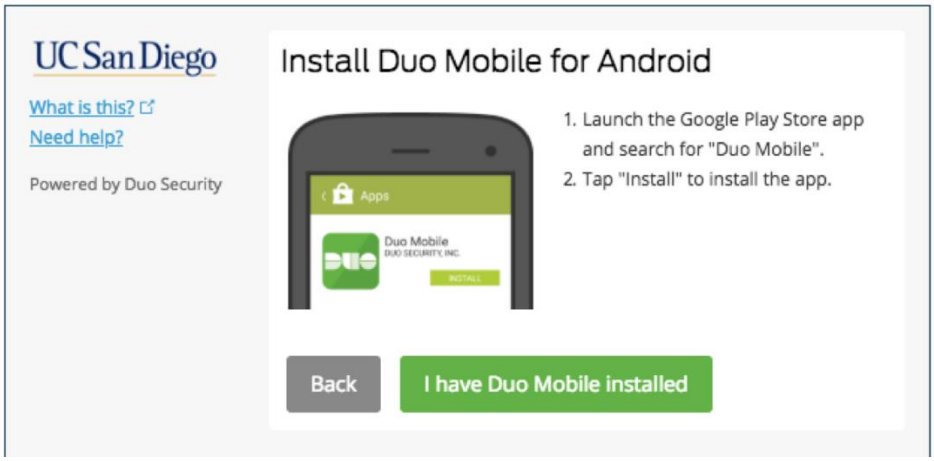


4. Choose the type of device you're registering, and click "Continue."

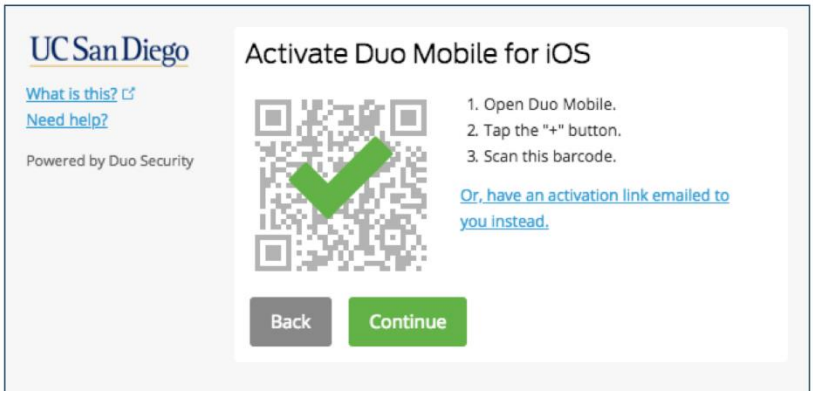


5. You'll be prompted to install the Duo mobile app (if you haven't already). See instructions above. Once the app is installed, click "I have Duo Mobile installed."

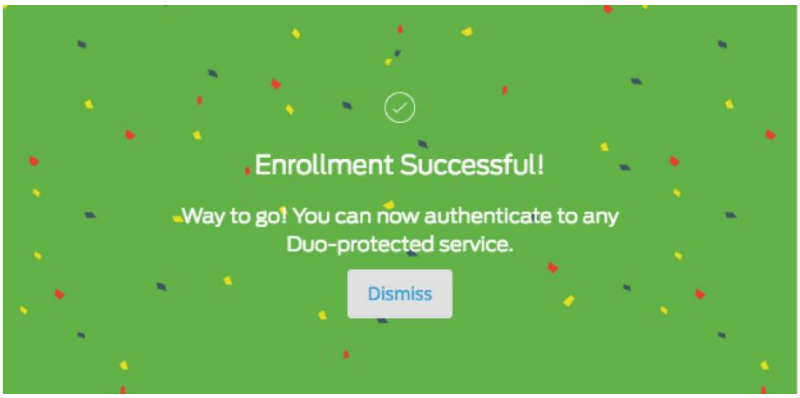




6. Follow the on-screen instructions to open your Duo app and scan the barcode that appears on screen. You may need to grant Duo permission to access your camera.
   This is the key step that ties your identity to your device!



7. Congrats! You've enrolled your device.



Clinical Translations Research Institute (CTRI) forms:

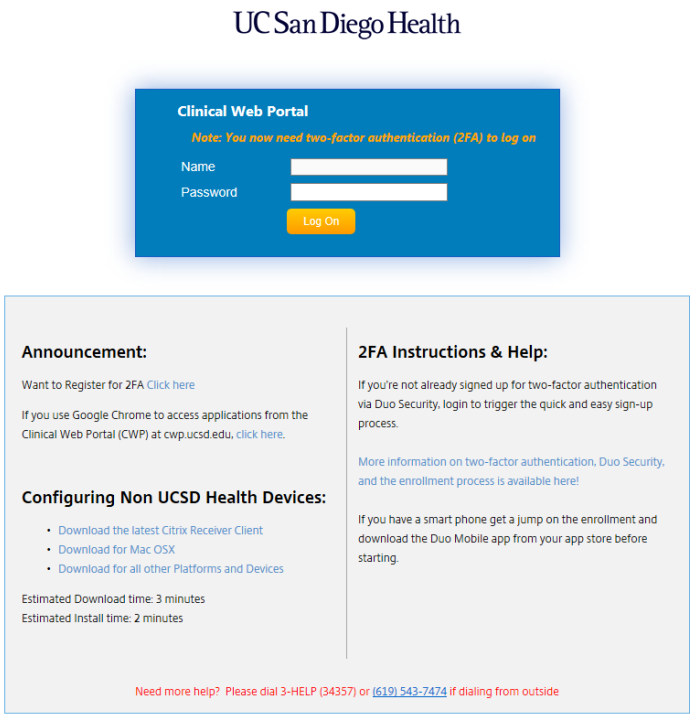
Once the research team members receive their AD account username, Samantha will also receive this username. She will submit it to the CTRI at UCSD, who will then send a REDCap User Access Request form that will need to be completed and electronically signed. The following information is requested on the form:

a) First, Middle, Last Name, and Title
b) Telephone # (include country code if outside the U.S.)
c) FAX # (include country code if outside the U.S.)
d) Department
e) Division (Hospital/Center Affiliation)

5C. REDCap Access Via UCSD Clinical Web Portal (CWP)

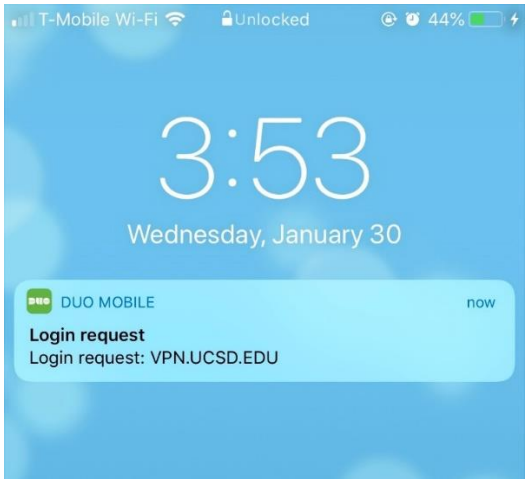
Once research team members have an AD account and have set up two step authorization with DUO, they can then access the REDCap.

1. Go to https://cwp.ucsd.edu

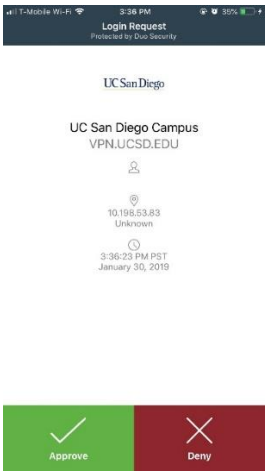


2. You will log in using your AD account username and password.

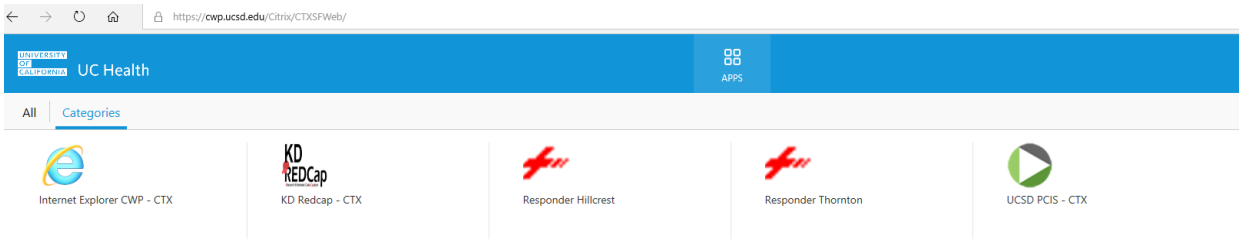
3. You should receive a login request on your phone from the Duo Mobile App.



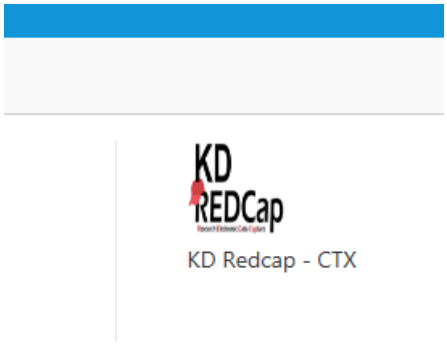
4. Open the Duo Mobile App on your phone and approve the login request.



5. Once you have approved the login request, your browser will be directed to the Clinical Web Portal (CWP):



6. Select the KD REDCap icon



7. The REDCap database will be opened up in another web page. You will use the same username and password for this REDCap as you used for the iDASH REDCap.

5D. Overview of Forms

Form Name	Study Event
Eligibility Evaluation	Enrollment*
Trail Arms From	Enrollment*
Demographics	Enrollment*
Study Drug Administration	Enrollment*
Enrollment Temperature Measurement	Enrollment
Temperature Measurement	24 hours post initiation of study tx, 24 hours post completion of study tx
Primary Temperature Outcome	24 hours post initiation of study tx
Secondary Treatment Outcome	24 hours post completion of study tx
Laboratory Results	Enrollment, 24 hours post completion of study tx, Follow-Up Visit
Center Echocardiogram	Enrollment*, Follow-Up, Other Data
Baseline Observation tool	24 h post completion of study tx
8-hour Observation tool	24 hours post completion of study tx
16-hour Observation Tool	24 hours post completion of study tx
24-hour Observation Tool	24 hours post completion of study tx
Crossover Temperature Measurement	Crossover of study tx
Crossover Study Drug Administration	Crossover of study tx
Crossover Laboratory Results	Crossover of study tx
Protocol Deviation Reporting Form	During Study (as applicable)
Adverse Event Reporting Form	During Study (as applicable)
Study Completion Form	Follow-Up Visit
Fever Days and Duration of Hospitalization	Other Data
Concomitant Medications	Other Data

* This study event name is associated with the REDCap event name and does not indicate when this data will be collected. Non-eligible patients are not enrolled into the study and the information gathered about why they did not enroll into the study is de-identified.

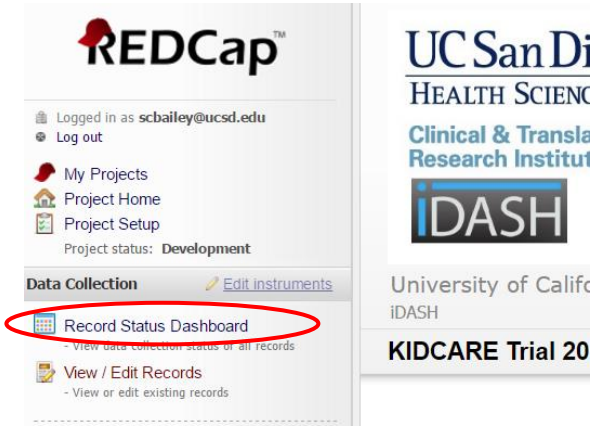
5E. Eligibility Evaluation Form and Informed Consent

Study participation will be offered without regard to age, sex, or ethnic background. Child assent will be obtained for all study patients ≥ 7-12 yrs. and adolescent assent will be obtained for patients 13-17 yrs. Recruitment of human subjects with written Informed Consent will be obtained by study personnel in the hospital inpatient units. There are occasions when no study personnel are available in the hospital, in which case one of the co-investigators is contacted by telephone. The Parent (child/ adolescent if applicable) is provided with the written consent form and HIPAA authorization by hospital personnel and the co-investigator reviews the written informed consent document(s) over the phone and answers any questions. The parent (child/adolescent if applicable) then signs and dates the consent document (s) and the witness signature is obtained at a later time from the co-investigator who obtained the informed consent. The Parent (child/ adolescent if applicable) will be provided with the signed written consent form and HIPAA authorization.

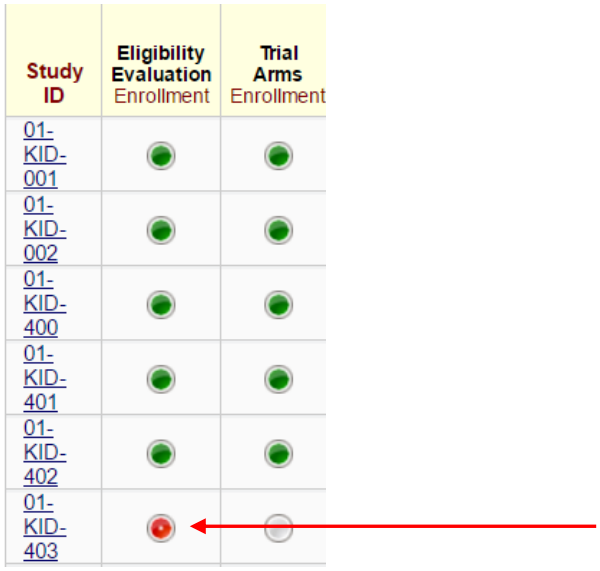
Screen Fails: All subjects who meet the AHA criteria for complete or incomplete KD and who had a fever (T ≥38°C orally or rectally or 37.5°C axillary/ T ≥100.4°F orally or rectally or ≥ 99.5°F axillary) between 36 hours and 7 days after the end of the first IVIG infusion without other likely cause will be included in the REDCap database. Some KD subjects who have a fever between 36 hours and 7 days after the end of the first IVIG infusion will not be eligible for the study because the subject did not meet entry criteria or the family refused to participate in this study. These subjects who have been screened for study participation, will have their screening information entered into the eligibility evaluation form REDCap without consent being obtained. This de-identified information is collected to understand why patients either were not eligible or refused participation for the study. All the information entered into the REDCap database is de-identified.

How to complete the Eligibility Evaluation Form in REDCap:

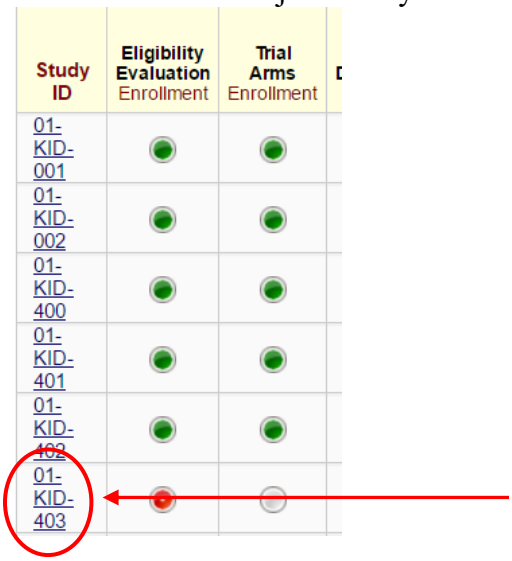
1) Go to https://cwp.ucsd.edu
2) You will log in using your AD account username and password
3) You should receive a login request on your phone from the Duo Mobile App
4) Open the Duo Mobile App on your phone and approve the login request
5) Once you have approved the login request, your browser will be directed to the Clinical Web Portal (CWP)
6) Select the KD REDCap icon
7) The REDCap database will be opened up in another web page.
8) Under My Projects, Choose **KIDCARE Trial 2017**
9) On the left side of the REDCap portal, you will see a section labeled ***Data Collection***
10) Click on the ***Record Status Dashboard*** under this section.



11) Choose the next subject that needs to be completed. To do this you will choose the subject ID that has the first ***RED*** circle.



12) Then click on that subjects study ID



13) You will then be taken to this subjects REDCap study dashboard. This lists the time points and the forms that can be completed at each time point. You will click on the circle under the ***Enrollment*** column and next to the ***Eligibly Evaluation*** form that you need to complete

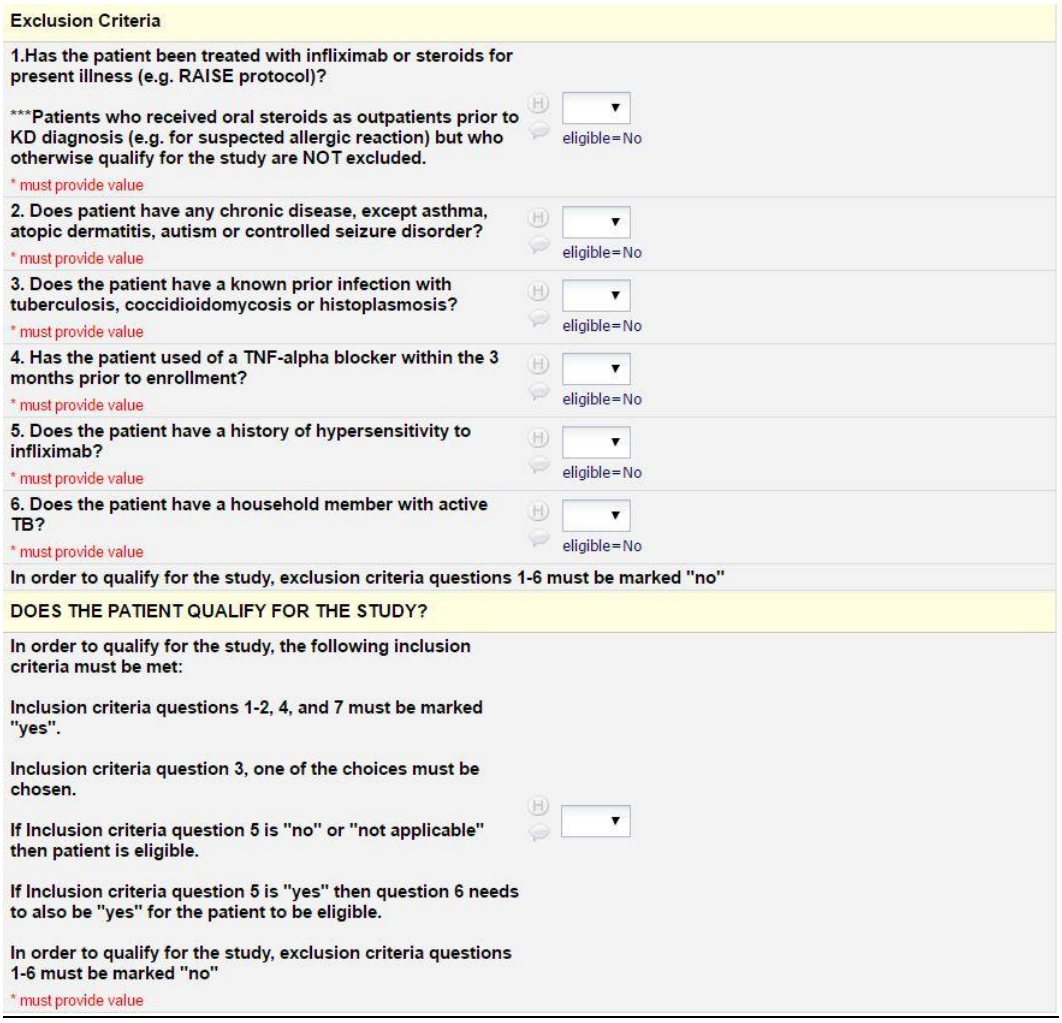
Study ID **01-KID-403**

Data Collection Instrument	Enrollment (1)	24h post initiation of tx (2)	24h post completion of tx (3)	Crossover of study tx (4)
Eligibility Evaluation	●			
Trial Arms	○			
Demographics	○			
Study Drug Administration	○			

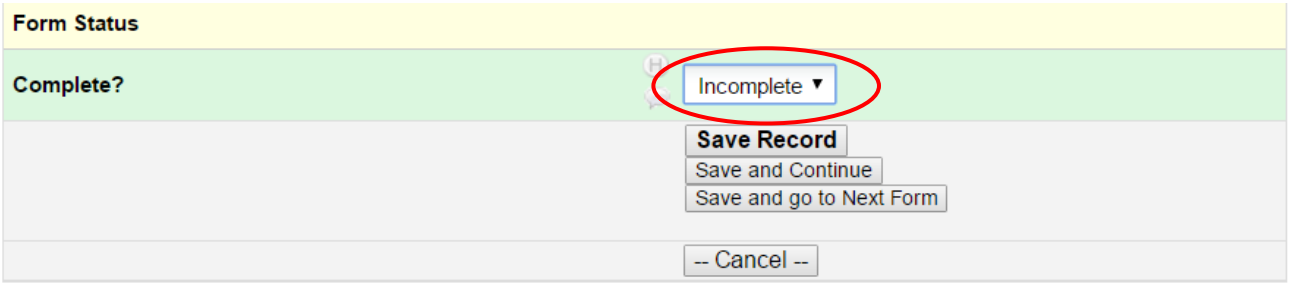
14) When you click on the circle you will be taken to the ***Eligibly Evaluation*** form

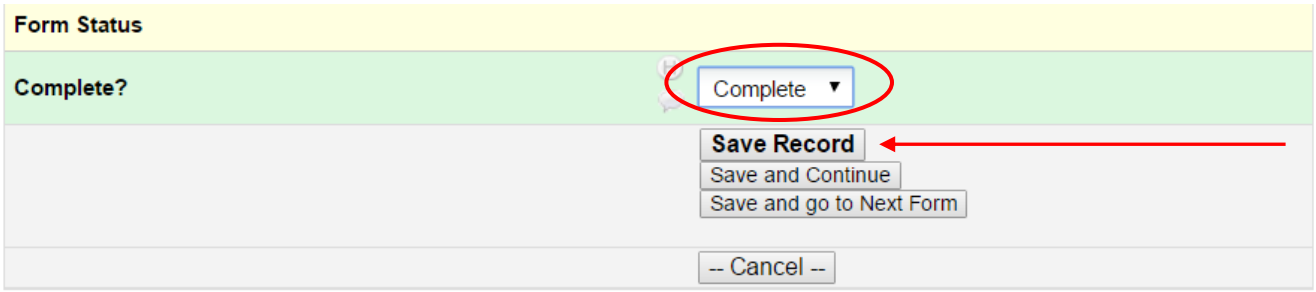
Event Name: **Enrollment**

Study ID	05-KID-900
Inclusion Criteria	
1. Is the patient 4 weeks to < 18 years old? * must provide value	▾ eligible=Yes
2. Did patient have fever by parental history for 3 to 10 days prior to initial IVIG treatment? * must provide value	▾ eligible=Yes
3. Does the patient meet AHA criteria for KD by one of the following? Please check one (See Table 1 below for clinical criteria and Table 2 for laboratory criteria) * must provide value	○ Four of five clinical KD criteria (see Table 1) ○ At least 2 clinical criteria with left anterior descending artery or right coronary artery z-score ? 2.5 ○ At least 2 clinical criteria with CRP ? 3 mg/dL or ESR ? 40 mm/hr and at least 3 supplemental laboratory criteria (see Table 2) reset
4. Does patient have fever (T ? 38°C orally or rectally or 37.5°C axillary) between 36 hours and 7 days after end of the first IVIG infusion without other likely cause? * must provide value	▾ eligible=Yes
5. Is patient sexually active? * must provide value	▾
6. If patient is sexually active is he/she willing to use contraception? * must provide value	○ No ○ Yes ○ Not applicable eligible=Yes reset
7. Is patient, or legal representative, capable and willing to give written informed consent? * must provide value	▾ eligible=Yes
In order to qualify for the study, the following inclusion criteria must be met: **Inclusion criteria questions 1-2, 4, and 7 must be marked "yes".** **Inclusion criteria question 3, one of the choices must be chosen.** **If Inclusion criteria question 5 is "no" or "not applicable" then patient is eligible.** **If Inclusion criteria question 5 is "yes" then question 6 needs to also be "yes" for the patient to be eligible.**	

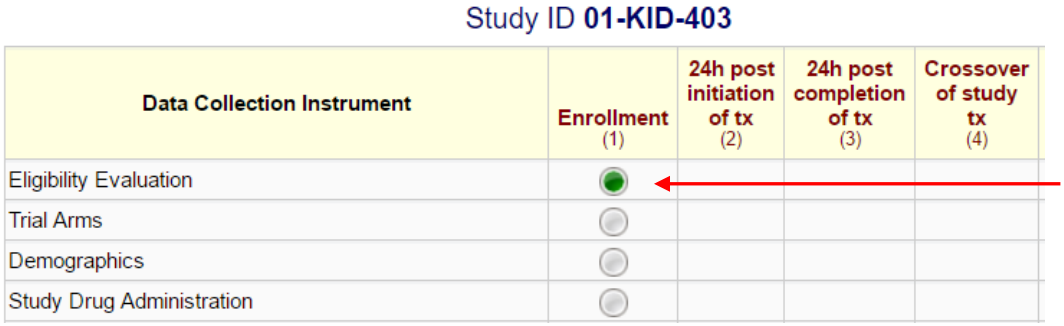


15) Answer all the questions within the ***Eligibility Evaluation*** form. **Make sure you answer the last question in this form correctly, which is: *Does the patient qualify for the study?* This question will determine if you will be able to randomize your subject**
16) Once you complete this form, change the status of the form ***Incomplete to Complete*** and then click ***Save Record***.





17) From here you will be directed back to the subjects study dashboard. The circle next to the ***Eligibly Evaluation*** form should be ***Green***.



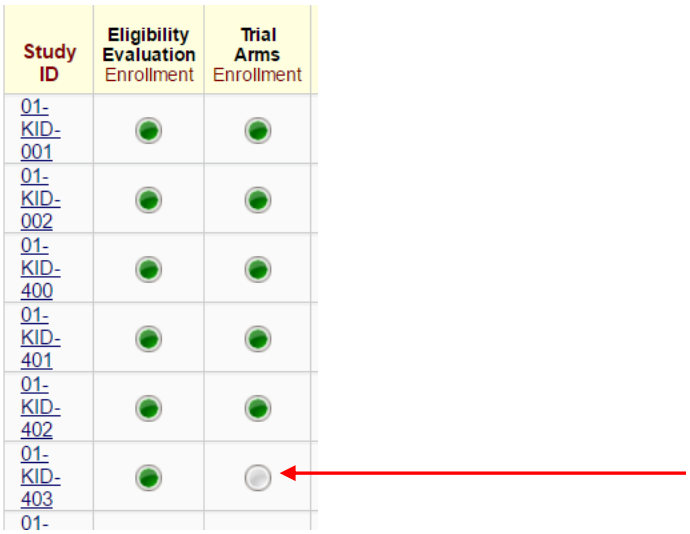
5F. Trial Arms Form-Randomization

Once eligibility and consent are confirmed and the eligibility evaluation form is completed, subjects will be assigned to a treatment arm (Infliximab or IVIG) by the REDCap online randomization module according to a pre-specified randomization scheme stratified by center and then sex (male/female) and age (dichotomous variable >12 months or ≤ 12 months) via a randomly permuted block design. The randomization sequence has been generated by the Biostatistics team using the software R (version 3.3.2).

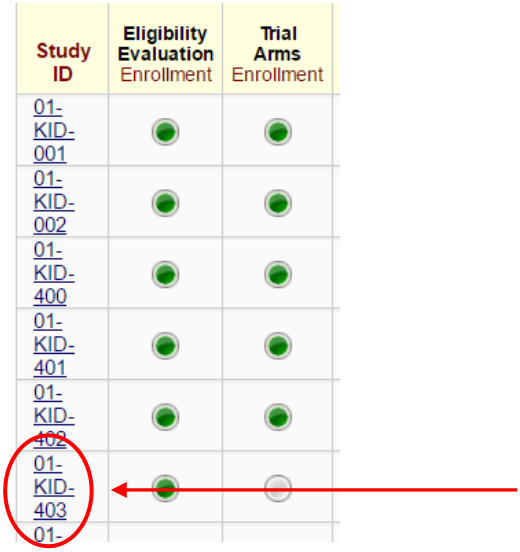
How to randomize your subject:

1) Go to https://cwp.ucsd.edu
2) You will log in using your AD account username and password
3) You should receive a login request on your phone from the Duo Mobile App
4) Open the Duo Mobile App on your phone and approve the login request
5) Once you have approved the login request, your browser will be directed to the Clinical Web Portal (CWP)
6) Select the KD REDCap icon
7) The REDCap database will be opened up in another web page. Under My Projects, Choose **KIDCARE Trial 2017**
8) On the left side of the REDCap portal, you will see a section labeled ***Data Collection***
9) Click on the ***Record Status Dashboard*** under this section.

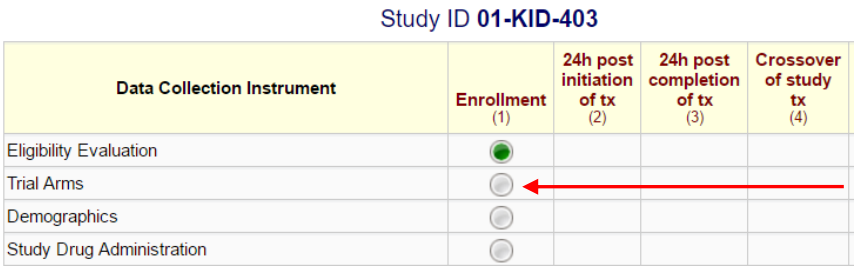
10) Choose the subject that needs to be randomized. To do this you will choose the subject ID that has the circle under the first from as ***GREEN*** but the circle under the ***Trial Arms*** form as ***UNFILLED***.



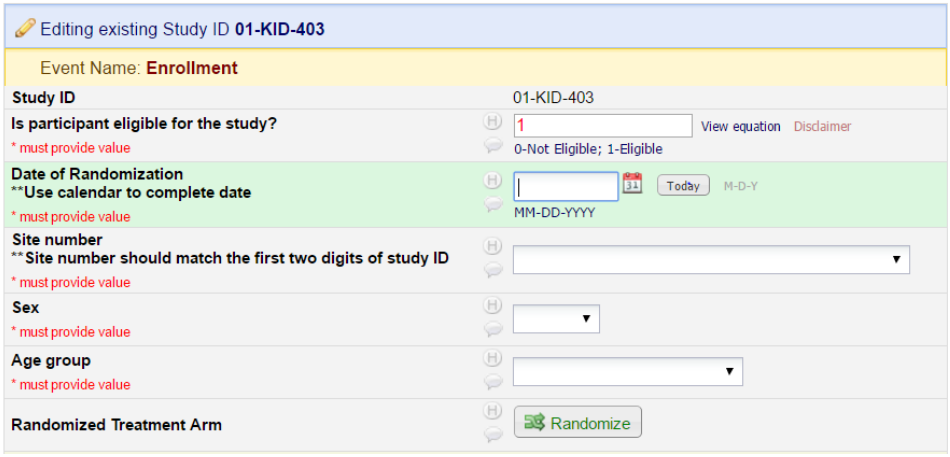
11) Then click on that subjects study ID



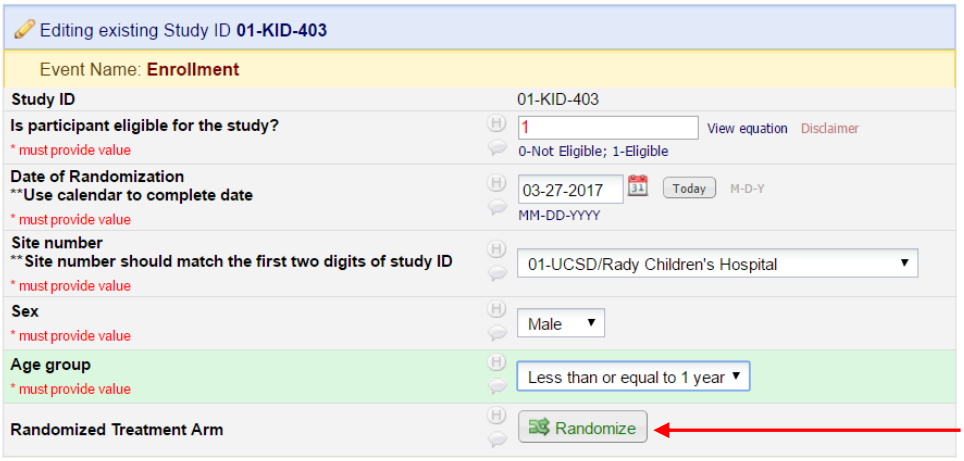
12) You will then be taken to this subjects REDCap study dashboard. This lists the time points and the forms that can be completed at each time point. You will click on the circle under the ***Enrollment*** column and next to the ***Trial Arms*** form you need to complete



13) Complete the ***Trial Arms*** form with the date, your site, sex of subject, and age category of subject (Less than or equal to 12 months or Greater than 12 months)

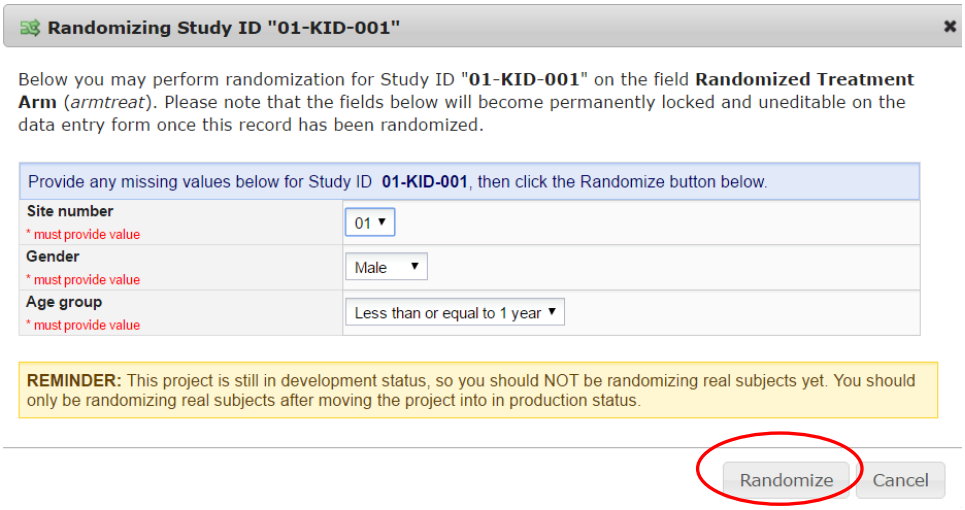


14) Click the ***Randomize*** button next to the ***Randomized Treatment Arm*** field

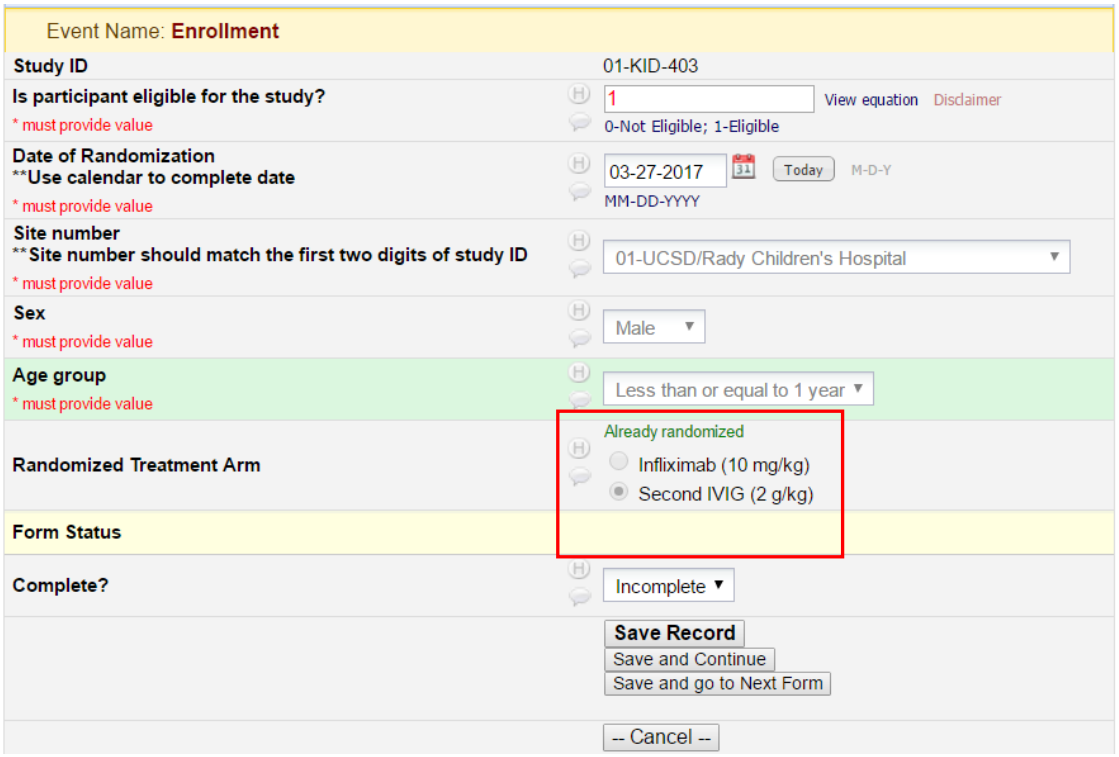


15) A window will pop up **Please check the data you entered. Make sure your site number is correct (the site number you picked should match the first two numbers of your subject ID).**

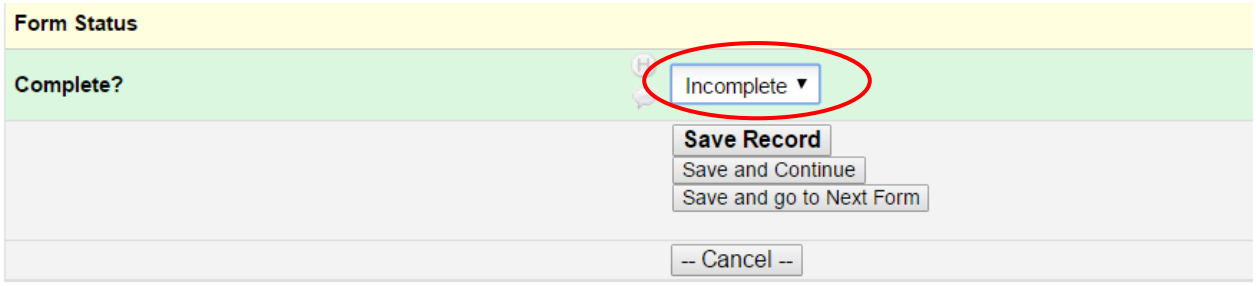
16) Once you check that the data you entered is correct, click the ***Randomize*** button.

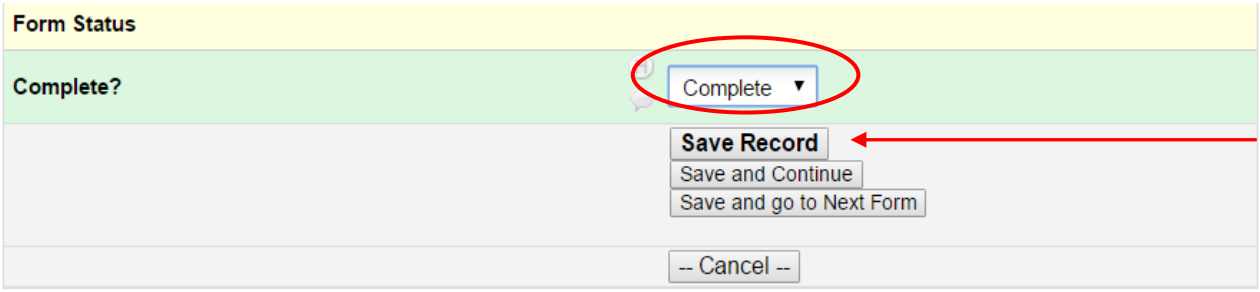


17) Your subject has been randomized to either infliximab or IVIG. This will show up ***Randomized Treatment Arm*** field

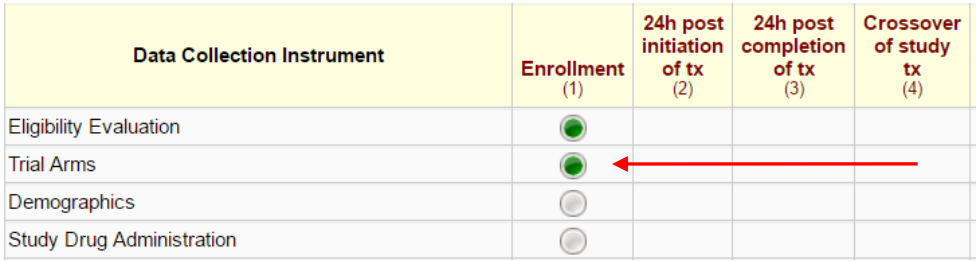


18) Once you have completed this form, change the status of the form ***Incomplete to Complete*** and then click ***Save Record***





19) From here you will be directed back to the subjects study dashboard. The circle next to the ***Trial Arms*** form should be ***GREEN***



Data Collection Instrument	Enrollment (1)	24h post initiation of tx (2)	24h post completion of tx (3)	Crossover of study tx (4)
Eligibility Evaluation				
Trial Arms				
Demographics				
Study Drug Administration				

5G. Demographics Form

Data collected in the form include:

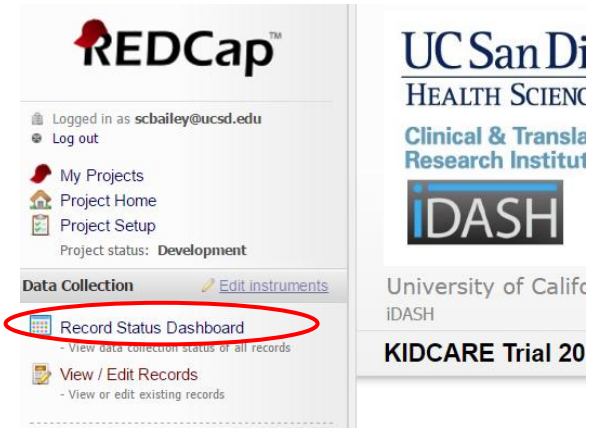
a) Patient's age in years at KD onset rounded to nearest 0.1 years, sex, self-reported ethnicity of each biologic parent

b) Illness day at 1st IVIG treatment (first day of fever = Illness Day 1) and illness day at randomization (each day is the 24h period from 12:01 am to 12:00 pm). Example: For a patient who is admitted at 6 pm on Illness Day 5 but starts treatment at 1 is that night, the Illness Day at 1st IVIG treatment is Illness Day 6.

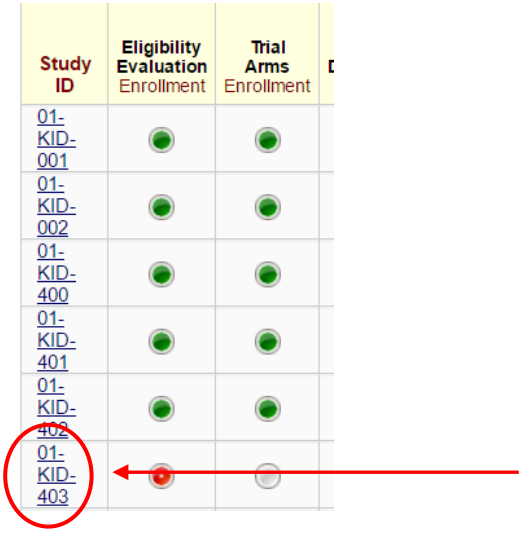
How to complete the Demographics Form in REDCap:

1) Go to https://cwp.ucsd.edu
2) You will log in using your AD account username and password
3) You should receive a login request on your phone from the Duo Mobile App
4) Open the Duo Mobile App on your phone and approve the login request

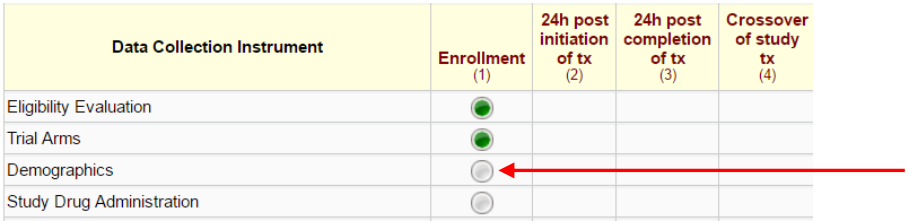
5) Once you have approved the login request, your browser will be directed to the Clinical Web Portal (CWP)
6) Select the KD REDCap icon
7) The REDCap database will be opened up in another web page. Under My Projects, Choose **KIDCARE Trial 2017**
8) On the left side of the REDCap portal, you will see a section labeled ***Data Collection***
9) Click on the ***Record Status Dashboard*** under this section.



10) Click the subject ID that needs to be completed.

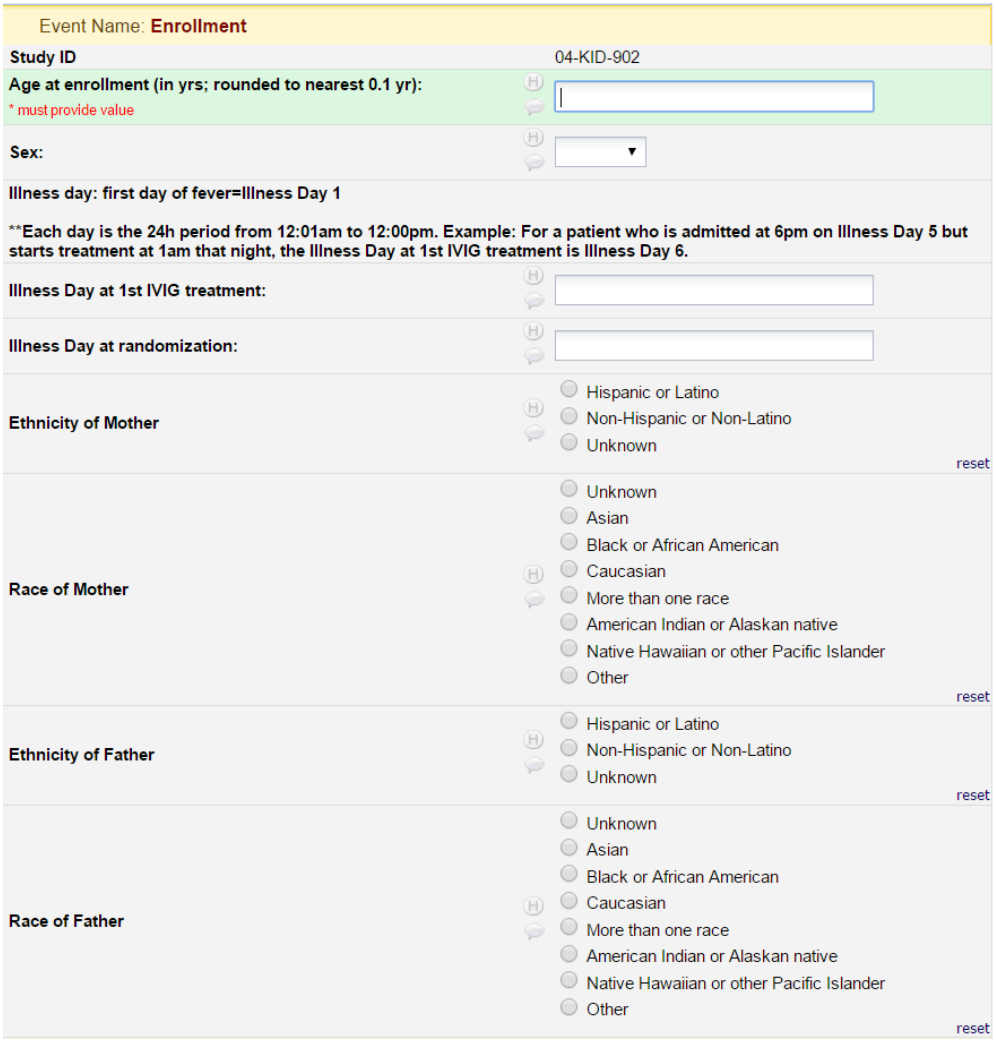


11) You will then be taken to this subject's REDCap study dashboard. This lists the time points and the forms that can be completed at each time point. You will click on the circle under the ***Enrollment*** column and next to the ***Demographics*** form you need to complete



Data Collection Instrument	Enrollment (1)	24h post initiation of tx (2)	24h post completion of tx (3)	Crossover of study tx (4)
Eligibility Evaluation				
Trial Arms				
Demographics				
Study Drug Administration				

12) When you click on the circle you will be taken to the ***Demographics*** form

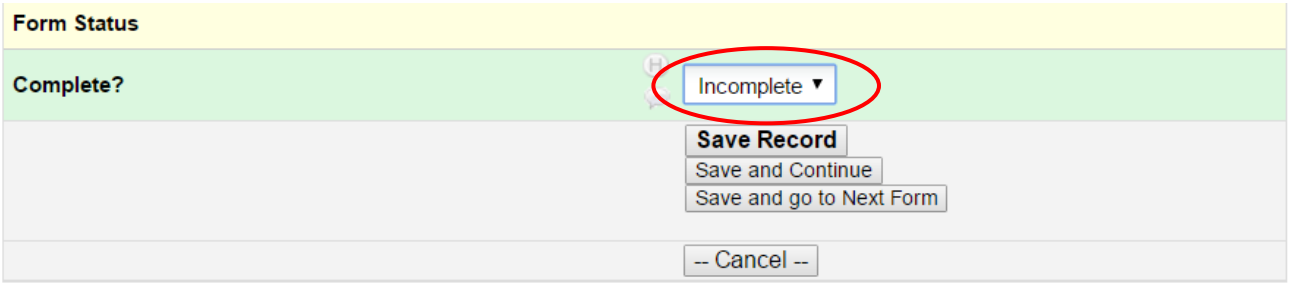


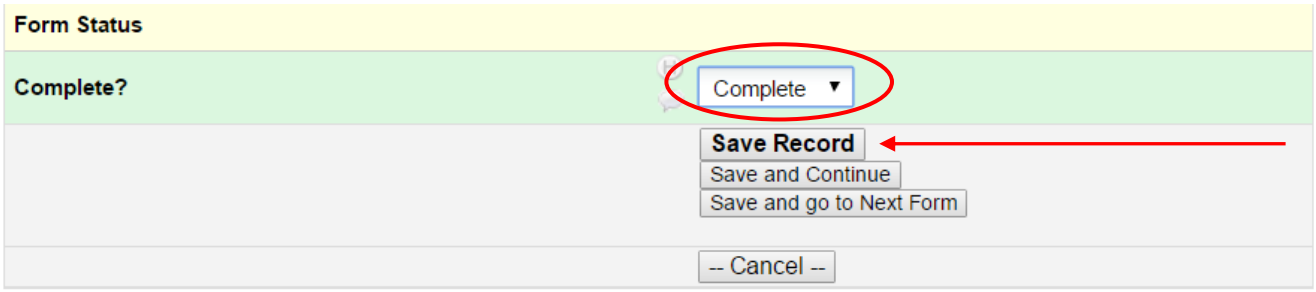
Event Name: **Enrollment**

Study ID	04-KID-902
Age at enrollment (in yrs; rounded to nearest 0.1 yr): * must provide value	
Sex:	
Illness day: first day of fever=Illness Day 1 ****Each day is the 24h period from 12:01am to 12:00pm. Example: For a patient who is admitted at 6pm on Illness Day 5 but starts treatment at 1am that night, the Illness Day at 1st IVIG treatment is Illness Day 6.**	
Illness Day at 1st IVIG treatment:	
Illness Day at randomization:	
Ethnicity of Mother	Hispanic or Latino Non-Hispanic or Non-Latino Unknown reset
Race of Mother	Unknown Asian Black or African American Caucasian More than one race American Indian or Alaskan native Native Hawaiian or other Pacific Islander Other reset
Ethnicity of Father	Hispanic or Latino Non-Hispanic or Non-Latino Unknown reset
Race of Father	Unknown Asian Black or African American Caucasian More than one race American Indian or Alaskan native Native Hawaiian or other Pacific Islander Other reset

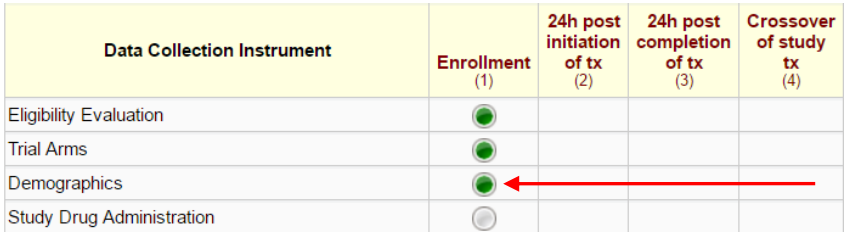
13) Answer all the questions within the ***Demographics*** form

14) Once you complete this form, change the status of the form ***Incomplete to Complete*** and then click ***Save Record***





15) From here you will be directed back to the subjects study dashboard. The circle next to the ***Demographics*** form should be ***GREEN***

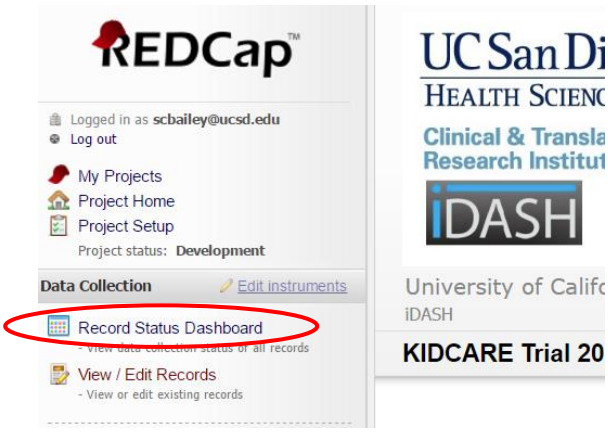


5H. Study Drug Administration Form

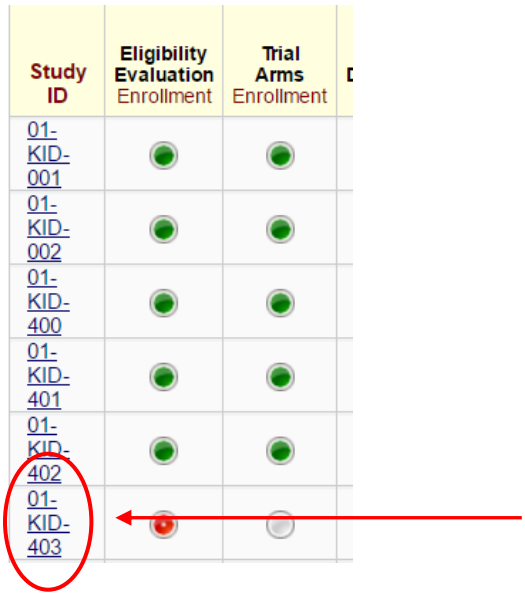
Name, brand, dose, start time/date and stop time/date of 1st study treatment and 2nd study treatment if subject crossed over to other study treatment.

How to complete the Study Drug Administration Form in REDCap:

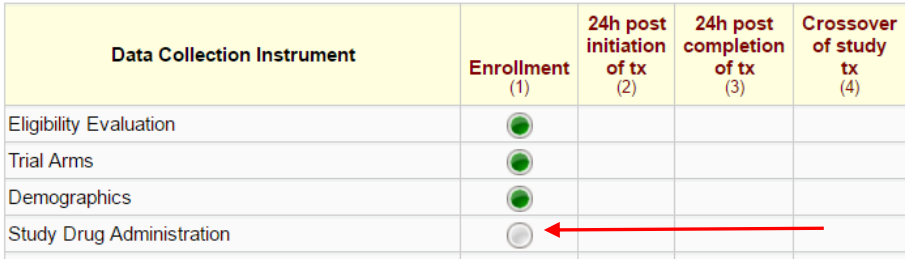
1) Go to https://cwp.ucsd.edu
2) You will log in using your AD account username and password
3) You should receive a login request on your phone from the Duo Mobile App
4) Open the Duo Mobile App on your phone and approve the login request
5) Once you have approved the login request, your browser will be directed to the Clinical Web Portal (CWP)
6) Select the KD REDCap icon
7) The REDCap database will be opened up in another web page. Under My Projects, Choose **KIDCARE Trial 2017**
8) On the left side of the REDCap portal,you will see a section labeled ***Data Collection***
9) Click on the ***Record Status Dashboard*** under this section



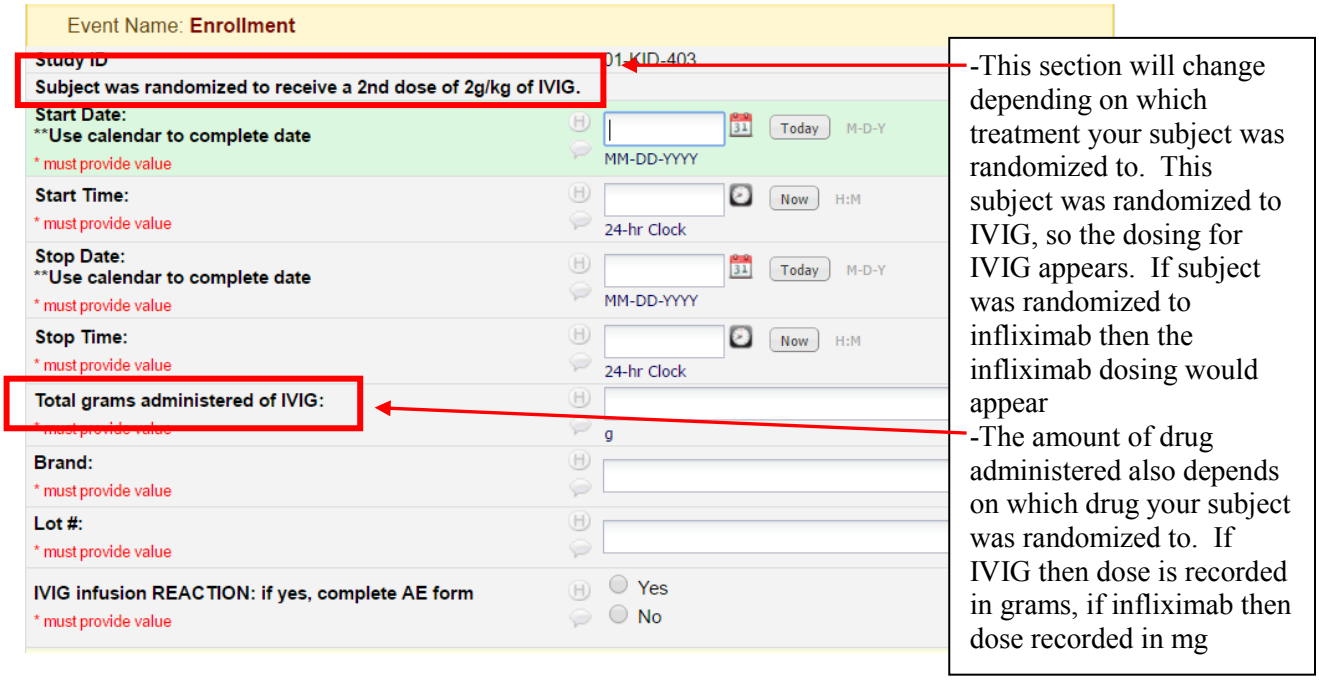
10) Click the subject ID that needs to be completed.



11) You will then be taken to this subjects REDCap study dashboard. This lists the time points and the forms that can be completed at each time point. You will click on the circle under the column ***Enrollment*** and next to the ***Study Drug Administration*** form you need to complete.



12) When you click on the circle you will be taken to the ***Study Drug Administration*** form

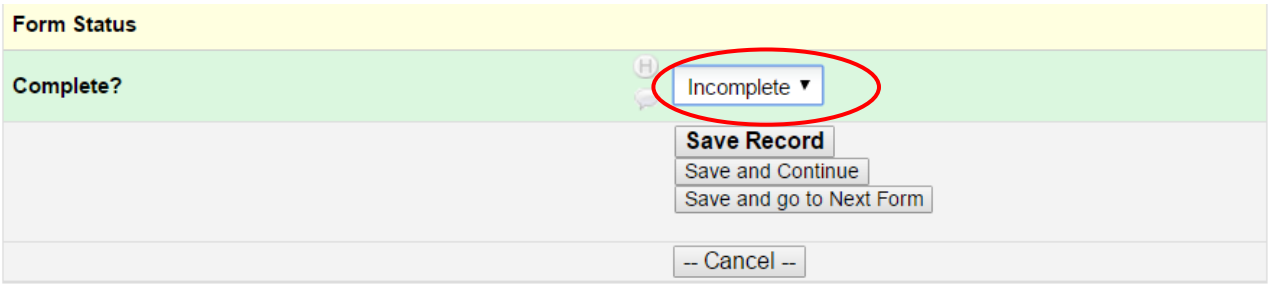


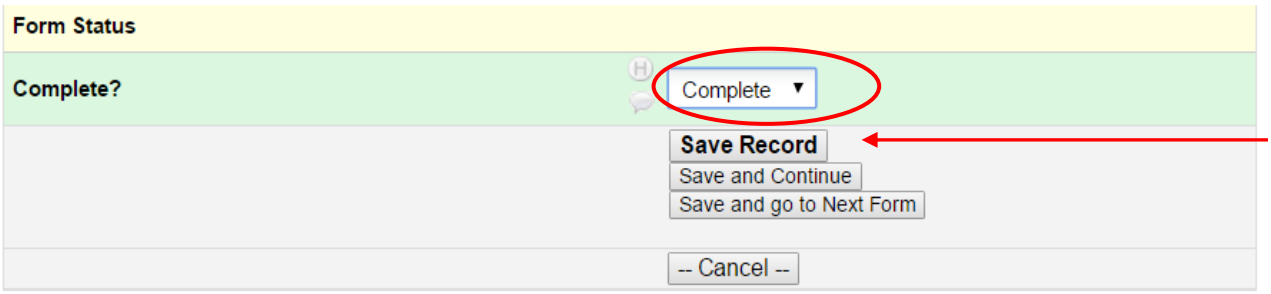
-This section will change depending on which treatment your subject was randomized to. This subject was randomized to IVIG, so the dosing for IVIG appears. If subject was randomized to infliximab then the infliximab dosing would appear

-The amount of drug administered also depends on which drug your subject was randomized to. If IVIG then dose is recorded in grams, if infliximab then dose recorded in mg

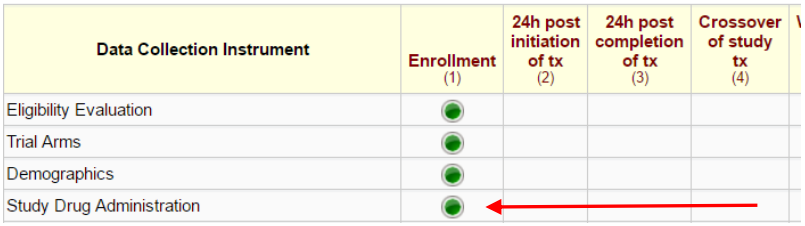
13) Answer all the questions within the ***Study Drug Administration*** Form

14) Once you complete the form, change the status of the form ***Incomplete to Complete*** and then click ***Save Record***





15) From here you will be directed back to the subjects study dashboard. The circle next to the ***Study Drug Administration*** form should be ***GREEN***



Data Collection Instrument	Enrollment (1)	24h post initiation of tx (2)	24h post completion of tx (3)	Crossover of study tx (4)
Eligibility Evaluation				
Trial Arms				
Demographics				
Study Drug Administration				

****If the subject crosses over to the other study treatment, repeat steps 1-10 for the ***Crossover Study Administration*** form located under the ***Crossover of study tx*** column.

5I. Enrollment Temperature Measurement/Temperature Measurement Form

The preferred routes for measuring the temperature are oral and rectal. A fever will be considered T ≥38°C/ T ≥100.4°F rectally or orally. Sites that are unable to obtain core temperatures via these routes can use axillary temperatures as an alternative with T ≥ 37.5°C/ T ≥ 99.5°F axillary considered to be a fever. While other methods can be used (temporal wand, tympanic temperature, etc.) to monitor patients, temperature time points (see below) required for the study MUST BE DOCUMENTED BY EITHER ORAL, RECTAL OR AXILLARY ROUTES. If another method was used for a key time point, enter that value with a comment on methods. If you do not use one of the preferred methods, completed the ***Protocol Deviation*** form on REDCap. Please work with your nursing staff to explain the importance of correct temperature measurement.

Temperature, route of measurement, date, and time (24h clock) for the following time points:

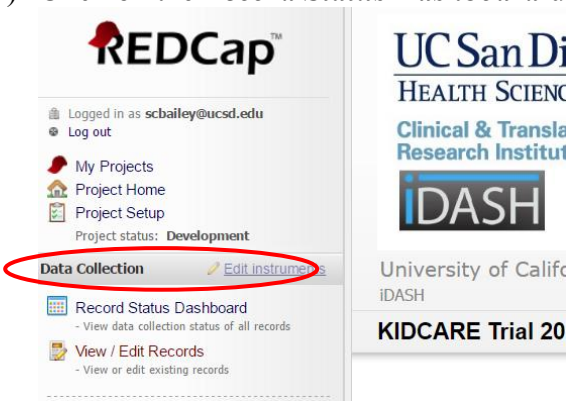
a. Qualifying temperature at study entry and route (Centigrade or Fahrenheit)
b. 24 hours (±2h) from initiation of study treatment;
c. 24 hours (±2h) from completion of study treatment
d. If 2nd study treatment administered, i-iii above for 2nd study treatment

** If you only have a temperature that is out of the window, enter the temperature that is closest to the desired window and enter the time. Complete the ***Protocol Deviation*** form on REDCap.

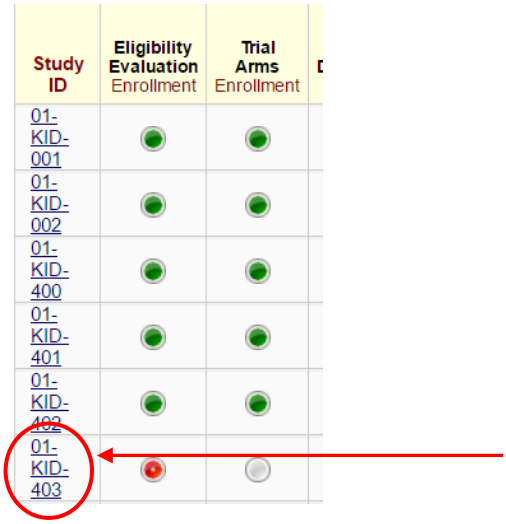
How to complete the Enrollment Temperature Measurement/Temperature Measurement Form in REDCap:

1) Go to https://cwp.ucsd.edu
2) You will log in using your AD account username and password
3) You should receive a login request on your phone from the Duo Mobile App
4) Open the Duo Mobile App on your phone and approve the login request
5) Once you have approved the login request, your browser will be directed to the Clinical Web Portal (CWP)
6) Select the KD REDCap icon
7) The REDCap database will be opened up in another web page. Under My Projects, Choose **KIDCARE Trial 2017**
8) On the left side of the REDCap portal, you will see a section labeled ***Data Collection***

9) Click on the ***Record Status Dashboard*** under this section.



10) Click the subject ID that needs to be completed.

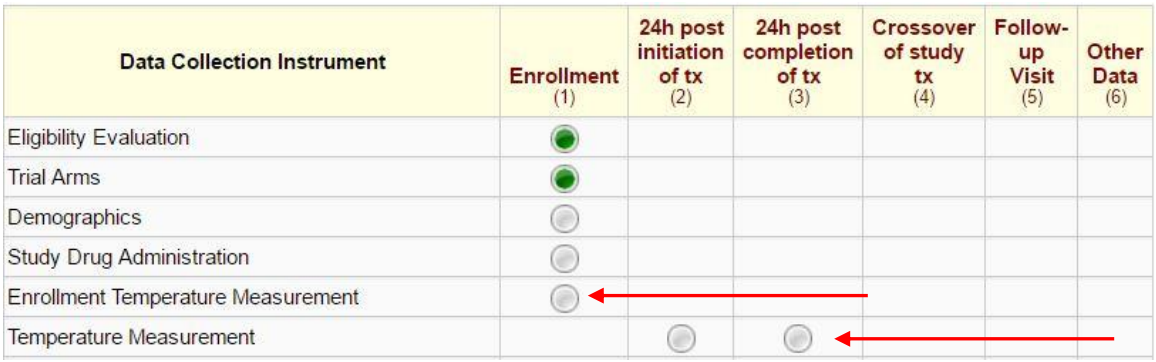


11) You will then be taken to this subjects REDCap study dashboard. This lists the time points and the forms that can be completed at each time point. You will click on the circle under the column for the time point (below) you are entering the data for and next to the ***Enrollment Temperature Measurement or Temperature Measurement*** form you need to complete

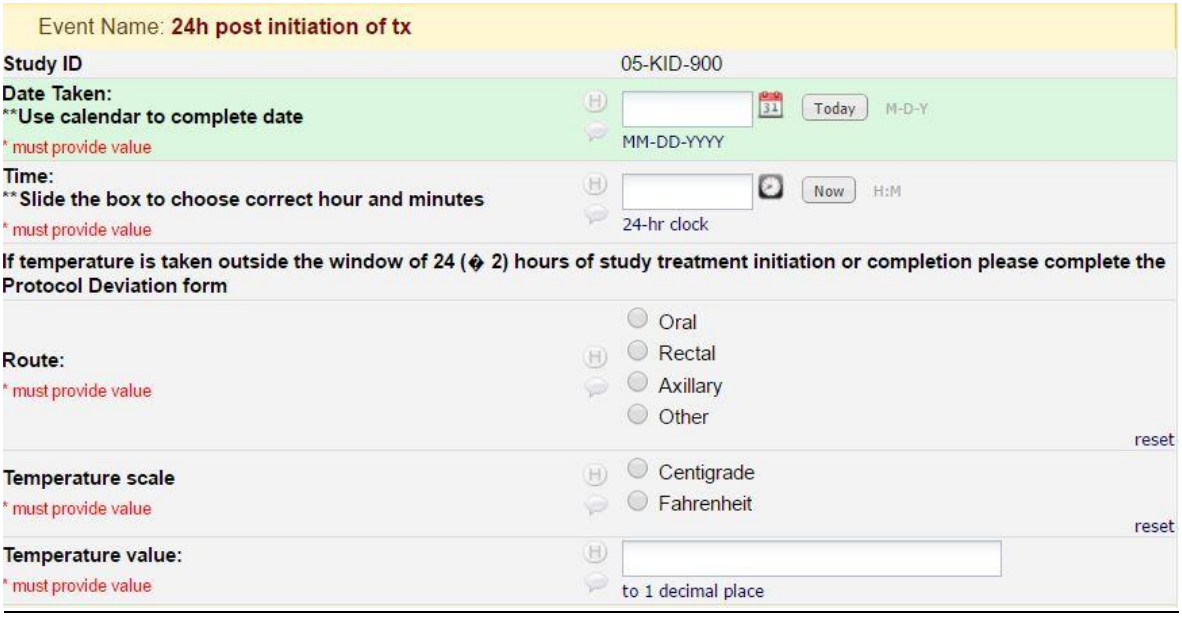
The Enrollment Temperature Measurement form is its own form to record the qualifying temperature at study entry and route.

The time points for the Temperature Measurement Form

a. **24 hours post initiation of study tx**
b. **24 hours post completion of study tx**

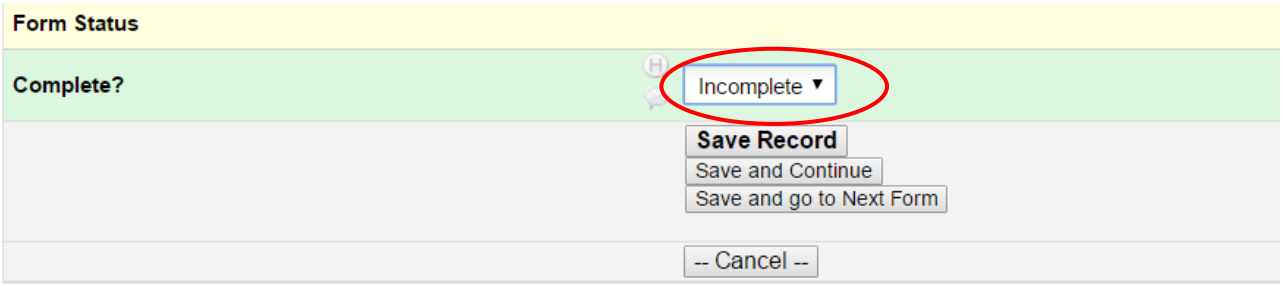


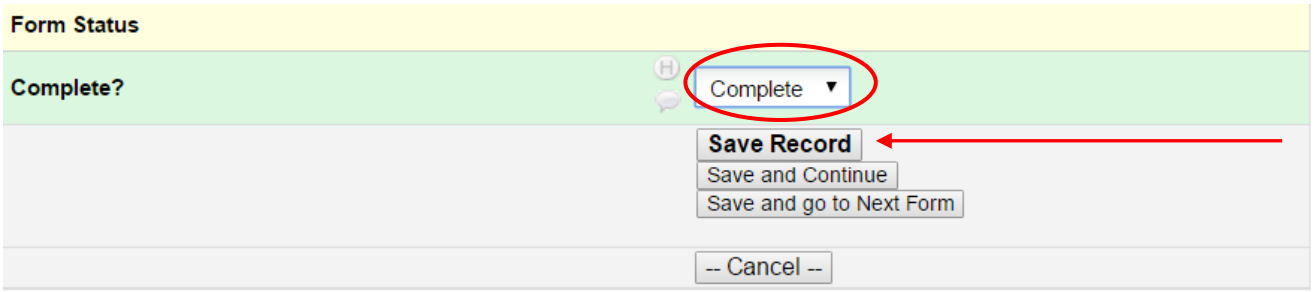
12) When you click on the circle you will be taken to the ***Enrollment Temperature Measurement or Temperature Measurement*** form.



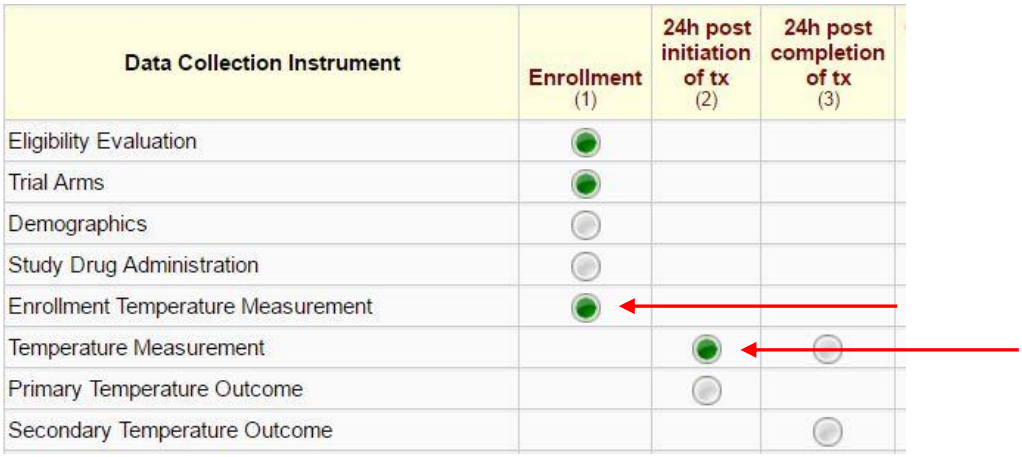
13) Answer all the questions within the ***Enrollment Temperature Measurement or Temperature Measurement*** form

14) Once you complete the form, change the status of the form ***Incomplete to Complete*** and then click ***Save Record***.





15) From here you will be directed back to the subjects study dashboard. The circle next to the ***Enrollment Temperature Measurement or Temperature Measurement*** form you completed should be green.



****If the subject crosses over to the other study treatment, repeat steps 1-10 for the ***Crossover Temperature Measurement*** form located under the ***Crossover of study tx*** column.

5J. Primary Temperature Outcome/Secondary Temperature Outcome

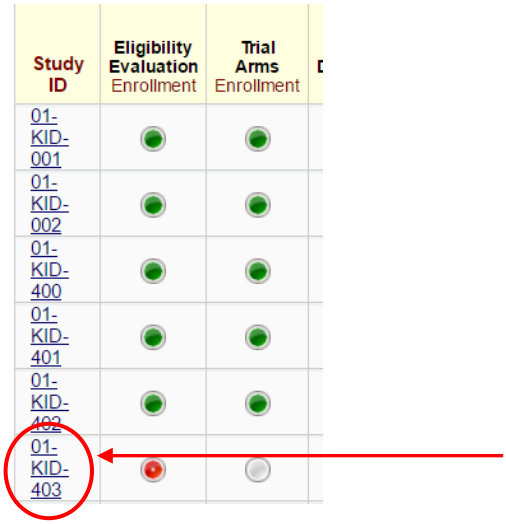
These forms are completed at 24 hours post initiation of study treatment (primary) and 24 hours post completion of study treatment (secondary). These two forms are **VERY** important and need to be completed. They are the main outcomes of the study, asking if the subject was afebrile at these two time points.

How to complete the Primary Temperature Outcome/Secondary Temperature Outcome Forms in REDCap:

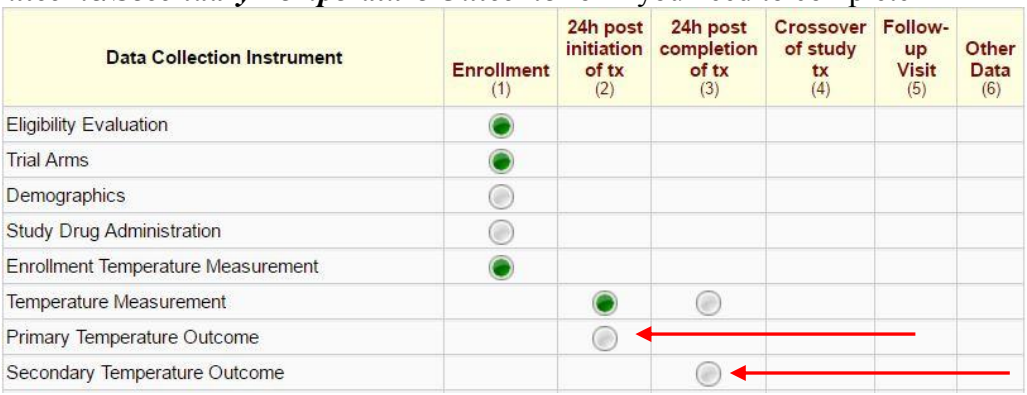
1) Go to https://cwp.ucsd.edu
2) You will log in using your AD account username and password
3) You should receive a login request on your phone from the Duo Mobile App
4) Open the Duo Mobile App on your phone and approve the login request
5) Once you have approved the login request, your browser will be directed to the Clinical Web Portal (CWP)
6) Select the KD REDCap icon

7) The REDCap database will be opened up in another web page. Under My Projects, Choose **KIDCARE Trial 2017**
8) On the left side of the REDCap portal, you will see a section labeled ***Data Collection***
9) Click on the ***Record Status Dashboard*** under this section.

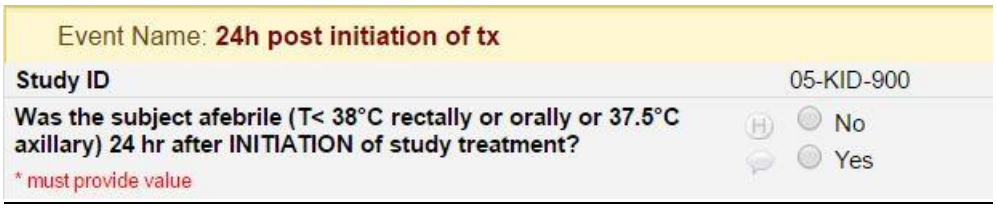
10) Click the subject ID that needs to be completed.

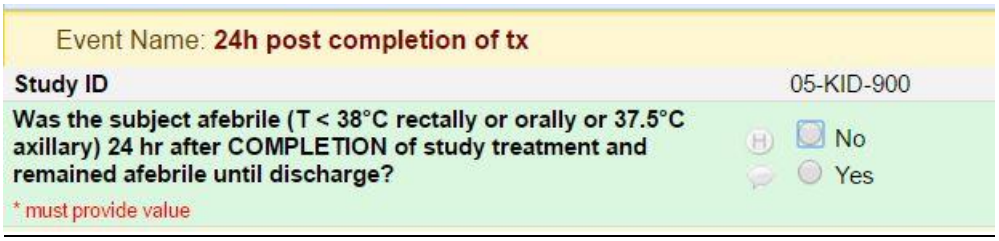


11) You will then be taken to this subjects REDCap study dashboard. This lists the time points and the forms that can be completed at each time point. You will click on the circle under the column for the time point (below) you are entering the data for and next to the ***Primary Temperature Outcome/Secondary Temperature Outcome*** form you need to complete



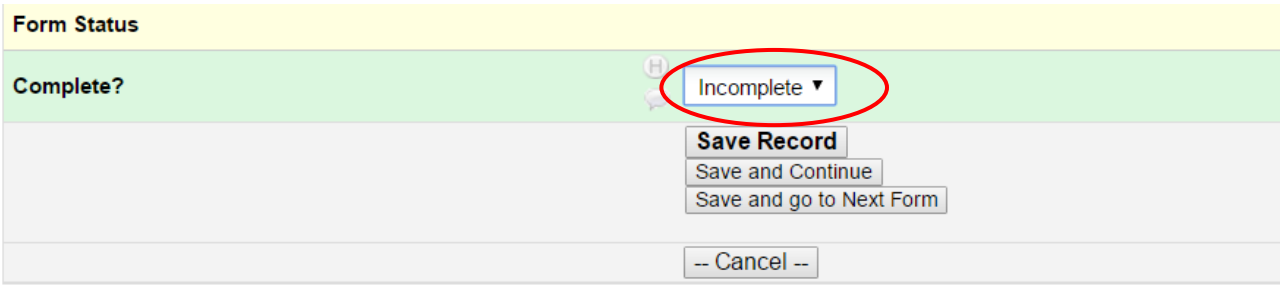
12) When you click on the circle you will be taken to the ***Primary Temperature Outcome/Secondary Temperature Outcome*** form

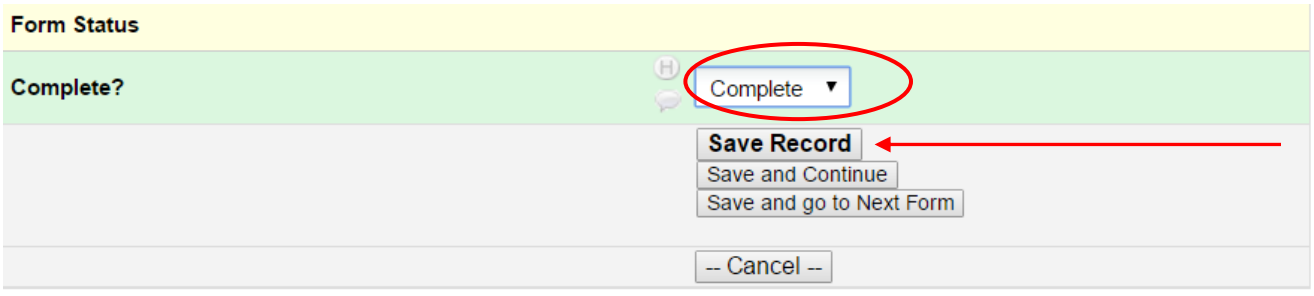




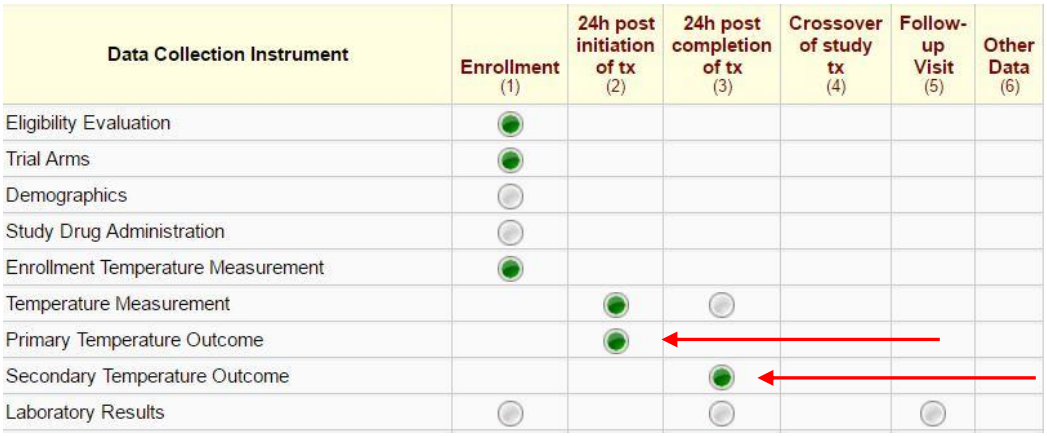
13) Answer the question within the ***Primary Temperature Outcome/Secondary Temperature Outcome*** form

14) Once you complete the form, change the status of the form ***Incomplete to Complete*** and then click ***Save Record***.





15) From here you will be directed back to the subjects study dashboard. The circle next to the ***Primary Temperature Outcome/Secondary Temperature Outcome*** form you completed should be green.



Data Collection Instrument	Enrollment (1)	24h post initiation of tx (2)	24h post completion of tx (3)	Crossover of study tx (4)	Follow-up Visit (5)	Other Data (6)
Eligibility Evaluation	●					
Trial Arms	●					
Demographics	○					
Study Drug Administration	○					
Enrollment Temperature Measurement	●					
Temperature Measurement		●	○			
Primary Temperature Outcome		●				
Secondary Temperature Outcome			●			
Laboratory Results	○		○		○	

5K. Laboratory Results Form

White blood count (WBC), absolute neutrophil count (ANC), hemoglobin (Hgb), platelet count, C-reactive (CRP, mg/dL) levels at following time points:

a. Pre-IVIG at diagnosis
b. 24 hours (± 2 hours) post-completion of study treatment
c. 5- 18 days following the completion of study treatment (follow-up visit)

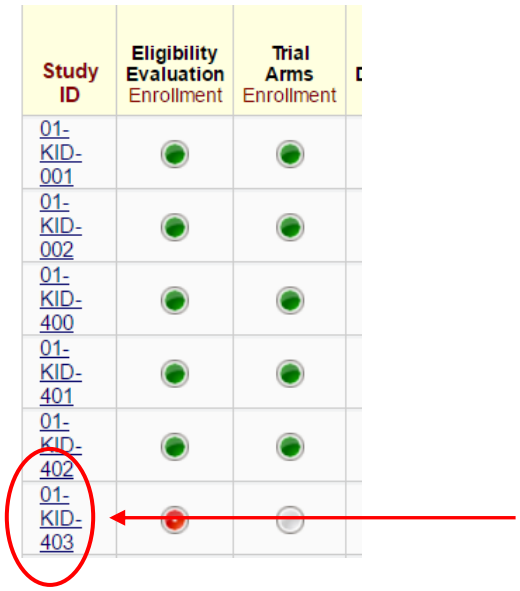
Erythrocyte sedimentation rate (ESR) at the following time points:

a. Pre-IVIG at diagnosis
b. 5- 18 days following the completion of study treatment (follow-up visit)

How to complete the Laboratory Results Form in REDCap:

1) Go to https://cwp.ucsd.edu
2) You will log in using your AD account username and password
3) You should receive a login request on your phone from the Duo Mobile App
4) Open the Duo Mobile App on your phone and approve the login request
5) Once you have approved the login request, your browser will be directed to the Clinical Web Portal (CWP)
6) Select the KD REDCap icon
7) The REDCap database will be opened up in another web page. Under My Projects, Choose KIDCARE Trial 2017
8) On the left side of the REDCap portal, you will see a section labeled ***Data Collection***
9) Click on the ***Record Status Dashboard*** under this section.

10) Click the subject ID that needs to be completed.



11) You will then be taken to this subjects REDCap study dashboard. This lists the time points and the forms that can be completed at each time point. You will click on the circle under the column for the time point (below) you are entering the data for and next to the ***Laboratory Results*** form you need to complete

The time points for the ***Laboratory Results*** form

a. Enrollment (pre-IVIG at diagnosis) (if multiple CBCs were performed prior to administration of IVIG, choose the CBC closest to time and date of 1st IVIG treatment
b. 24 hours (± 2 hours) post-completion of study treatment
c. 5- 18 days following the completion of study treatment

*** Erythrocyte sedimentation rate (ESR) completed at a and c above

Data Collection Instrument	Enrollment (1)	24h post initiation of tx (2)	24h post completion of tx (3)	Crossover of study tx (4)	Follow-up Visit (5)	Other Data (6)
Eligibility Evaluation	●					
Trial Arms	●					
Demographics	○					
Study Drug Administration	○					
Enrollment Temperature Measurement	○					
Temperature Measurement		○	○			
Primary Temperature Outcome		○				
Secondary Temperature Outcome			○			
Laboratory Results	○		○		○	

12) When you click on the circle you will be taken to the ***Laboratory Results*** form

Event Name: **Enrollment**

Study ID 01-KID-403

*****IF ENROLLMENT TIME POINT******
If multiple CBCs were preformed prior to administration of IVIG, choose the CBC that is closest to time and date of 1st IVIG infusion and before the start of the infusion.

Hematology

Date of CBC
****Use calendar to complete date**
* must provide value
MM-DD-YYYY Today M-D-Y

Time
* must provide value
24-hr clock Now H:M

White Blood Cell Count (X 10^3/uL)
* must provide value

Hemoglobin (g/dL)
* must provide value

Platelet Count (X 10^3/uL)
* must provide value

Method for differential count:
* must provide value
○ Auto differential
○ Manuel differential
reset

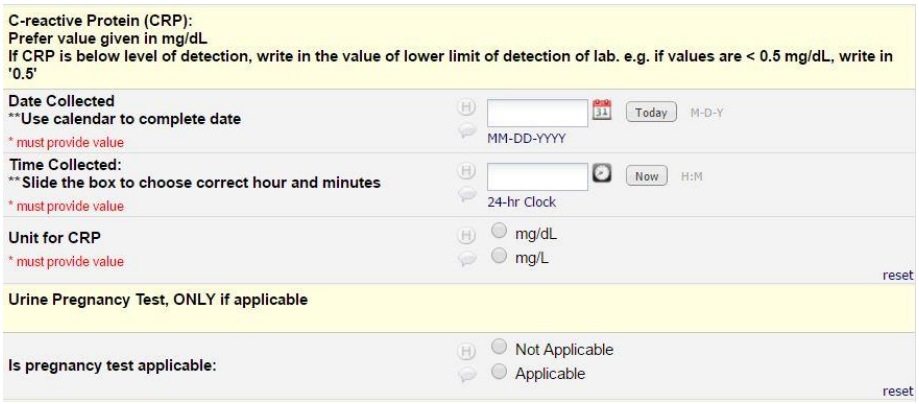
Absolute Neutrophil Count (ANC)
* must provide value

Erythrocyte sedimentation rate (ESR)
*****ONLY COMPLETED AT ENROLLMENT AND WEEK 2*****
If ESR > 140 write in '140'

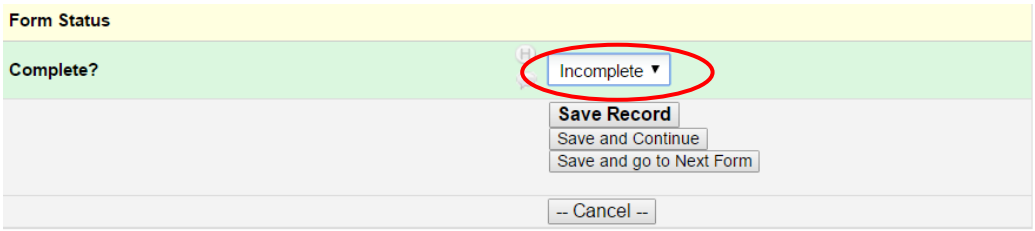
Date Collected
****Use calendar to complete date**
MM-DD-YYYY Today M-D-Y

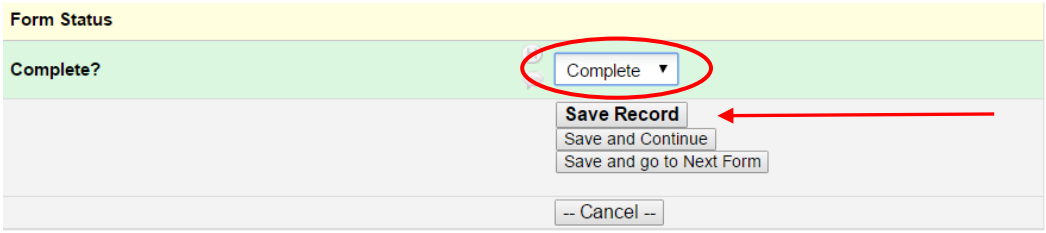
Time Collected
24-hr Clock Now H:M

ESR (mm)

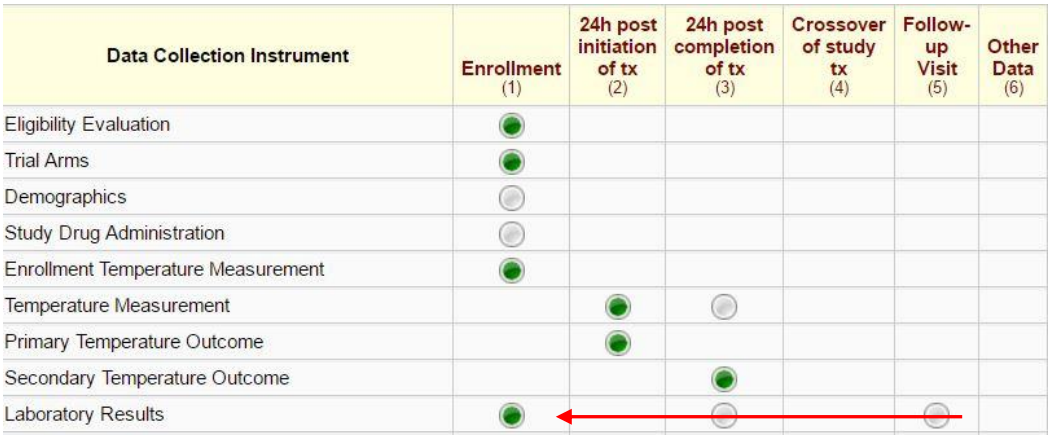


13) Answer all the questions within the ***Laboratory Results*** form
14) Once you complete this form, change the status of the form ***Incomplete to Complete*** and then click ***Save Record.***





15) From here you will be directed back to the subjects study dashboard. The circle next to the ***Laboratory Results*** form should be ***GREEN***



****If the subject crosses over to the other study treatment, repeat steps 1-10 for the ***Crossover Laboratory Results*** form located under the ***Crossover of study tx*** column.

5L. Center Echocardiogram Form

An echocardiogram will be performed at the following time points per standard of care:

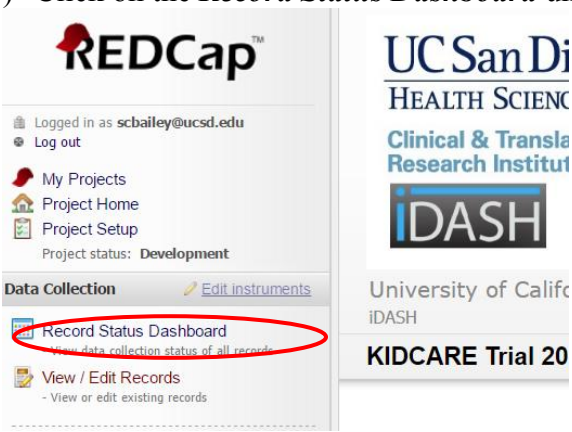
i. During initial hospitalization at the time of diagnosis (If multiple 2-D echoes are obtained on a given patient prior to diagnosis, then the echo closest to the time of the first IVIG infusion should be used on Echocardiogram Form)
ii. Capturing the worst ever echo between echo closest to 1st IVIG and echo at follow-up visit
iii. 5-18 days following the completion of study (follow-up visit)

2-D transthoracic echocardiograms (2-D Echo) will be performed on all KD subjects according to a standardized protocol recommended by the Pediatric Heart Network and the AHA. 2-D Echo will be performed at KD diagnosis (preferably within 24h of first *IVIG infusion* prior to study enrollment*) and again at two weeks (± 4 days) following enrollment*. Sedation for children younger than 3 years is recommended. *The patient's height and weight and internal lumen diameters in millimeters of the left main (LMCA), proximal LAD, circumflex, and proximal and mid RCA will each be measured and recorded on the CRF. Dimensions of the LMCA, proximal LAD, circumflex, and proximal RCA will be adjusted for body surface area and expressed in standard deviation units (Z-scores) at the Coordinating Center.*

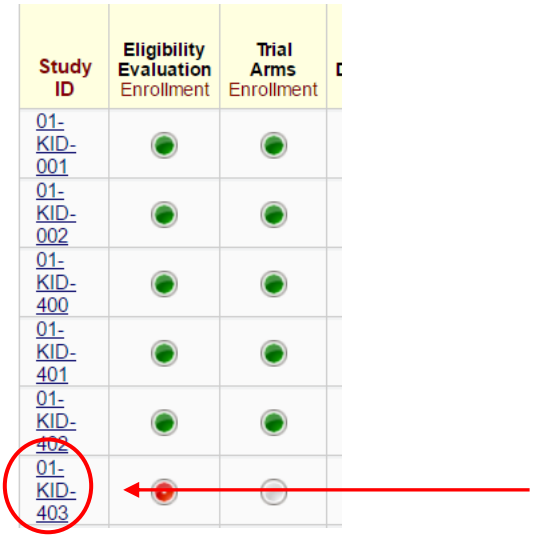
Weight of subject should be measured with shoes off. We recommend that height is measured by a nurse and confirmed by a second nurse using a stadiometer.

How to complete the Center Echocardiogram Form in REDCap:

1) Go to https://cwp.ucsd.edu
2) You will log in using your AD account username and password
3) You should receive a login request on your phone from the Duo Mobile App
4) Open the Duo Mobile App on your phone and approve the login request
5) Once you have approved the login request, your browser will be directed to the Clinical Web Portal (CWP)
6) Select the KD REDCap icon
7) The REDCap database will be opened up in another web page. Under My Projects, Choose **KIDCARE Trial 2017**
8) On the left side of the REDCap portal, you will see a section labeled ***Data Collection***
9) Click on the ***Record Status Dashboard*** under this section.



10) Click the subject ID that needs to be completed.

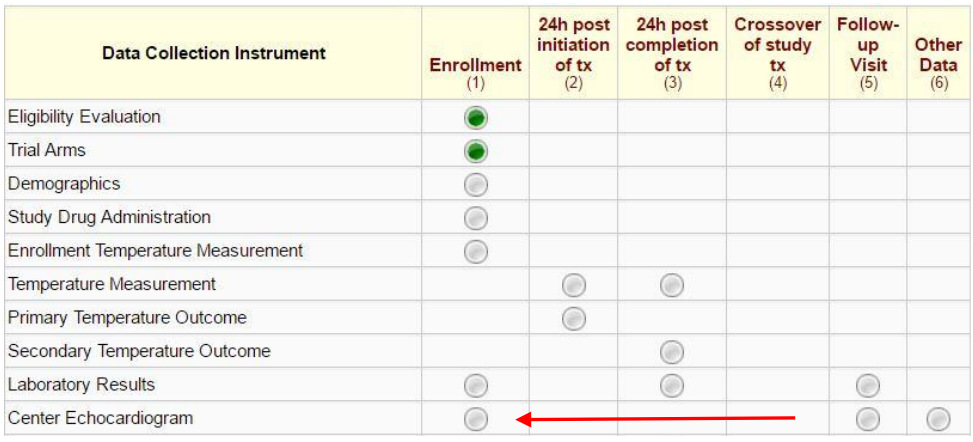


Study ID	Eligibility Evaluation Enrollment	Trial Arms Enrollment	D
01-KID-001			
01-KID-002			
01-KID-400			
01-KID-401			
01-KID-402			
01-KID-403			

11) You will then be taken to this subjects REDCap study dashboard. This lists the time points and the forms that can be completed at each time point. You will click on the circle under the column for the time point (below) you are entering the data for and next to the ***Center Echocardiogram*** form you need to complete

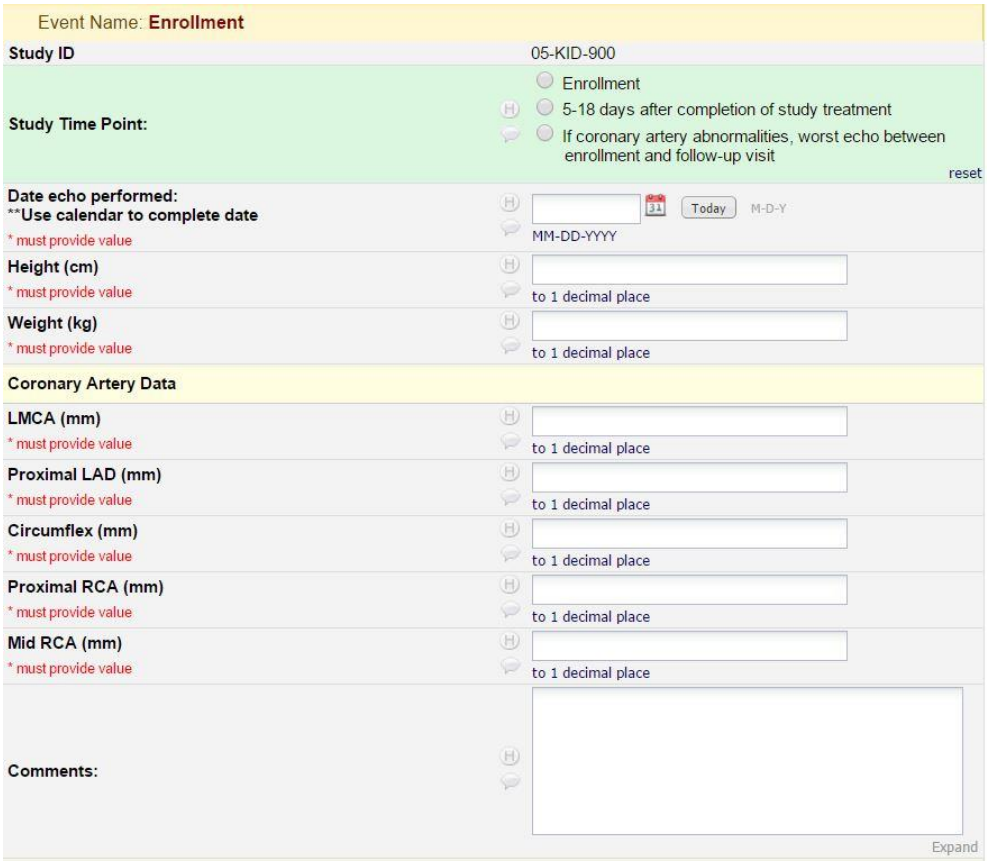
The time points for the Echocardiogram Form

a. Enrollment (pre-IVIG at diagnosis)
b. 5-18 days following the completion of study treatment (follow-up visit)
c. Other data entry

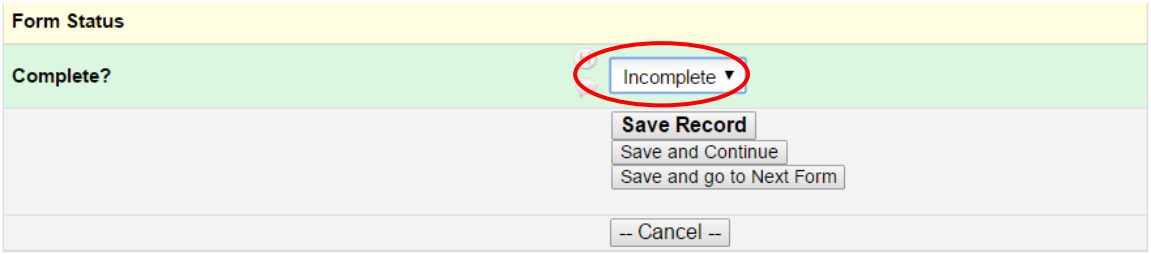


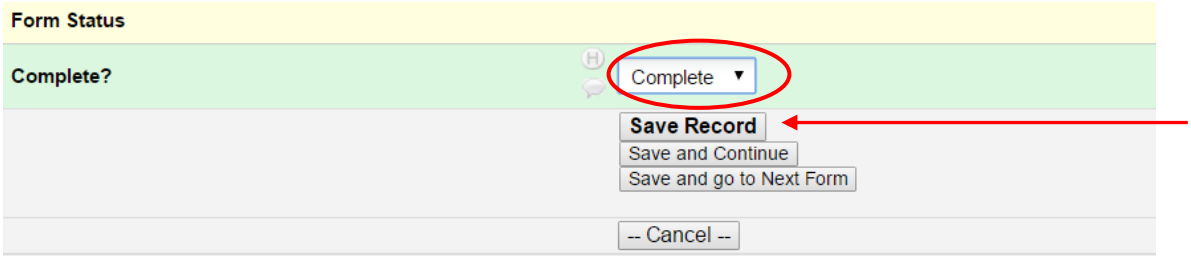
Data Collection Instrument	Enrollment (1)	24h post initiation of tx (2)	24h post completion of tx (3)	Crossover of study tx (4)	Follow-up Visit (5)	Other Data (6)
Eligibility Evaluation						
Trial Arms						
Demographics						
Study Drug Administration						
Enrollment Temperature Measurement						
Temperature Measurement						
Primary Temperature Outcome						
Secondary Temperature Outcome						
Laboratory Results						
Center Echocardiogram						

12) When you click on the circle you will be taken to that ***Center Echocardiogram*** form

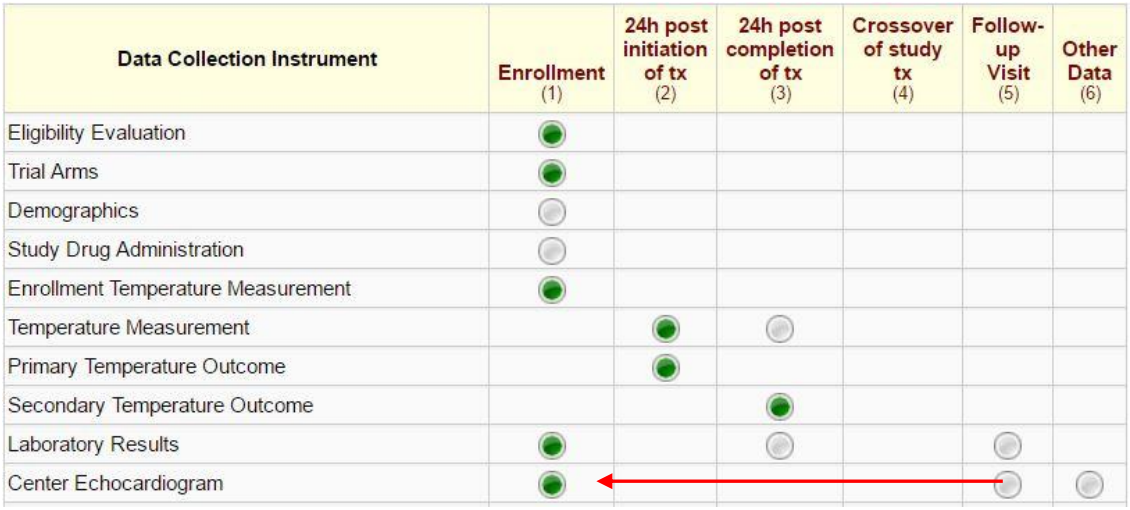


13) Answer all the questions within the ***Center Echocardiogram*** form
14) Once you complete this form, change the status of the form ***Incomplete to Complete*** and then click ***Save Record***





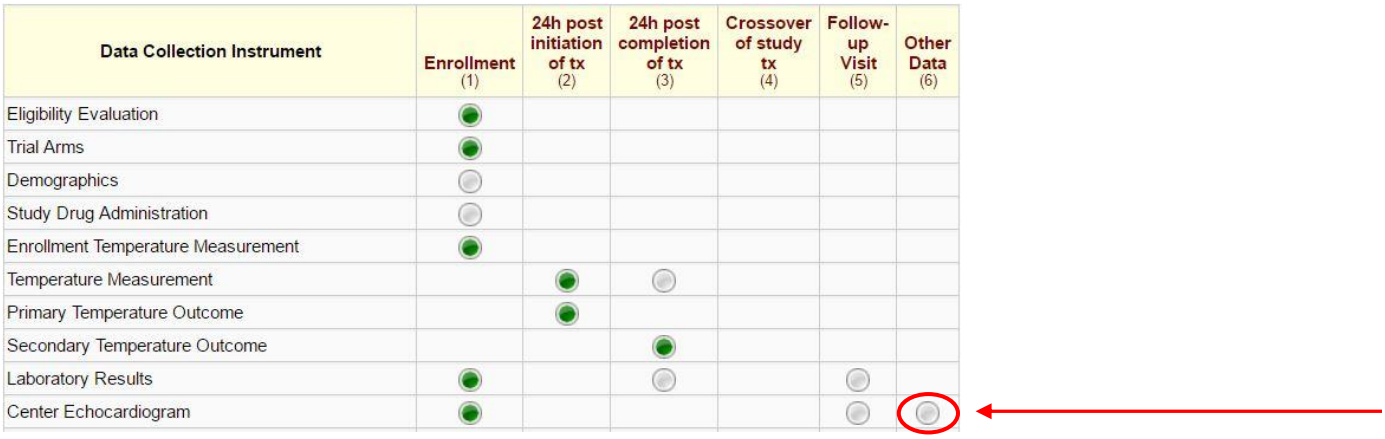
15) From here you will be directed back to the subjects study dashboard. The circle next to the ***Center Echocardiogram*** form should be ***GREEN***



Data Collection Instrument	Enrollment (1)	24h post initiation of tx (2)	24h post completion of tx (3)	Crossover of study tx (4)	Follow-up Visit (5)	Other Data (6)
Eligibility Evaluation	●					
Trial Arms	●					
Demographics	○					
Study Drug Administration	○					
Enrollment Temperature Measurement	●					
Temperature Measurement		●	○			
Primary Temperature Outcome		●				
Secondary Temperature Outcome			●			
Laboratory Results	●		○		○	
Center Echocardiogram	●				○	○

Worst Ever Echo

If multiple 2-D echoes are obtained after the first IVIG and prior to the 2-week visit, then the largest dimension in mm of the LMCA, RCA, LAD and circumflex should be recorded on the CRF entitled ***Center Echocardiogram*** form located under ***Other Data*** column in REDCap ‘”. If only two 2-D echoes are performed (at diagnosis and again at follow-up visit), then form echo at other should not be completed.



Data Collection Instrument	Enrollment (1)	24h post initiation of tx (2)	24h post completion of tx (3)	Crossover of study tx (4)	Follow-up Visit (5)	Other Data (6)
Eligibility Evaluation	●					
Trial Arms	●					
Demographics	○					
Study Drug Administration	○					
Enrollment Temperature Measurement	●					
Temperature Measurement		●	○			
Primary Temperature Outcome		●				
Secondary Temperature Outcome			●			
Laboratory Results	●		○		○	
Center Echocardiogram	●				○	○

5M. Fever Days and Duration of Hospitalization Form

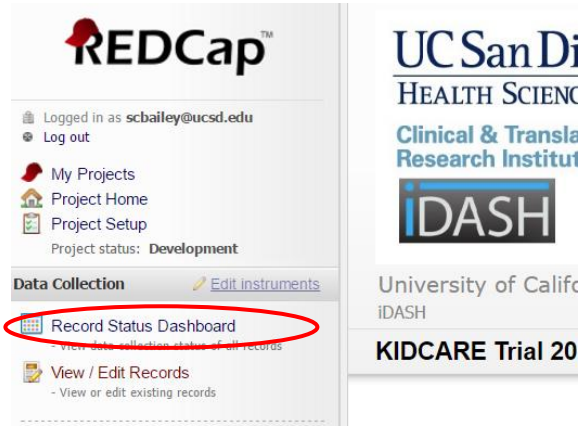
Total Fever Days and Duration of Hospitalization data are only collected once on the form located under the Other Data column in REDcap. Data collected in the form include:

a) Total number of fever days (24 hour period with a T ≥38°C orally or rectally or ≥37.5°C axillary/ T ≥100.4°F orally or rectally or ≥ 99.5°F axillary) from the time of start of infusion of first study treatment. A day is from 12:01 am to 12:00 midnight. Example: If the patient starts first study treatment at 1:00 am and becomes afebrile at 11:00 pm that night, then that is one fever day. If fever returns two days later at 1:00 am and the patient receives second study treatment and becomes afebrile at 11:00 pm that night, then this counts as another fever day. The total number of fever days this patient will have had is 2.

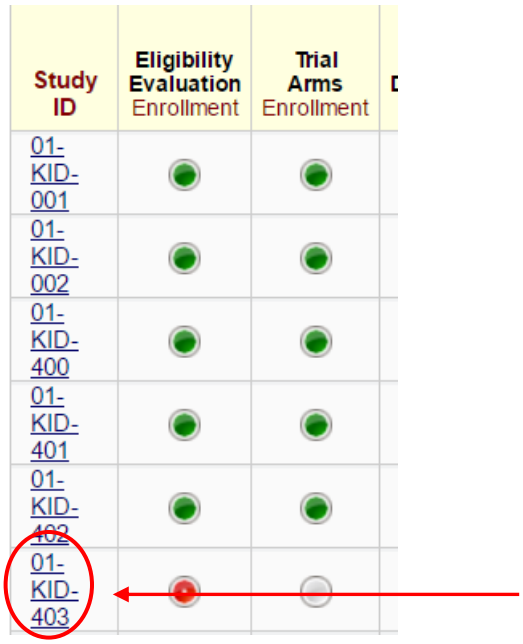
b) Duration of hospitalization following randomization (count number of days from randomization; each 24h-period from 12:01 am to 12-midnight counts as one calendar day)

How to complete the Fever Days and Hospitalization Form in REDCap:

1) Go to https://cwp.ucsd.edu
2) You will log in using your AD account username and password
3) You should receive a login request on your phone from the Duo Mobile App
4) Open the Duo Mobile App on your phone and approve the login request
5) Once you have approved the login request, your browser will be directed to the Clinical Web Portal (CWP)
6) Select the KD REDCap icon
7) The REDCap database will be opened up in another web page. Under My Projects, Choose **KIDCARE Trial 2017**
8) On the left side of the REDCap portal, you will see a section labeled ***Data Collection***
9) Click on the ***Record Status Dashboard*** under this section.



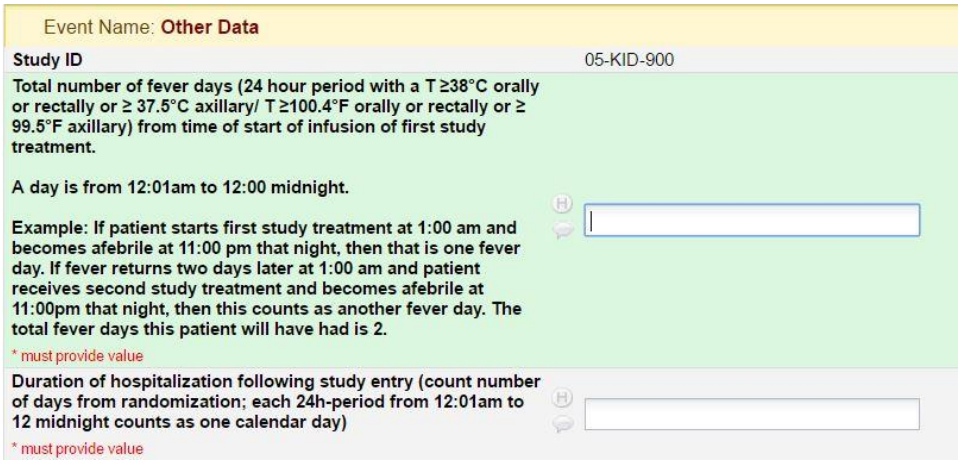
10) Click the subject ID that needs to be completed.



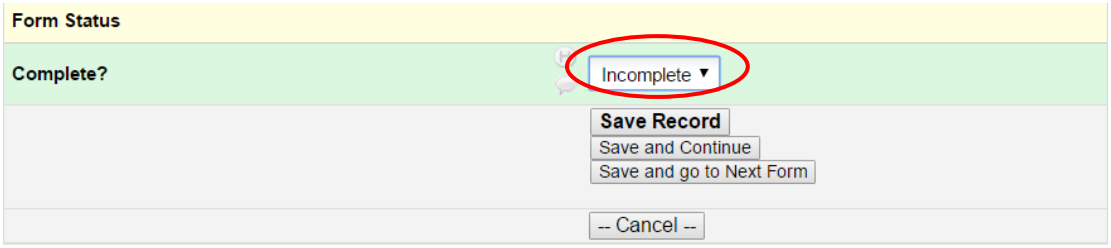
11) You will then be taken to this subjects REDCap study dashboard. This lists the time points and the forms that can be completed at each time point. You will click on the circle under ***Other Data*** column and next to the ***Fever Days and Duration of Hospitalization*** form you need to complete.

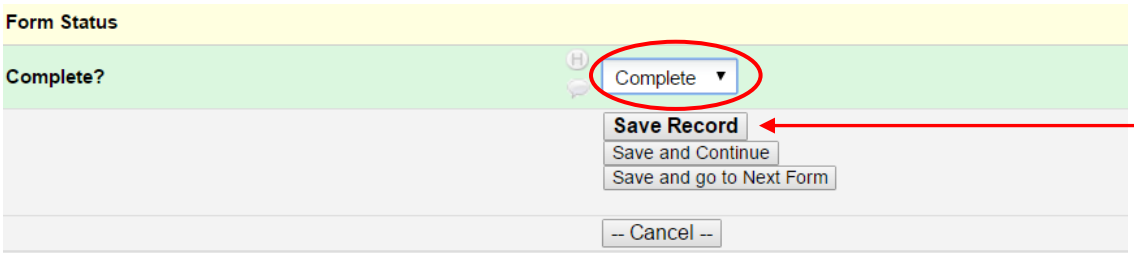
Data Collection Instrument	Enrollment (1)	24h post initiation of tx (2)	24h post completion of tx (3)	Crossover of study tx (4)	Follow-up Visit (5)	Other Data (6)
Eligibility Evaluation	●					
Trial Arms	●					
Demographics	○					
Study Drug Administration	○					
Enrollment Temperature Measurement	○					
Temperature Measurement		○	○			
Primary Temperature Outcome		○				
Secondary Temperature Outcome			○			
Laboratory Results	○		○		○	
Center Echocardiogram	○				○	○
Baseline Observation Tool (Start of Study Treatment)			○			
8 Hours After Start Of Study Treatment			○	○		
16 Hours After Start Of Study Treatment			○	○		
24 Hours After Start Of Study Treatment			○	○		
Parent Tool Followup			○			
Crossover Temperature Measurement				○		
Crossover Study Drug Administration				○		
Crossover Laboratory Results				○		
Protocol Deviation Form	○	○	○	○	○	○
Adverse Event Reporting Form	○	○	○	○	○	○
Study Completion Form					○	
Fever Days and Duration of Hospitalization						○
Concomitant Medication						○

12) When you click on the circle you will be taken to that ***Fever Days and Duration of Hospitalization*** form.



13) Answer all the questions within the ***Fever Days and Duration of Hospitalization*** Form
14) Once you complete this form, change the status of the form ***Incomplete to Complete*** and then click ***Save Record***.





15) From here you will be directed back to the subjects study dashboard. The circle next to the ***Fever Days and Duration of Hospitalization*** form should be ***GREEN***

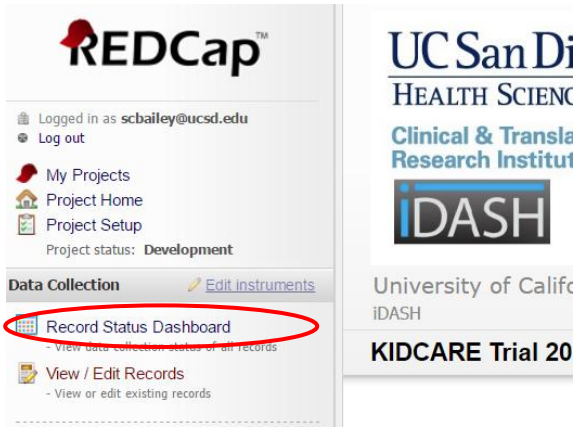
Data Collection Instrument	Enrollment (1)	24h post initiation of tx (2)	24h post completion of tx (3)	Crossover of study tx (4)	Follow-up Visit (5)	Other Data (6)
Eligibility Evaluation	●					
Trial Arms	●					
Demographics	○					
Study Drug Administration	○					
Enrollment Temperature Measurement	●					
Temperature Measurement		●	○			
Primary Temperature Outcome		●				
Secondary Temperature Outcome			●			
Laboratory Results	●		○		○	
Center Echocardiogram	●				○	○
Baseline Observation Tool (Start of Study Treatment)			○			
8 Hours After Start Of Study Treatment			○	○		
16 Hours After Start Of Study Treatment			○	○		
24 Hours After Start Of Study Treatment			○	○		
Parent Tool Followup			○			
Crossover Temperature Measurement				○		
Crossover Study Drug Administration				○		
Crossover Laboratory Results				○		
Protocol Deviation Form	○	○	○	○	○	○
Adverse Event Reporting Form	○	○	○	○	○	○
Study Completion Form					○	
Fever Days and Duration of Hospitalization						●
Concomitant Medication						○

5N. Concomitant Medication

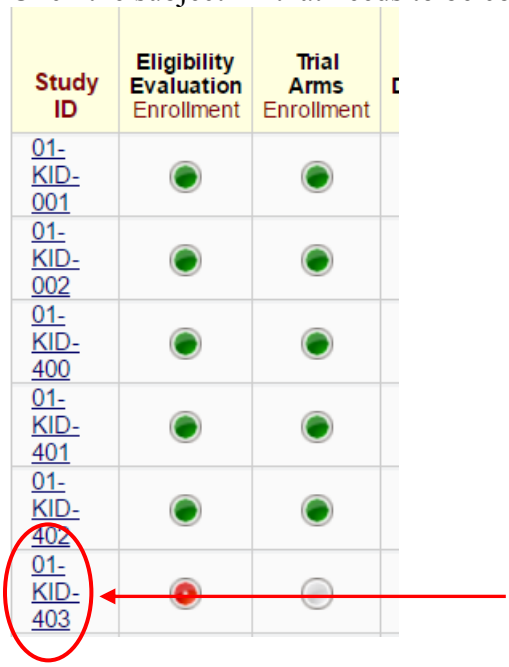
Name, dose, date, time and reason for all concomitant medications taken while on the study. Aspirin medication will be reported in this form. You can include up to 50 concomitant medications. Please do not include topical medication. If a medication is prescribed to be taken as needed (i.e. Tylenol), only include the time it was administered, each administration will be its own entry.

How to complete the Concomitant Medication Form in REDCap:

1) Go to https://cwp.ucsd.edu
2) You will log in using your AD account username and password
3) You should receive a login request on your phone from the Duo Mobile App
4) Open the Duo Mobile App on your phone and approve the login request
5) Once you have approved the login request, your browser will be directed to the Clinical Web Portal (CWP)
6) Select the KD REDCap icon
7) The REDCap database will be opened up in another web page. Under My Projects, Choose **KIDCARE Trial 2017**
8) On the left side of the REDCap portal, you will see a section labeled ***Data Collection***
9) Click on the ***Record Status Dashboard*** under this section.



10) Click the subject ID that needs to be completed.

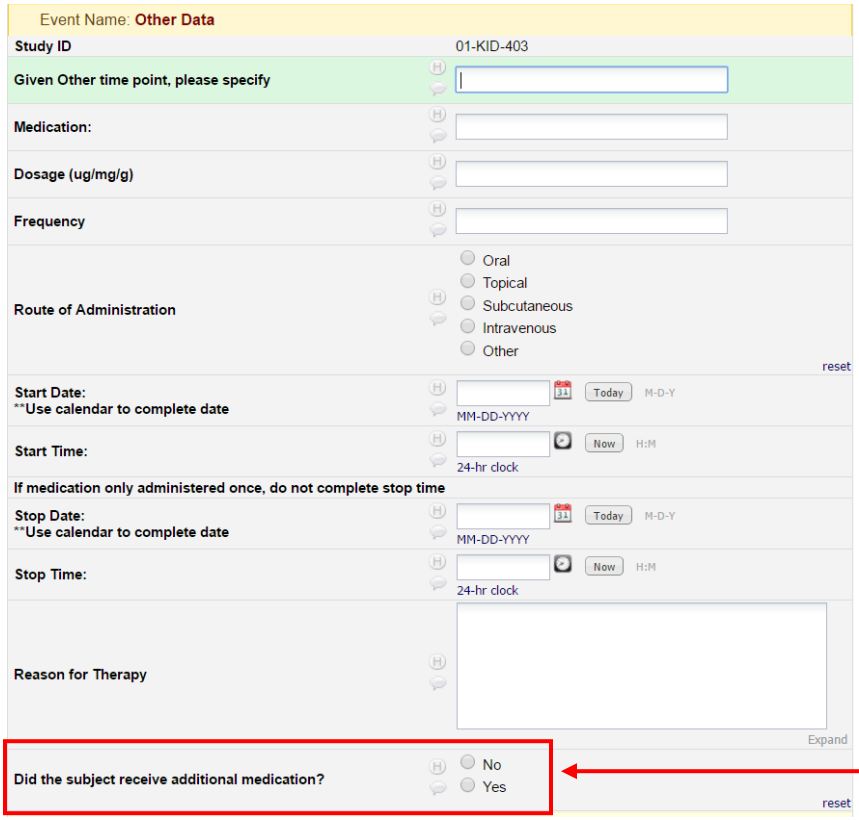


Study ID	Eligibility Evaluation Enrollment	Trial Arms Enrollment
01-KID-001		
01-KID-002		
01-KID-400		
01-KID-401		
01-KID-402		
01-KID-403		

11) You will then be taken to this subjects REDCap study dashboard. This lists the time points and the forms that can be completed at each time point. You will click on the circle under the ***Other Data*** column and next to the ***Concomitant Medication*** form you need to complete.

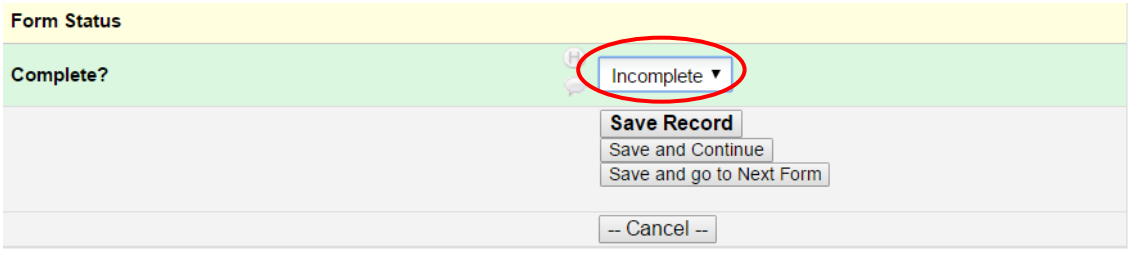
Data Collection Instrument	Enrollment (1)	24h post initiation of tx (2)	24h post completion of tx (3)	Crossover of study tx (4)	Follow-up Visit (5)	Other Data (6)
Eligibility Evaluation						
Trial Arms						
Demographics						
Study Drug Administration						
Enrollment Temperature Measurement						
Temperature Measurement						
Primary Temperature Outcome						
Secondary Temperature Outcome						
Laboratory Results						
Center Echocardiogram						
Baseline Observation Tool (Start of Study Treatment)						
8 Hours After Start Of Study Treatment						
16 Hours After Start Of Study Treatment						
24 Hours After Start Of Study Treatment						
Parent Tool Followup						
Crossover Temperature Measurement						
Crossover Study Drug Administration						
Crossover Laboratory Results						
Protocol Deviation Form						
Adverse Event Reporting Form						
Study Completion Form						
Fever Days and Duration of Hospitalization						
Concomitant Medication						

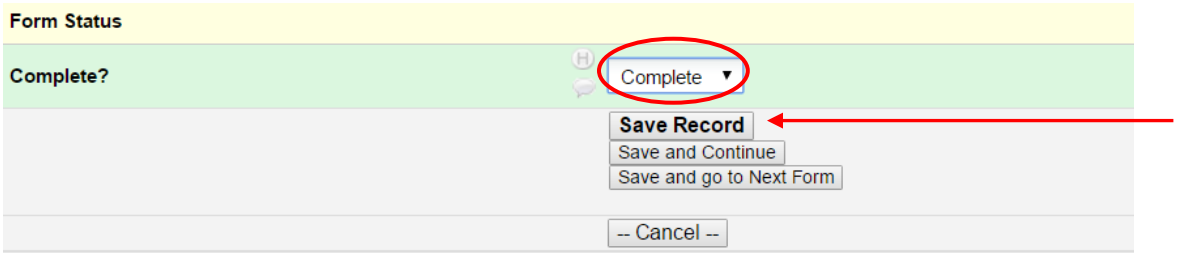
12) When you click on the circle you will be taken to the ***Concomitant Medication*** form



If you have more than 1 concomitant medication, answer yes to this question. All the question will appear again for an additional entry.

13) Answer all the questions within the ***Concomitant Medication*** Form
14) Once you complete this form, change the status of the form ***Incomplete to Complete*** and then click ***Save Record***.





15) From here you will be directed back to the subjects study dashboard. The circle next to the ***Concomitant Medication*** form should be ***GREEN***

5O. Patient Observation Tool

After discharge subjects will be monitored for 2 weeks to evaluate for adverse events. The UC Davis team (Kathy Kim and Sakib Jalil) developed an instrument that will be presented as a survey either via email to the parents/legal guardians. Parents/legal guardians will have the option to choose between paper or email as their preferred way of reporting. Their preference will be recorded on p. 6 of the observation tool form in Appendix B. During the 2 weeks following discharge, parents/legal guardians will be prompted to complete the survey once each day. Any medical conditions reported by the parents (e.g. recurrent fever, arthritis/arthralgia interfering with ambulation, new-onset rash) will prompt a message to the parent to contact their study doctor. A reminder message is included in the daily contact for the first week only after discharge reminding parents to call the study physician if fever has recurred.

Name of forms:

a) Baseline Observation Tool (Start of Study Treatment)
b) 8-hour Observation Tool
c) 16-hour Observation Tool
d) 24-hour Observation Tool

Parents and legal guardians will complete the Parent Observation Tool to record observations about their child. The paper copy of the form must be given to the responsible adult by the site study doctor at the time of randomization. The parent/guardian will complete this form at four times during the first 24-hour period that their child is in the study:

The four time points for completion of the observation tool while in the hospital are:

1. Before start of study treatment
2. Around 8 hours after start of 1st study treatment
3. Around 16 hours after start of treatment
4. Around 24 hours after start of treatment.

If a child receives a second study treatment as a cross-over in the protocol, the parent/legal guardian will complete the tool for an additional 24 hours.

1. Around 8 hours after start of second study treatment
2. Around 16 hours after start of second treatment
3. Around 24 hours after start of second treatment

The observation tool is attached as Appendix B. Note that there are 7 pages to the tool. Provide pages 1-6 to the parent. Page 7 is an example of the monitoring questions that will be collected at home and is for the study team reference only. If you have any questions about the this observation tool you can contact the UC Davis team by calling Katherine Kim at 510-761-5406 or emailing Katherine at kathykim@ucdavis.edu.

The parent should return the form to the site study physician/coordinator after completing of all time points and prior to discharge from the hospital. The site study physician/coordinator will enter the data into REDcap forms: Baseline Observation Tool (Start of Study Treatment), 8-hour Observation Tool, 16-hour Observation Tool, 24-hour Observation Tool Follow the instructions above to enter these data into REDCap.

On the day of hospital discharge, call the 24h-monitored phone number at UC Davis (510-761-5406) and leave a message with the following information so that team can schedule the monitoring emails to be sent to the family starting the day after discharge.

When you call, please provide:
1. Subject study ID
2. Date of the call
3. Parent's preferred email
4. Your name
5. Your contact information

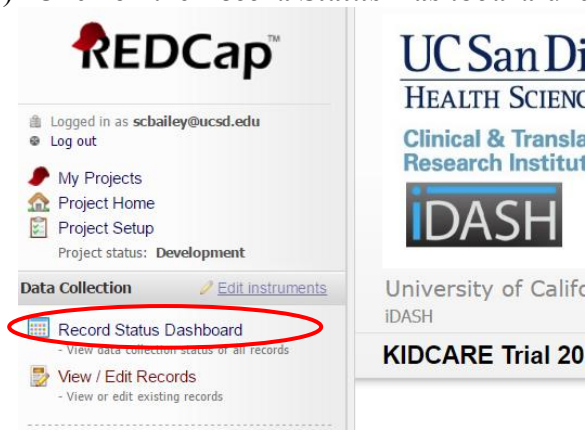
If the parent chooses paper, please collect the paper questionnaire at the follow-up visit. Then scan and email the completed questionnaire to Samantha Roberts at sroberts@ucsd.edu.

Compensation for Participation

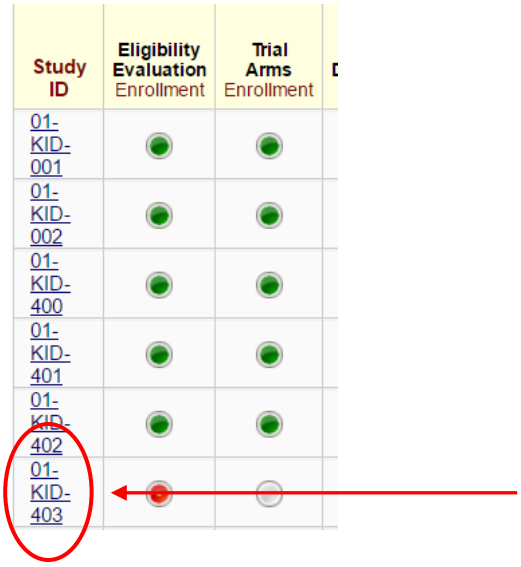
On completion of the parent observation daily observations, subjects will be provided with a $25 gift card at the follow-up visit to offset any incidental expenses for participation. The gift cards will be supplied by the UC Davis team to all sites at study initiation. Requests for additional cards should be made to calling Samantha Roberts at 858-966-8799 or email sroberts@ucsd.edu.

How to complete the Parent Observation Tool Form in REDCap:

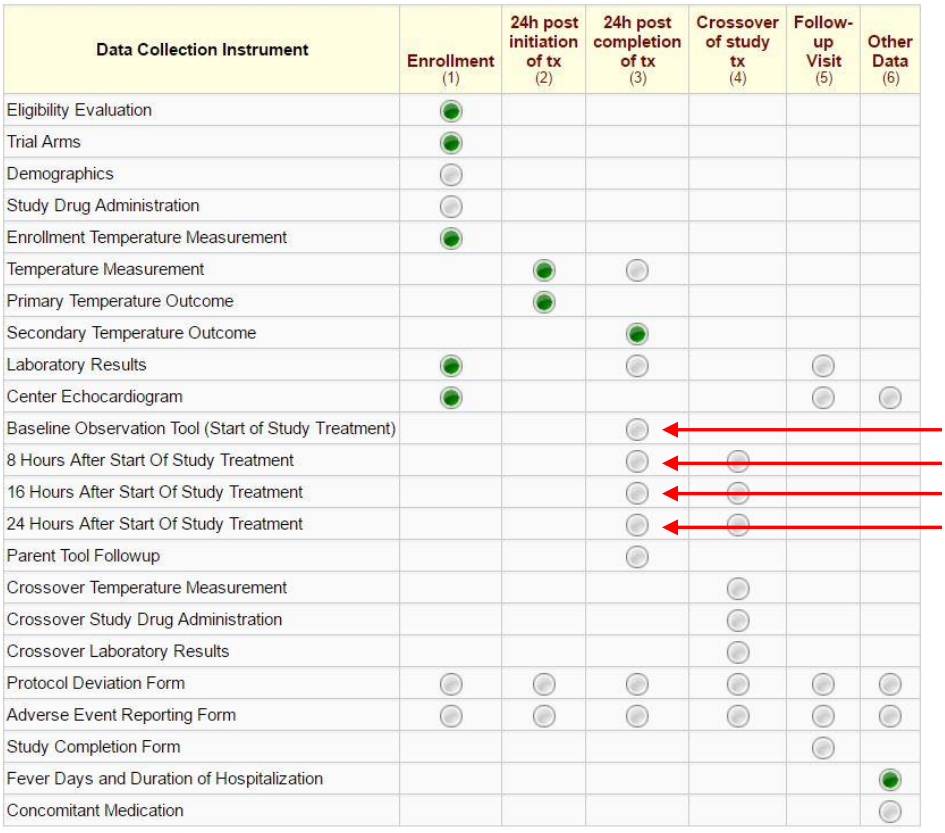
1) Go to https://cwp.ucsd.edu
2) You will log in using your AD account username and password
3) You should receive a login request on your phone from the Duo Mobile App
4) Open the Duo Mobile App on your phone and approve the login request
5) Once you have approved the login request, your browser will be directed to the Clinical Web Portal (CWP)
6) Select the KD REDCap icon
7) The REDCap database will be opened up in another web page. Under My Projects, Choose **KIDCARE Trial 2017**
8) On the left side of the REDCap portal you will see a section labeled ***Data Collection***
9) Click on the ***Record Status Dashboard*** under this section.



10) Click the subject ID that needs to be completed.

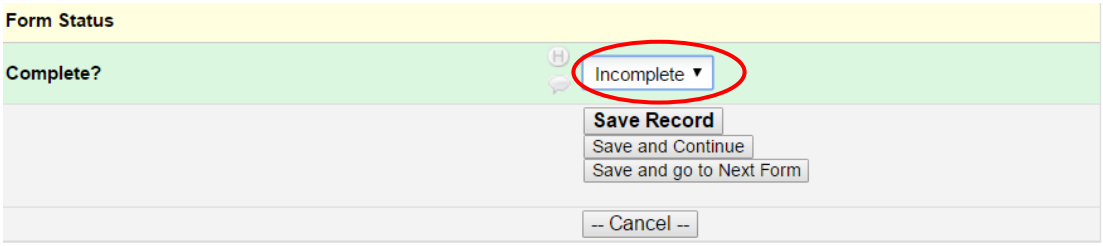


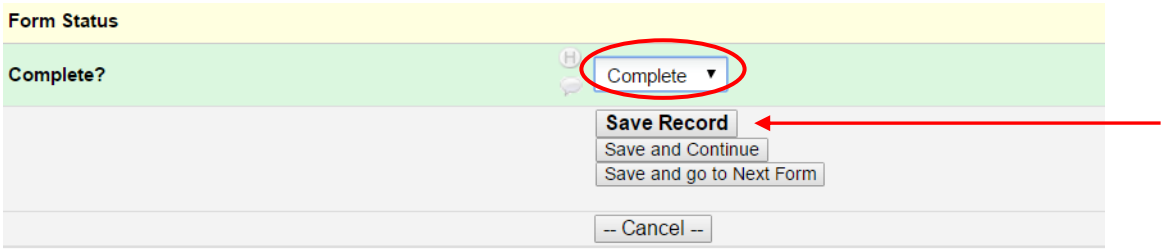
11) You will then be taken to this subjects REDCap study dashboard. This lists the time points and the forms that can be completed at each time point. You will click on the circle under the ***24h post completion of tx*** column and next to the ***Baseline***, ***8, 16, 24h Observation Tool*** for you need to complete



12) When you click on the circle you will be taken to the ***Baseline***, ***8, 16, 24h Observation Tool*** form (Appendix B).
13) Answer all the questions within the ***Baseline***, ***8, 16, 24h Observation Tool*** forms.

14) Once you complete this form, change the status of the form ***Incomplete to Complete*** and then click ***Save Record***





15) From here you will be directed back to the subjects study dashboard. The circles next to the ***Baseline***, ***8, 16, 24h Observation Tool*** forms should be ***GREEN***

If the subject crosses over to the other study treatment, repeat steps 1-10 for the ***8, 16, 24h Observation Tool*** form located under the ***Crossover of study tx*** column.

5P. Adverse Event Reporting From

1. Risks associated with second IVIG treatment

1) Infusion reaction: Usually occurs during the first 1-2 hours of the infusion and is characterized by a sudden rise in temperature accompanied by rigors, hypotension, and distress. Caution must be exercised not to confuse fever from KD with fever and systemic signs associated with an infusion reaction. Treatment for a reaction is to stop the infusion, administer acetaminophen (15 mg/kg) and diphenhydramine (1mg/kg), and resume the IVIG infusion at half the rate at which the reaction occurred. Once the infusion is tolerated, the rate can be increased per standard nursing protocols. There are no published data re: frequency of this reaction with the second IVIG infusion. The rate is 10-15% for the first infusion. In our previous infliximab clinical trial, none of 22 subjects receiving a second IVIG infusion had a reaction.
2) Pain and tenderness at the infusion site. IVIG extravasation (pH 4.0) from a leaking IV can cause a 3rd degree burn.
3) Headache (13%)(Stiehm 2013)
4) Abdominal pain (<5%)
5) Sterile meningitis (<1%)(Orbach, Katz et al. 2005)
6) Hemolytic anemia due to titers of anti-A and anti-B blood groups in the IVIG preparation. This is an emerging problem among treated patients with A, B, or AB blood types (3% in our experience at RCHSD) (Berard, Whittemore et al. 2012)

2. Risks associated with infliximab treatment

1) Reactivation of latent mycobacterial or fungal infection: History of known TB, histoplasmosis, or coccidiomycosis would exclude subject from participating in the trial. Theoretically, an unrecognized latent infection with these agents could be converted to an active infection, although this has not been reported following a single dose.
2) Infusion reactions (<1% for 1st infusion)

3. Adverse Events

An **adverse event** is any untoward medical occurrence experienced by a subject. An event constitutes a disease, a set of related symptoms or signs, or a single symptom or sign.

Adverse Events (AE) will be recorded according to the date and time of first occurrence, severity, and their duration, as well as any treatment, prescribed. Following initiation of study treatment, all new or continuing adverse events that were not present at enrollment will be recorded. Any medical condition present at the initial visit, which remains unchanged or improves, will not be recorded as an adverse event at subsequent visits. However, worsening of a medical condition that was present at the initial visit will be considered a new adverse event and reported. Abnormal laboratory values, if felt by the investigator to be clinically significant, will also be recorded on the AE form and assessed in terms of severity and relationship to study drug. Laboratory values that are abnormal at study entry and that do not worsen will not be recorded on the AE form. The Adverse Events Committee will adjudicate the adverse events and determine if the event was 'Not Related', 'Possible Related" or "Probably Related" to the study treatment. The members of the Adverse Events Committee are Jane Burns, Adriana Tremoulet, Jane Newburger, and Anne Rowley

The following will NOT be considered adverse events as these are commonly associated with KD:

Neutropenia at follow-up visit when patients typically develop lymphocytic predominance
Periungual desquamation
Thrombocytosis

4. Serious Adverse Events

An SAE is defined as any event which:

1. Is fatal; or
2. Is life-threatening (the patient was, in the view of the Principal Investigator, in immediate danger of death from the event as it occurred); or
3. Requires hospital admission or prolongs hospitalization; or
4. Is persistent or causing significant disability; or
5. Required medical intervention, such as major surgery, to prevent a serious outcome; or
6. Is associated with a congenital anomaly
7. The Clinical Site Principal Investigator considers it to be a serious adverse event.

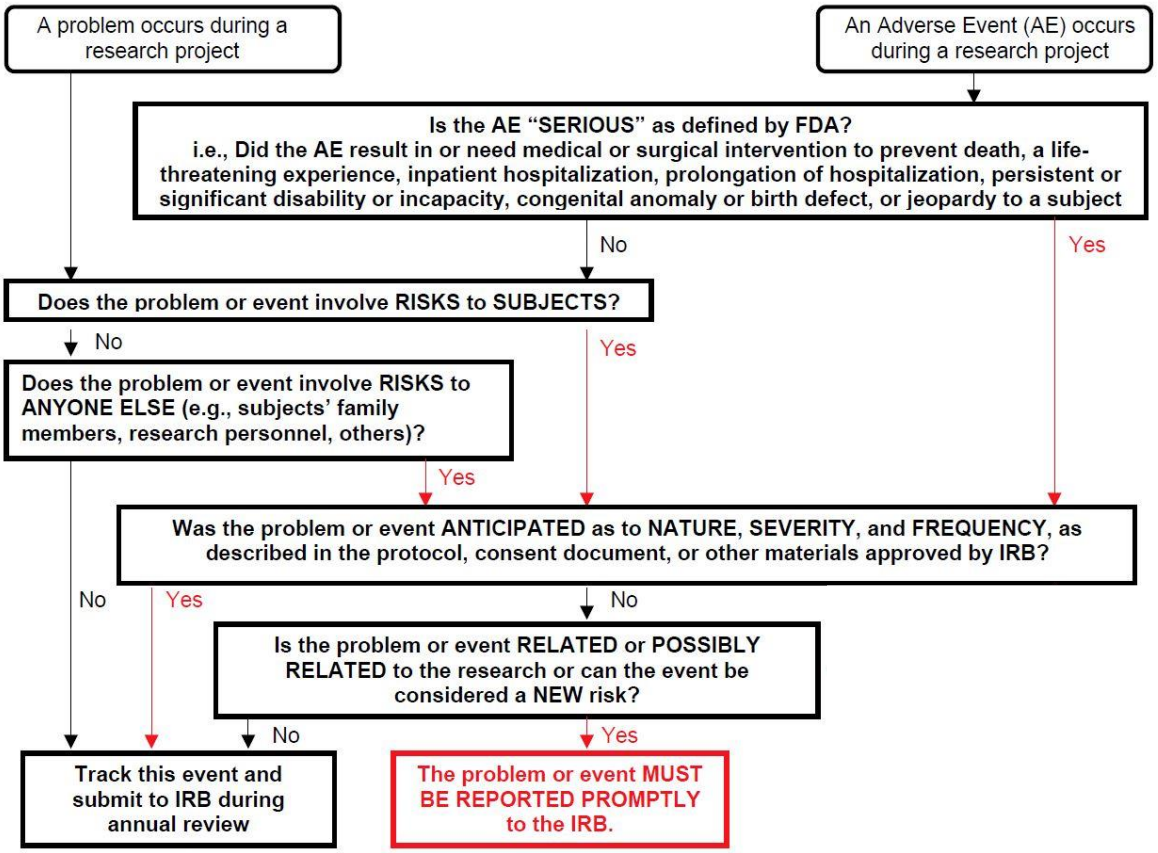
SAEs for this trial include but are not limited to, **prolonged hospitalization due to study treatment crossover,** anaphylaxis, arrhythmia, cardiac arrest, cardiogenic shock, death, hearing loss, myocardial infarction, renal failure, seizures, sepsis (confirmed), or serious infection requiring hospitalization.

Reporting Unanticipated Problems involving risk to subjects or others (URPs)

What to report. The following events meets the definition of a URP and should be reported to Samantha Roberts (sroberts@ucsd.edu) within 5 working days:

a) Any serious adverse event (SAE) (including injured, side effects, deaths or other problems) that in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was at least possibly related to the research procedures.
b) Any serious accidental or unintentional change in the IRB-approved protocol that alters the level of risk
c) Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject
d) Any new information (e.g. publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio of the research
e) Any breach in confidentiality that may involve risk to the subject or others
f) Any complaint of a subject that indicated an unanticipated risk or that cannot be resolved by the Principal Investigator

Decision Tree for Reporting Unanticipated Problems and Adverse Events in Research to the IRB and RCP



Problems/events that are unanticipated and serious should be reported to the Samantha Roberts (sroberts@ucsd.edu) within 5 working days only if in the opinion of the Principal Investigator they are possibly, probably or definitely related to the research procedures. Those serious, unanticipated problems/events that the Principal Investigator deems unlikely or not related do NOT meet the IRB's definition of UPRs; however, these events must be reported to the IRB at least annually at the time of 7-

year “re-submission” or Continuing Review submission. Please report these events in the Adverse Event Form.

Serious Adverse Events (SAEs) need to be entered into REDCap within 5 days of occurrence. PCORI requires us to report all SAEs within 10 working days.

Hemolytic Anemia

This is a serious adverse event that can happen to subjects who are randomized to receive a second dose of IVIG. Subjects with A ,B, or AB blood types are at higher risk to get hemolytic anemia. **If a subject is diagnosed with hemolytic anemia, please complete the *Adverse Event Reporting* form as well as the *Hemolytic Anemia AE* form.** The hemolytic anemia form includes some additional information that is collected once a patient is diagnosed with hemolytic anemia. Not all of the requested information is required, but strongly suggested as a work up of hemolytic anemia in patients with KD. Please include whatever information is standard of care at your institution for the work up of hemolytic anemia.

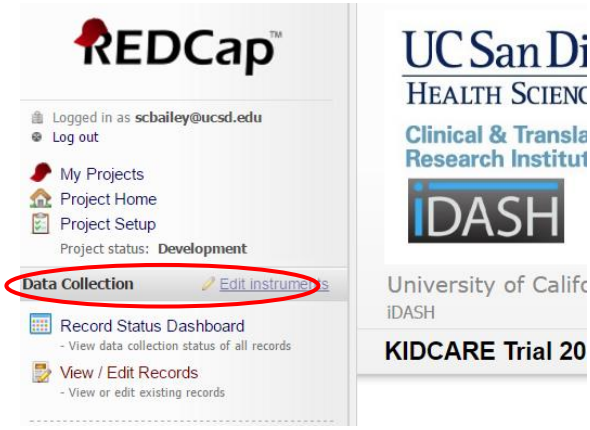
Here is a list of the information we are requesting:

- Blood Type
- Creatinine
- Total and direct bilirubin
- Plasma hemoglobin
- Urine hemoglobin
- Haptoglobin
- CBC with reticulocyte count
- Direct and indirect antiglobulin test
- Blood smear

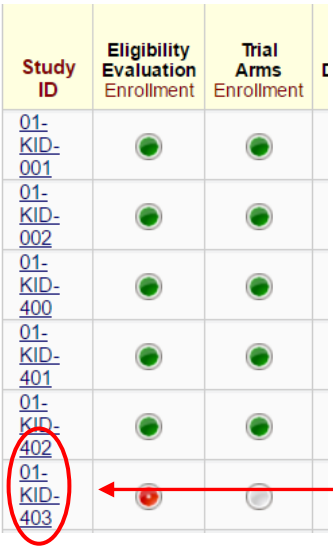
How to complete the Adverse Event Form in REDCap:

1) Go to https://cwp.ucsd.edu
2) You will log in using your AD account username and password
3) You should receive a login request on your phone from the Duo Mobile App
4) Open the Duo Mobile App on your phone and approve the login request
5) Once you have approved the login request, your browser will be directed to the Clinical Web Portal (CWP)
6) Select the KD REDCap icon
7) The REDCap database will be opened up in another web page. Under My Projects, Choose **KIDCARE Trial 2017**
8) On the left side of the REDCap portal, you will see a section labeled ***Data Collection***

9) Click on the ***Record Status Dashboard*** under this section.



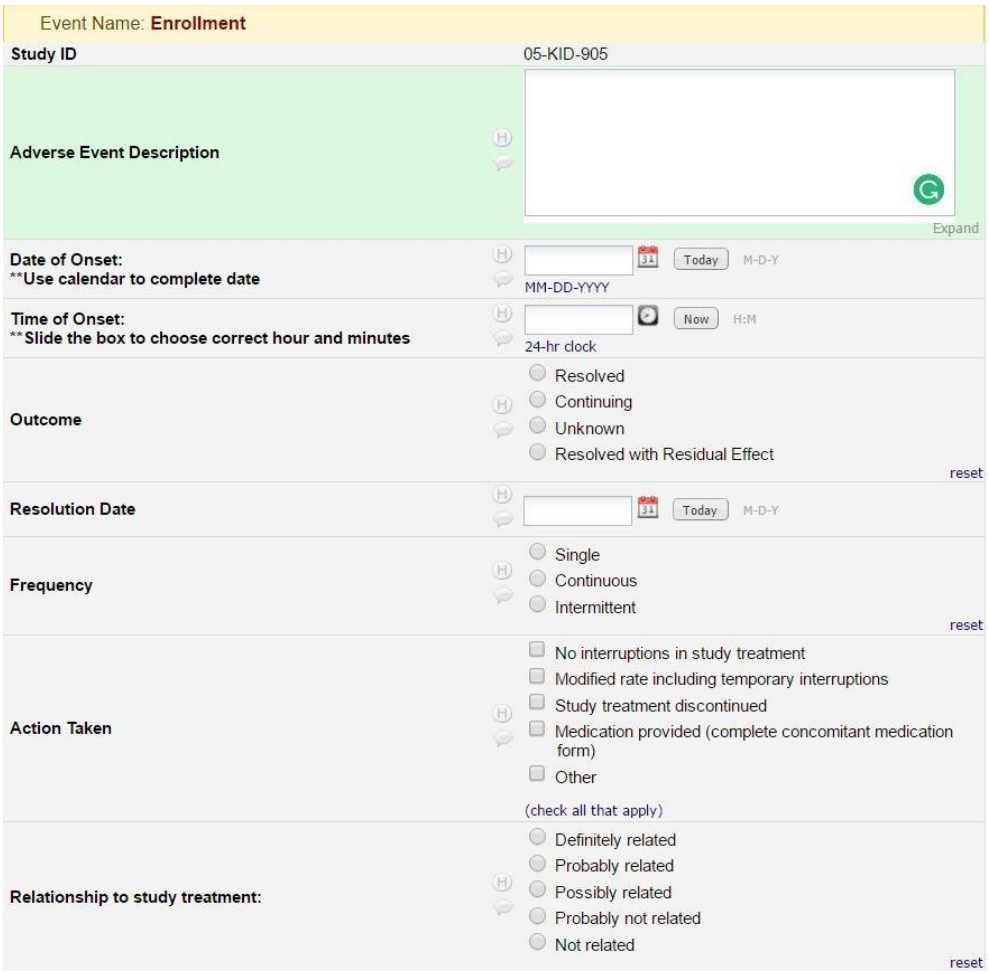
10) Click the subject ID that needs to be completed.

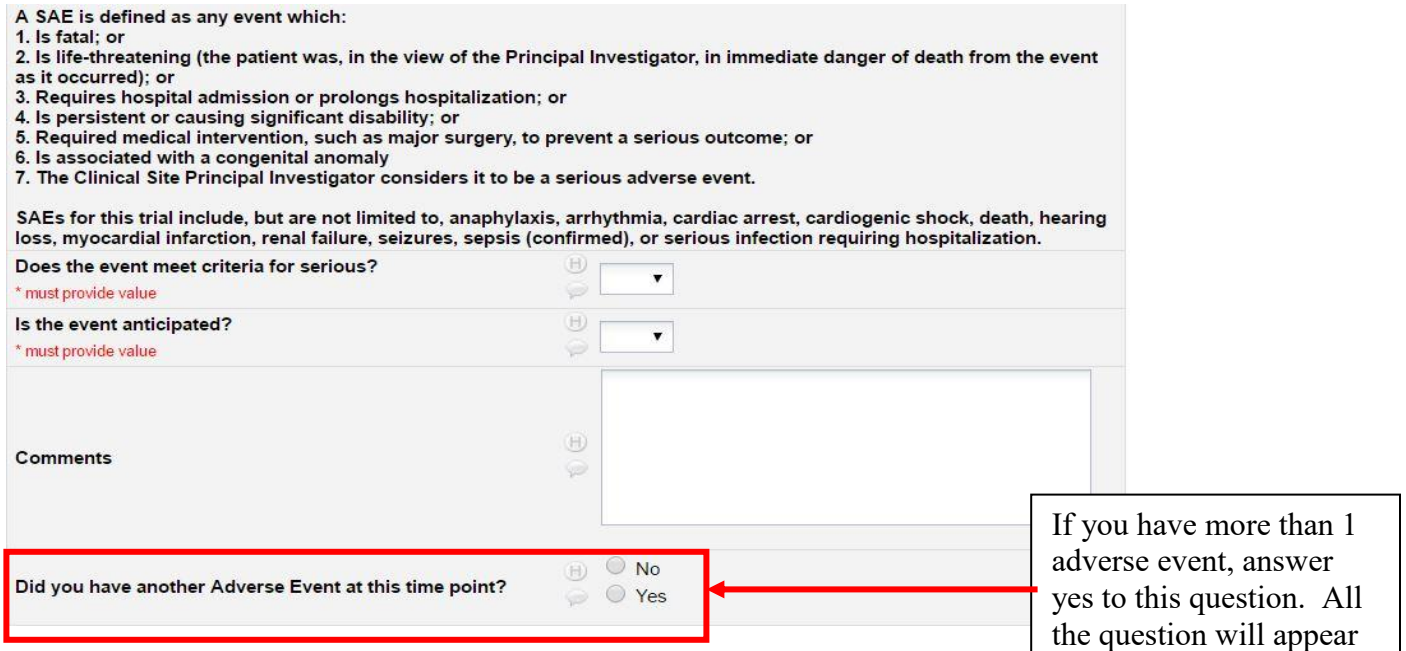


11) You will then be taken to this subjects REDCap study dashboard. This lists the time points and the forms that can be completed at each time point. You will click on the circle under the *Other Data* column and next to the ***Adverse Event*** form you need to complete. If applicable you can also complete the ***Hemolytic Anemia AE*** form, which is below the ***Adverse Event*** form.

Data Collection Instrument	Enrollment (1)	24h post INITIATION of tx (2)	24h post COMPLETION of tx (3)	Crossover Study tx (4)	Follow-Up Visit (5)	Other Data (6)
Eligibility Evaluation	●					
Trial Arms	●					
Demographics	●					
Study Drug Administration	●					
Enrollment Temperature Measurement	●					
Temperature Measurement		●	●			
Primary Temperature Outcome		●				
Secondary Temperature Outcome			●			
Laboratory Results	●		●		○	
Center Echocardiogram	●				○	○
Baseline Observation Tool (Start of Study Treatment)			●			
8 Hours After Start Of Study Treatment			●	○		
16 Hours After Start Of Study Treatment			●	○		
24 Hours After Start Of Study Treatment			●	○		
Parent Tool Follow-Up			●			
Crossover Temperature Measurement				○		
Crossover Study Drug Administration				○		
Crossover Laboratory Results				○		
Protocol Deviation Form	○	○	○	○	○	○
Adverse Event Reporting Form						○ ←
Hemolytic Anemia AE Form						○ ←
Study Completion Form					○	
Fever Days And Duration Of Hospitalization						●
Concomitant Medication						○

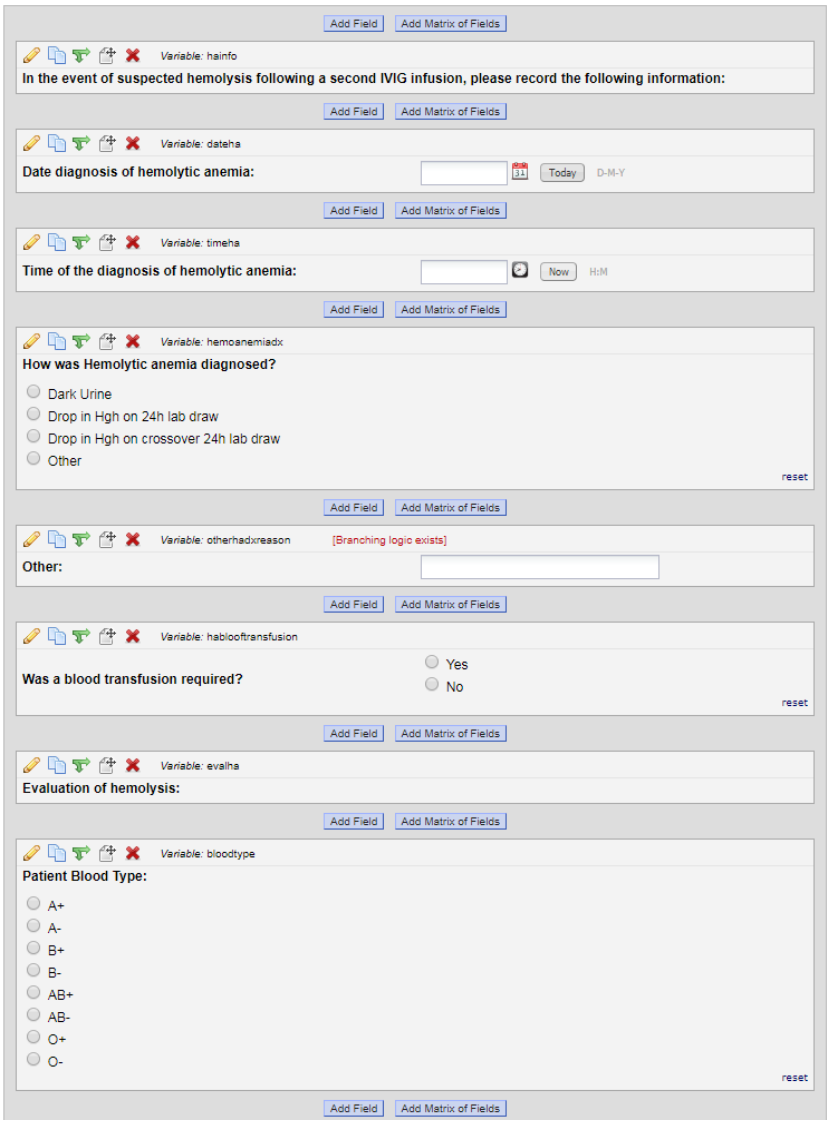
12) When you click on the circle you will be taken to the ***Adverse Event*** form
13) Answer all the questions within the ***Adverse Event*** form:

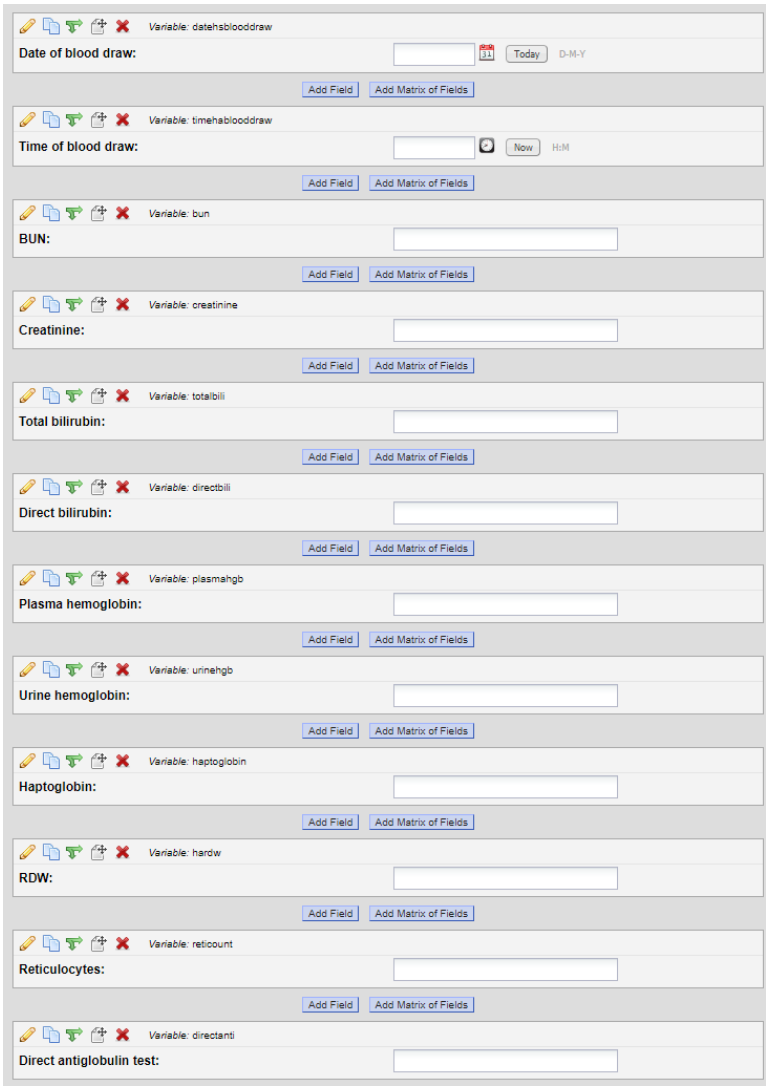




If you have more than 1 adverse event, answer yes to this question. All the question will appear again for an additional entry.

If applicable complete the ***Hemolytic Anemia AE*** Form:

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Date of blood draw:
Today
D-M-Y
Add Field
Add Matrix of Fields
Variable: timehablooddraw
Time of blood draw:
Now
H:M
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Add Matrix of Fields
Variable: bun
BUN:
Add Field
Add Matrix of Fields
Variable: creatinine
Creatinine:
Add Field
Add Matrix of Fields
Variable: totalbili
Total bilirubin:
Add Field
Add Matrix of Fields
Variable: directbili
Direct bilirubin:
Add Field
Add Matrix of Fields
Variable: plasmahgb
Plasma hemoglobin:
Add Field
Add Matrix of Fields
Variable: urinehgb
Urine hemoglobin:
Add Field
Add Matrix of Fields
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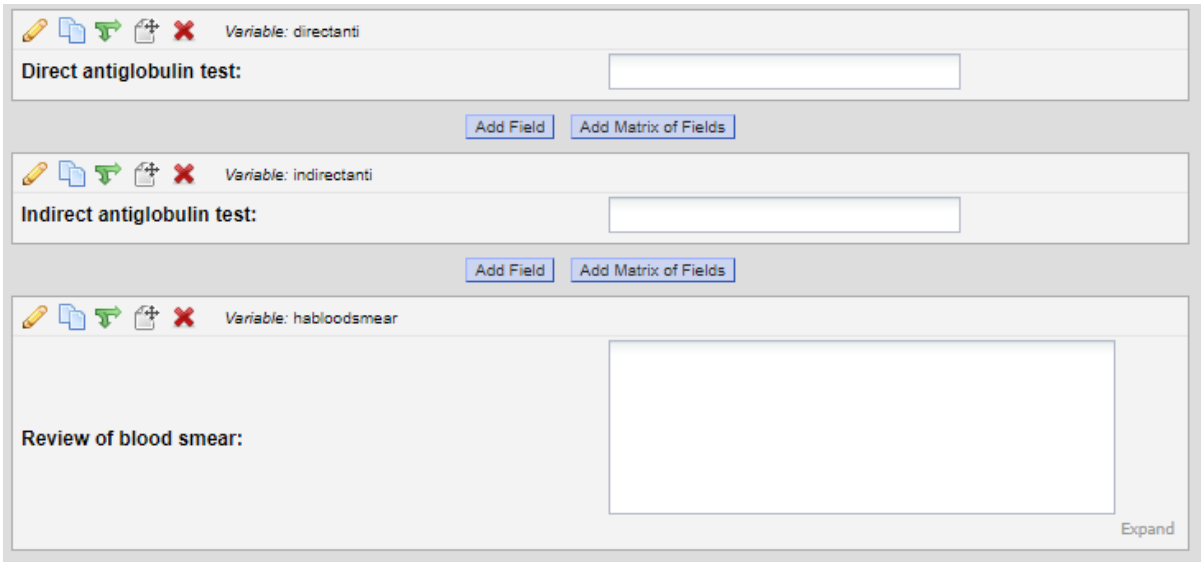
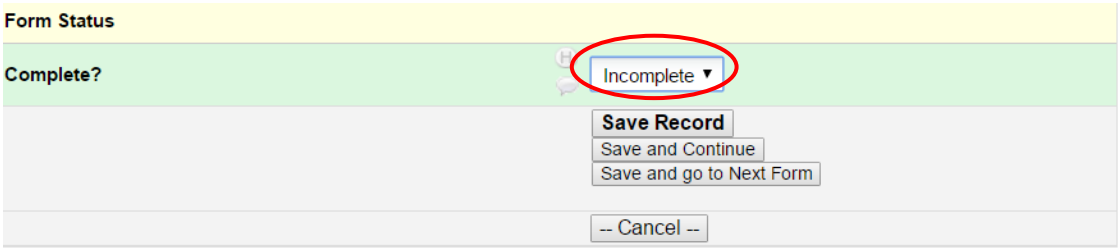
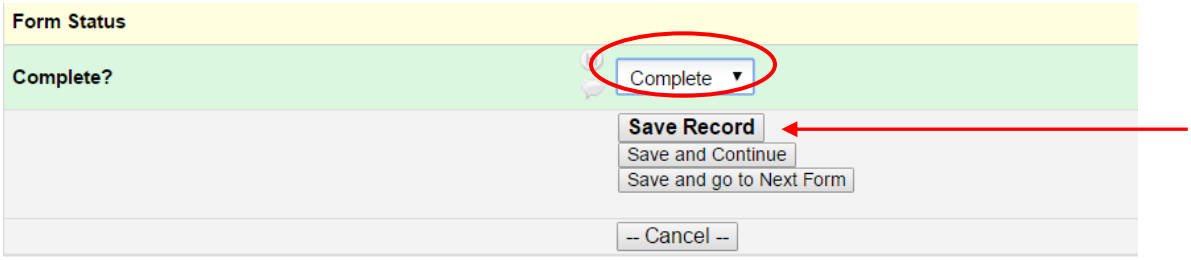
Variable: directanti
Direct antiglobulin test:


Variable: directanti
Direct antiglobulin test:
Add Field
Add Matrix of Fields
Variable: indirectanti
Indirect antiglobulin test:
Add Field
Add Matrix of Fields
Variable: habloodsmear
Review of blood smear:
Expand

14) Once you complete this form, change the status of the form ***Incomplete to Complete*** and then click ***Save Record***





15) From here you will be directed back to the subjects study dashboard. The circle next to the ***Adverse Event*** form should be ***GREEN.*** If you completed the ***Hemolytic Anemia AE*** form, that should also be ***GREEN.***

5Q. Protocol Deviations Form

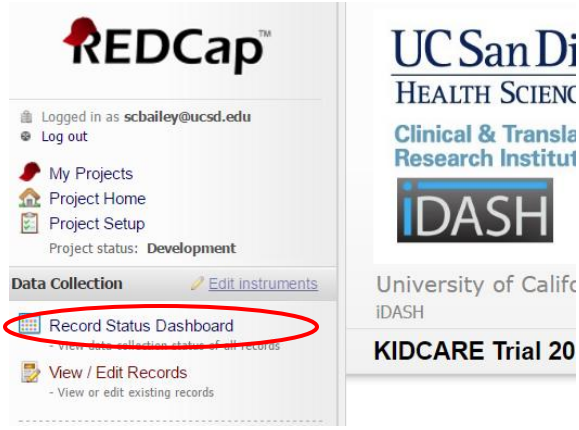
The following are examples of protocol deviations that need to be reported:

1) Temperature route if measurement is not oral, rectal, or axillary
2) Temperature is not taken at study enrollment or is taken outside the window of 24 (± 2) hours of study treatment initiation or study treatment completion.
3) Laboratory measurements not completed within 24 (± 2) hours after completion of study treatment
4) Laboratory measurements not completed within 5-18 days after completion of study treatment
5) Echocardiogram measurement not completed within 5-18 days after completion of study treatment
6) Follow-Up Visit not completed within 5-18 days after completion of study treatment

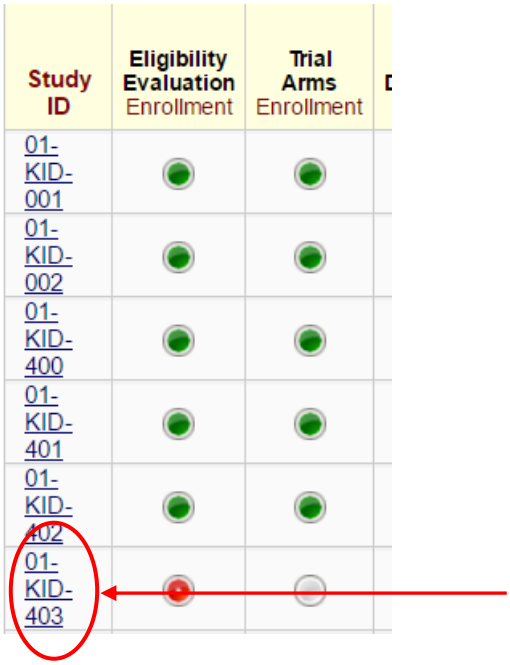
If you have a protocol deviation, please complete the protocol deviation from on iDASH REDCap

How to complete the Protocol Deviations Form in REDCap:

1) Go to https://cwp.ucsd.edu
2) You will log in using your AD account username and password
3) You should receive a login request on your phone from the Duo Mobile App
4) Open the Duo Mobile App on your phone and approve the login request
5) Once you have approved the login request, your browser will be directed to the Clinical Web Portal (CWP)
6) Select the KD REDCap icon
7) The REDCap database will be opened up in another web page. Under My Projects, Choose **KIDCARE Trial 2017**
8) On the left side of the REDCap portal you will see a section labeled ***Data Collection***
9) Click on the ***Record Status Dashboard*** under this section.



10) Click the subject ID that needs to be completed.



11) You will then be taken to this subjects REDCap study dashboard. This lists the time points and the forms that can be completed at each time point. You will click on the circle under the column and next to the ***Protocol Deviation*** form you need to complete. You can complete this ***Protocol Deviation*** form at any time point. Enter the adverse event into to the time point it happened closest to.

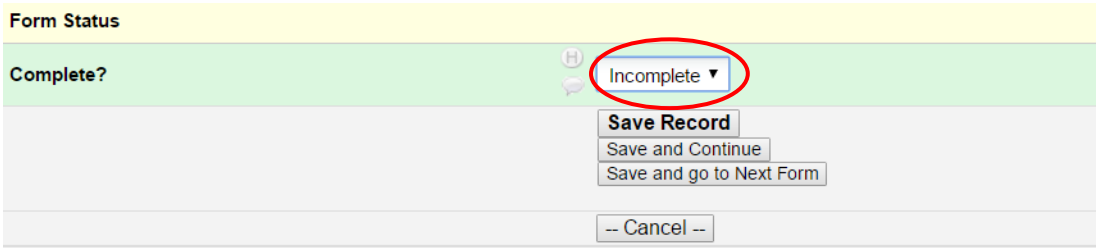
Data Collection Instrument	Enrollment (1)	24h post initiation of tx (2)	24h post completion of tx (3)	Crossover of study tx (4)	Follow-up Visit (5)	Other Data (6)
Eligibility Evaluation	●					
Trial Arms	●					
Demographics	○					
Study Drug Administration	○					
Enrollment Temperature Measurement	●					
Temperature Measurement		●	○			
Primary Temperature Outcome		●				
Secondary Temperature Outcome			●			
Laboratory Results	●		○		○	
Center Echocardiogram	●				○	○
Baseline Observation Tool (Start of Study Treatment)			○			
8 Hours After Start Of Study Treatment			○	○		
16 Hours After Start Of Study Treatment			○	○		
24 Hours After Start Of Study Treatment			○	○		
Parent Tool Followup			○			
Crossover Temperature Measurement				○		
Crossover Study Drug Administration				○		
Crossover Laboratory Results				○		
Protocol Deviation Form	○	○	○	○	○	○

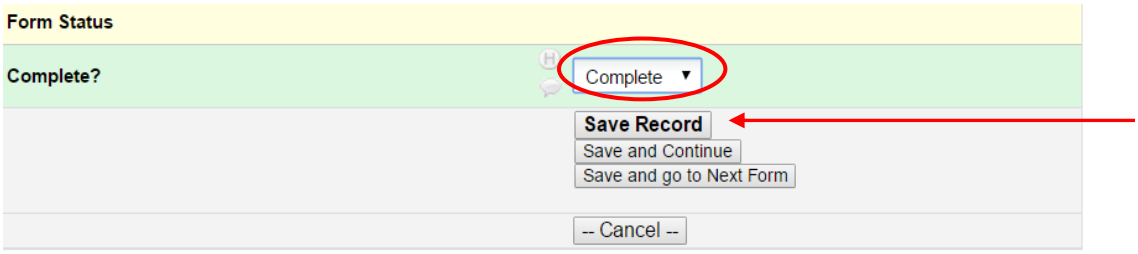
12) When you click on the circle you will be taken to the ***Protocol Deviation*** form

Event Name: **Enrollment**

Study ID	01-KID-403
Date of occurence ****Use calendar to complete date**	Today M-D-Y MM-DD-YYYY
Describe the protocol deviation:	Expand
Explain the reason for the protocol deviation:	Expand
Was the subject adversely affected by the deviation?	if Yes, complete AE form
Describe action taken to prevent recurrence:	Expand

13) Answer all the questions within the ***Protocol Deviation*** form
14) Once you complete this form, change the status of the form ***Incomplete to Complete*** and then click ***Save Record***





15) From here you will be directed back to the subject's study dashboard. The circle next to the ***Protocol Deviation*** form should be ***GREEN***

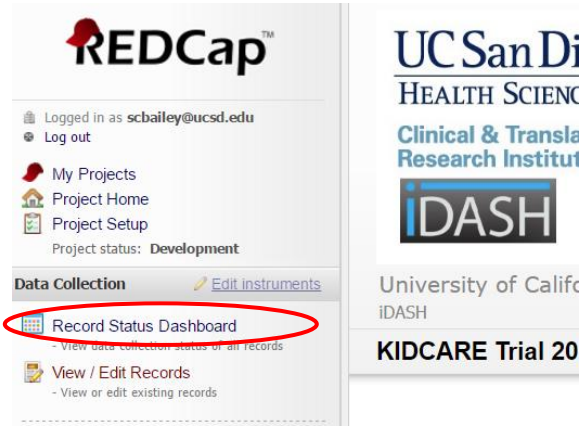
5R. Study Completion From

Completed this form at the follow-up study Visit

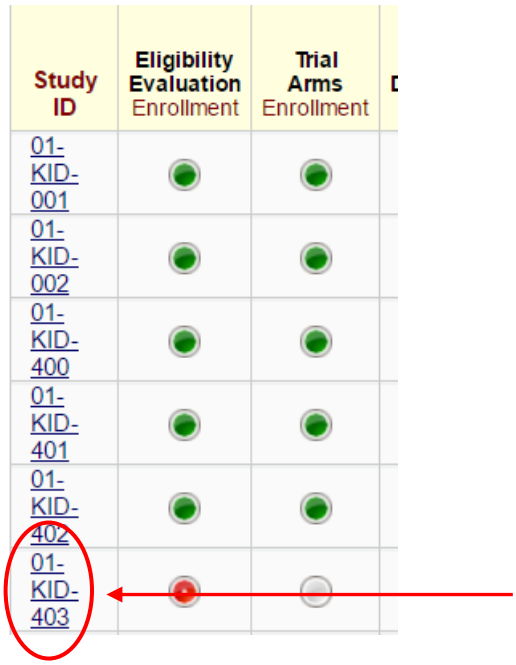
How to complete the Study Completion Form in REDCap:

1) Go to https://cwp.ucsd.edu
2) You will log in using your AD account username and password
3) You should receive a login request on your phone from the Duo Mobile App
4) Open the Duo Mobile App on your phone and approve the login request
5) Once you have approved the login request, your browser will be directed to the Clinical Web Portal (CWP)
6) Select the KD REDCap icon
7) The REDCap database will be opened up in another web page. Under My Projects, Choose **KIDCARE Trial 2017**
8) On the left side of the REDCap portal, you will see a section labeled ***Data Collection***

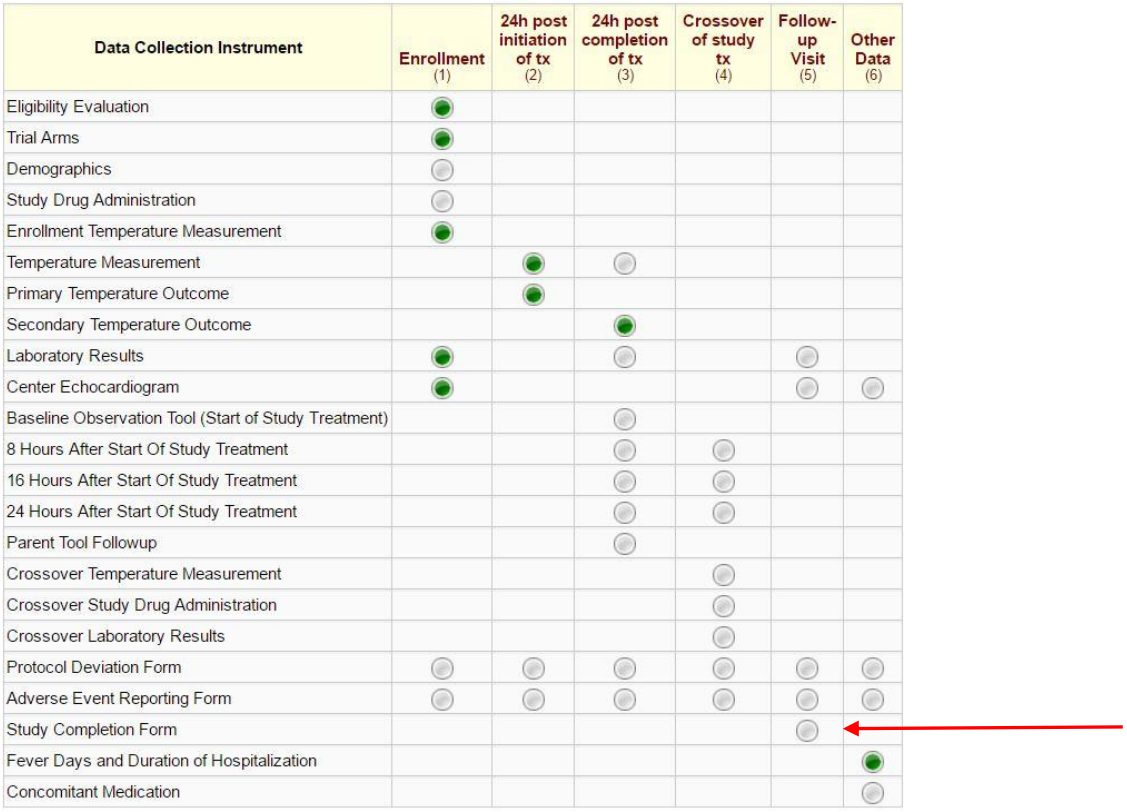
9) Click on the ***Record Status Dashboard*** under this section.



10) Click the subject ID that needs to be completed.

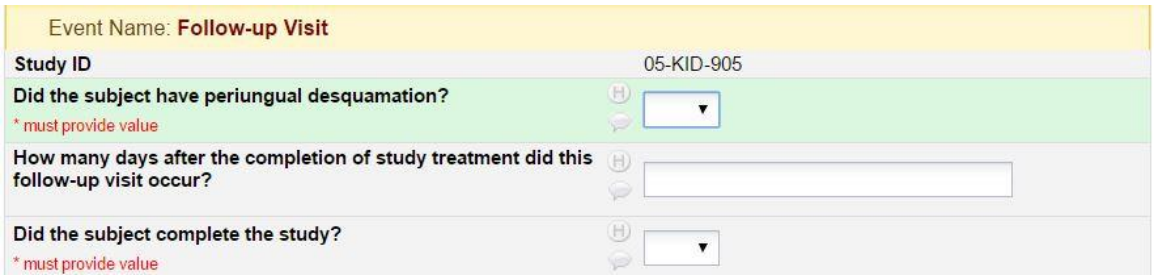


11) You will then be taken to this subjects REDCap study dashboard. This lists the time points and the forms that can be completed at each time point. You will click on the circle under the ***Follow-Up Visit*** column and next to the ***Study Completion*** form you need to complete.



Data Collection Instrument	Enrollment (1)	24h post initiation of tx (2)	24h post completion of tx (3)	Crossover of study tx (4)	Follow-up Visit (5)	Other Data (6)
Eligibility Evaluation	●					
Trial Arms	●					
Demographics	○					
Study Drug Administration	○					
Enrollment Temperature Measurement	●					
Temperature Measurement		●	○			
Primary Temperature Outcome		●				
Secondary Temperature Outcome			●			
Laboratory Results	●		○		○	
Center Echocardiogram	●				○	○
Baseline Observation Tool (Start of Study Treatment)			○			
8 Hours After Start Of Study Treatment			○	○		
16 Hours After Start Of Study Treatment			○	○		
24 Hours After Start Of Study Treatment			○	○		
Parent Tool Followup			○			
Crossover Temperature Measurement				○		
Crossover Study Drug Administration				○		
Crossover Laboratory Results				○		
Protocol Deviation Form	○	○	○	○	○	○
Adverse Event Reporting Form	○	○	○	○	○	○
Study Completion Form					○	
Fever Days and Duration of Hospitalization						●
Concomitant Medication						○

12) When you click on the circle you will be taken to the ***Study Completion*** form

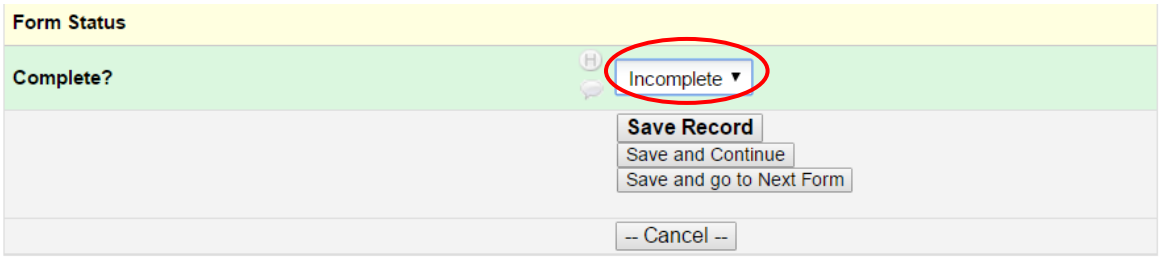


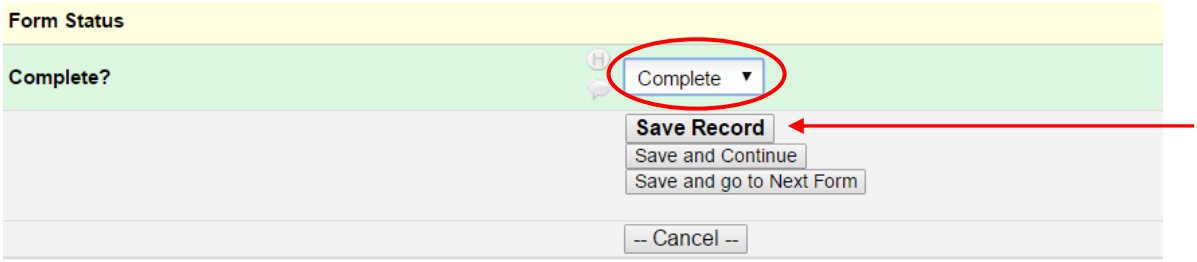
Event Name: **Follow-up Visit**

Study ID	05-KID-905
Did the subject have periungual desquamation? * must provide value	
How many days after the completion of study treatment did this follow-up visit occur?	
Did the subject complete the study? * must provide value	

13) Answer all the questions within the ***Study Completion*** form

14) Once you complete this form, change the status of the form ***Incomplete to Complete*** and then click ***Save Record***





15) From here you will be directed back to the subject's study dashboard. The circle next to the ***Study Completion*** form should be ***GREEN***

6. Additional Therapy

6A. Crossover treatment

Subjects with a fever (T ≥38°C orally or rectally or ≥37.5°C axillary/ T ≥100.4°F orally or rectally or ≥ 99.5°F axillary) at 24 hours after completion of 1st study treatment will cross-over to receive the other study treatment. You will need to document this in REDCap. This is also considered a Serious Adverse Event (SAE), since this additional treatment will prolong the hospitalization of the subject. You will need to complete the following forms:

1) Crossover Drug Administration Form
2) Crossover Temperature Form
3) Crossover Laboratory Results Form
4) 8, 16, 24hr Observation Tool
5) Adverse Event Reporting form

6B. Management of Treatment-resistant Subjects

Treatment-resistance will be defined as persistent or recrudescent fever (T ≥38°C orally or rectally or ≥37.5°C axillary/ T ≥100.4°F orally or rectally or ≥ 99.5°F axillary) ≥ 24 hours and <7 days following completion of infusion of the 2nd (crossover) study treatment. Subjects who meet criteria for treatment-resistance will be treated at the Center PI's discretion. Treatments will be recorded on the Concomitant Medication Form.

6C. Additional Therapy for Coronary Artery Abnormalities

Additional therapy for coronary artery abnormalities will be at the Center PI's discretion. If possible, additional anti-inflammatory therapies (steroids, cyclosporine, cyclophosphamide) should be avoided. However, if clinically indicated in the opinion of the Center PI, the subject should remain on study and all ancillary treatment should be recorded on the Con Med CRF. Cardiac medications (B-blockers, enoxaparin, dobutamine, etc.) are administered at the discretion of the Center PI and recorded on the Con Med CRF.

6D. Allowable concomitant medications

The following medications may be given after patient enrollment into the study:

1) Acetominophen: may be administered for documented fever but should NOT be given to treat pain (e.g. headache, joint pain) during hospitalization. If administered at home while on study, parent should be queried about medication usage and this should be documented at the follow-up visit.
2) Naproxen: may be administered for arthralgia/arthritis, suggested dose of 15 mg/kg/day divided q12h for 5 days; suspend aspirin therapy while on naproxen. This therapy may mask fever and should only be used when clearly clinically indicated.
3) Opioids: may be administered for pain

This information will be entered into REDCap at the following time points (Appendix C):

1) Enrollment
2) 24 hours post imitation of study treatment
3) 24 hours post completion of study treatment
4) Follow-up study visit
5) Any other time from enrollment to the follow-up study visit

The following medications should NOT be administered to patients while on study:

1) Ibuprofen while taking ASA

7. Privacy and Confidentiality of Data

Study personnel at each site will log on to the private study portal on the REDCap web page with individual user names and passwords to securely perform study data entry and edits.

1. Data Access: Access to research data collected in this trial will be restricted to study team members at each site and UCSD study personnel. REDCap features include individualized user roles and privileges, password and user authentication security, SSL encryption, comprehensive auditing to record and monitor access and data changes, and electronic signatures (http://www.project-redcap.org/software.php).

2. Server Security: The database will be stored on a secure electronic server with user name and password log on for individual users and will be backed up nightly. The REDCap servers are virtual machines (VMs) located on secure UCSD CTRI space.

Data privacy: Sensitive and protected health information (PHI) will not be collected as part of this clinical trial. The trial investigators are committed to uphold the highest ethical standard in addition to internationally recognized standards of privacy protection for ensuring responsible patient data use. Computer and database security: Access to data and applications can be defined on a per user basis. Direct

database access is strictly controlled. User access to each data set/table must be explicitly granted. Every transaction performed on the database is logged with a timestamp and user information to establish an audit log, as outlined by FDA guidelines (CFR 21, Part 11).

8. Statistical Considerations

8A. Power and Sample Size Justification

The study is sufficiently powered for a superiority clinical trial. For the primary endpoint, if we assume 53 evaluable subjects per group (total N=106) in this 2-arm trial, we will have 80% power to detect a difference between the group proportions of 0.155. We assume that the reference group proportion (i.e. 2nd IVIG arm is 67%, i.e. 8 of 12 patients responding will be similar to our published clinical trial (Burns, Best et al. 2008). The infliximab arm proportion is assumed to be 89% (based on published clinical trial, i.e. 11 of 12 patients responding). The power was computed for the case in which the actual infliximab arm proportion is lower at 82.5%. Statistical power is based on a two-sided, two sample binomial test for proportions, and a two-sided alpha=0.05 was used. Subjects will be in the study for two weeks following administration of study drug and there is a possibility that subjects could be lost to follow-up. Assuming 5% attrition, we will need to enroll 112 subjects to get 106 evaluable patients.

8B. Statistical Analysis Plan

This section briefly describes the planned statistical analysis. The Statistical Analysis Plan (SAP) provides details. In case the language in this section differs from the language in the SAP, the SAP takes precedence. The SAP will be finalized prior to the study's database lock.

Since this is a superiority study design, an intent-to-treat (ITT) analysis will be used to analyze the outcome data regarding patient outcomes. Results will be reported as point estimates (odds ratios or mean differences across groups, as appropriate) and interval estimates (95% confidence intervals). All tests of significance for the secondary outcomes will be 2-sided and Hochberg adjustments will be made for multiple comparisons. A p-value ≤ 0.05 will be considered statistically significant. Statistical analysis will be conducted using the statistical software R 3.3.2. (www.rproject.org). Demographic and baseline characteristics will be compared between the study arms using Fisher's exact test for categorical variables, and a two-sample t-test for continuous variables. Appropriate non-parametric alternatives will be considered, if parametric assumptions fail. There will be no planned interim analyses for efficacy or futility conducted for this study, but the Data and Safety Monitoring Board (DSMB) may modify this during ongoing safety monitoring.

Analysis of Primary Outcome:
The primary outcome (Specific Aim 1) of the study is cessation of fever within the specified time frame, which is a dichotomous (binary) variable. Comparison between the infliximab and second IVIG arms will be compared using a Fisher's exact test for proportions. Differences in the rates between the two groups, along with the odds ratio (OR) and their 95% confidence intervals will be reported. As a secondary/sensitivity analysis, multivariable logistic regression analysis will be performed to study the association between clinical and demographic factors (age < 1 yr., sex, ESR, WBC, ANC, CRP) and intervention arm, adjusting for baseline demographic, stratification variables, and clinical characteristics. Variables significantly associated with both treatment group and outcome ($p<0.10$) will be included in a multivariable logistic regression model as covariates.

Analysis of Secondary Outcomes:
The first secondary outcome will test the hypothesis that infliximab treatment will result in more rapid resolution of inflammation compared to second IVIG as measured by WBC, ANC, and levels of CRP at 24 hours and 5-18 days following completion of study treatment. We cannot make power estimates for this secondary aim as there are no prior data to guide assumptions. Comparisons between the Infliximab and second IVIG arms will be compared using a two-sample, two-sided t-test at each time point separately. Point estimates and their 95% confidence intervals will be reported. As a secondary/sensitivity analysis, multiple linear regression at each time point will be performed to study the association between clinical and demographic factors (age < 1 yr., sex, ESR, WBC, and ANC) and intervention arm, adjusting for baseline demographic, stratification variables, and clinical characteristics, including baseline CRP. Variables significantly associated with both treatment group and outcome ($p<0.10$) will be included in a multiple regression model as covariates. Appropriate non-parametric alternatives will be considered, if parametric assumptions fail. A mixed model repeated measures (MMRM) model with three repeated measures (baseline, 24 hours, and at 5-18 days following completion of study treatment) will evaluate changes between the study arms for the major dependent variables, i.e. WBC, ANC, and CRP. Participants will only be included in the MMRM model if they have both a baseline and at least one post-baseline measurement. The model will include as the dependent variable the change from baseline in the inflammation variable at each post-baseline visit for each dependent inflammation marker separately. Independent variables in the MMRM model will include treatment arm, visit, treatment arm-by-visit interaction, the inflammation variable at baseline and other covariates. Visits will be treated as a categorical variable. Unstructured variance-covariance structure will be used.

Analysis of Secondary Outcomes:
This secondary outcome (Specific Aim 3) will test the hypothesis that infliximab treatment will result in a change in coronary artery Zworst score of ≥ 0.5 standard deviation units as compared to second IVIG at 5-18 days following completion of study treatment measured by echocardiography. We cannot make power estimates for this secondary aim as this there are no prior data to guide assumptions. Methods analogous to the analysis of Specific Aim 2 will be applied, including t-tests and regression models. There is a concern about inter-rater reliability of different readers for the echocardiograms at the 25 sites. Inter-rater reliability analysis will be conducted using Cohen's Kappa statistics and multi-level modeling to measure agreement. In addition, to minimize disagreement, the Coordinating Center has developed manuals used in previous clinical trials to help standardize performance of echocardiograms and the measurement of the coronary arteries. During the run in period, a de-identified echocardiogram on a KD patient will be submitted to the coordinating center at UCSD and the quality will be assessed and feedback given to the center PI.

Analysis of Parent Observation Tool:
We have already engaged the advisory board in development of this aim beginning with the pSCANNER grant in 2015. Within the first two months of this project, we will conduct in-depth, semi-structured interviews of 6 parents who have recently had a child treated with IVIG and treated with infliximab to further understand the experience of the different treatments and confirm PROs of relevance to patients/parents. Qualitative analysis will be performed using a grounded theory approach to inductively develop themes (Charmaz 2006, Corbin and Strauss 2014). The research team and advisory board will create questions that represent the categories of themes. The questionnaire will then be pre-tested with 6 KD parents with children recently treated for KD at UC San Diego or UC Davis for logic and clarity using cognitive interviewing by phone (Beatty and Willis 2007). The questionnaire will be implemented with parents whose children are enrolled in the trial in order to compare the PROs and experience of treatment. The questionnaire responses will be numerically tabulated overall and by study arm. The results of the analysis will be summarized descriptively (point estimates and confidence intervals). The amount of

missing data will also be evaluated and compared between study arms. Comparisons by study arm will be evaluated by a two-sample t-test if parametric assumptions hold. If the assumptions are violated, we will compare treatment arms by the Wilcoxon rank sum test. No adjustments for multiple comparisons will be made, since the questions will be determined *a priori* as the questions of interest that will determine parental preference to the treatment arms. In addition, multiple regression (Likert scaled items) and logistic regression (binary items) will be applied to assess the contribution of demographic factors, e.g. age of child and parent, and experiential factors, e.g. previous illnesses, on the ratings of items. Open-ended questions will be analyzed with thematic content analysis based on grounded theory as described above.

8C. Evaluation of Safety Outcomes

Demographic and disposition data, drug administration, medical history, prior and concomitant medications, adverse events (AEs), clinical laboratory measurements, vital signs, physical exam (PE) findings, and all other safety data will be listed by subject and time point. All subjects who receive any study medication (even if infusion is stopped prematurely) will be included in the safety analysis. All safety data, including AEs, serious adverse events (SAEs), vital sign data, PE findings, clinical laboratory test results, and concomitant medications, will be listed by subject. Adverse events will be summarized by method of collection type, frequency, severity, relationship to study drug, any change in study drug administration, and number of subjects per treatment. The severity of all AEs and all hematologic and biochemical toxicities will be rated according to a pre-specified rating system to be finalized at the first All-Hands investigator meeting. Changes in PE and laboratory values that are expected will be excluded as AEs. For example, normocytic, normochromic anemia and peeling of the extremities are expected as the normal evolution of the disease process. However, hemolytic anemia (a potential risk for second IVIG arm) or upper respiratory tract infection (a potential risk for infliximab arm) would not be expected and would be classified as AEs. Frequency of treatment-emergent AEs and SAEs will be described by each treatment group and compared using Fisher Exact tests. These data will be included in monthly reports prepared for the study team and in the regular reporting to the DSMB.

9. Data Safety Monitoring Board

The clinical trial will utilize a DSMB to evaluate ongoing data from this randomized phase III trial. The board will be composed of a pediatric infectious disease specialist, a pharmacologist, a pediatric cardiologist and a biostatistician who are not investigators in this specific project and have no real or potential conflicts of interest with the clinical study.

The DSMB will meet every six months (or more frequently, if desired by the committee) to review enrollment and safety data. The proposed study will not have any planned interim analyses for efficacy or futility. The safety review will be prepared by the biostatistician, Dr. Sonia Jain. An open review will include demographics and trial summary for the total population. The committee, statistician, Project Manager, and the PI will attend the open portion. During the closed review, the PI and other study personnel will not see the data reported by study arm. The committee will review safety data by arm. A formal recommendation by the DSMB committee will be given to the PI, which will be reported to the participating sites, UCSD HRPP, and PCORI as appropriate.

Appendix A: List of study sites and site investigators (from west to east)

Site No.	Collaborating Organization	PI
01	**University of California San Diego/Rady Children's Hospital**	Jane Burns Adriana Tremoulet
03	Children's Hospital of Orange County	Negar Ashouri
04	Miller Children's Hospital, Long Beach	David Michalik
05	Harbor-UCLA Medical Center	Sylvia Yeh
06	Children's Hospital Los Angeles, Division of Cardiology	Jackie Szmuszkovicz
07	David Geffen School of Medicine at UCLA	Yvonne Bryson
08	Cedars-Sinai Medical Center	Moshe Arditi
09	Stanford School of Medicine	Cornelia Dekker
10	UCSF Benioff Children's Hospital-Oakland	Gregory Kurio
11	UCSF Benioff Children's Hospital-San Francisco	Amy McNelis
12	UC Davis Children's Hospital	Katherine Kim
13	Seattle Children's	Michael Portman
14	University of Utah Health Care	Dongngan Truong
15	Children's Hospital Colorado	Pei-Ni Jone
16	Texas Children's Hospital	S. Kristen Sexson Tejtel
17	Children's Health, University of Texas Southwestern Medical Center	Kavita Sharma, M.D.
18	University of South Dakota, Sanford School of Medicine	Archana Chatterjee
19	Children's Mercy, Kansas City	Mary Anne Jackson
20	Arkansas Children's Hospital	Jose Romero
21	Batson Children’s Hospital	Rana El Feghaly

22	The Ann & Robert H. Lurie Children's Hospital of Chicago	Anne Rowley
23	The University of Chicago Department of Pediatrics	Robert Daum
24	Vanderbilt School of Medicine	Natasha Halasa
25	Emory University School of Medicine	David Lloyd
26	Nationwide Children's Hospital	Guliz Erdem
27	Children's National Health System	Roberta DeBiasi
29	Maria Fareri Children's Hospital at Westchester Medical Center	Supriya Jain, M.D.
30	Children's Hospital Boston	Jane Newburger
31	Riley Children's Hospital	John Manaloor
32	University of Nebraska Medical Center	Kari Simonsen
33	Children's Hospital of Michigan	Jocelyn Ang
34	Children's Hospital of Pittsburgh of UPMC	Margalit Rosenkranz
35	The University of Alabama at Birmingham	Nichole Samuy

Appendix B: Parent observation tool

Study ID _____ **Date _____**
(To be filled in by study doctor)

Please use this form to record observations about your child during treatment. We ask that you record these observations at four times during the first 24-hour period that your child is in the study:

5. Start of study treatment
6. 8 hours after start of treatment
7. 16 hours after start of treatment
8. 24 hours after start of treatment.

If your child receives an additional study treatment, we ask that you also record for the second 24-hours.

4. 8 hours after start of second treatment
5. 16 hours after start of second treatment
6. 24 hours after start of second treatment.

Before you leave the hospital return this form to _____ (your study doctor).

Study ID _____ Date _____ Time recorded _____ am/pm

A. Start of study treatment.

	At any time from end of first IVIG until start of the current treatment did your child show any of the following signs or symptoms?	**Check ☑ Yes or**	**No**
1	Does your child seem like his/her usual self?	☐	☐
2	Rash	☐	☐
3	Red/bloodshot eyes	☐	☐
4	Eyes are sensitive to light	☐	☐
5	Swelling in hands	☐	☐
6	Redness on hands/fingers	☐	☐
7	Swelling in feet	☐	☐
8	Redness on feet/toes	☐	☐
9	Peeling on hands/fingers	☐	☐
10	Peeling on feet/toes	☐	☐
11	Headache	☐	☐
12	Muscle/Joint Pain	☐	☐
13	Difficulty eating or drinking	☐	☐
14	Unwilling to smile	☐	☐
15	Irritability	☐	☐
16	Lack of interest in playing	☐	☐
17	Lack of interest in physical activity	☐	☐
18	Lack of interest in interacting with others	☐	☐
19	Difficulty falling or staying asleep	☐	☐
20	Describe any other issues you notice such as pain, discomfort, or unusual behaviors that appeared during this period. Any other comments?		

Study ID _____ Date _____ Time recorded _____ am/pm

B. 8 hours after start of study treatment.

	At any time from start of the study treatment did your child show any of the following signs or symptoms?	**Check ☑ Yes**	**or No**
1	Does your child seem like his/her usual self?	☐	☐
2	Rash	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
3	Red/bloodshot eyes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
4	Eyes are sensitive to light	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
5	Swelling in hands	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
6	Redness on hands/fingers	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
7	Swelling in feet	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
8	Redness on feet/toes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
9	Peeling on hands/fingers	☐	☐
10	Peeling on feet/toes	☐	☐
11	Headache	☐	☐
12	Muscle/Joint Pain	☐	☐
13	Difficulty eating or drinking	☐	☐
14	Unwilling to smile	☐	☐
15	Irritability	☐	☐
16	Lack of interest in playing	☐	☐
17	Lack of interest in physical activity	☐	☐
18	Lack of interest in interacting with others	☐	☐
19	Difficulty falling or staying asleep	☐	☐
20	Describe any other issues you notice such as pain, discomfort, or unusual behaviors that appeared during this period. Any other comments?		

Study ID _____ Date _____ Time recorded _____ am/pm

C. 16 hours after start of study treatment.

	At any time within 8 to 16 hours since the start of the study treatment did your child show the following signs or symptoms?	**Check ☑ Yes or No**	
1	Does your child seem like his/her usual self?	☐	☐
2	Rash	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
3	Red/bloodshot eyes		
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
4	Eyes are sensitive to light	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
5	Swelling in hands		
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
6	Redness on hands/fingers	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
7	Swelling in feet		
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
8	Redness on feet/toes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
9	Peeling on hands/fingers		
10	Peeling on feet/toes	☐	☐
11	Headache		
12	Muscle/Joint Pain	☐	☐
13	Difficulty eating or drinking		
14	Unwilling to smile	☐	☐
15	Irritability		
16	Lack of interest in playing	☐	☐
17	Lack of interest in physical activity	☐	☐
18	Lack of interest in interacting with others	☐	☐
19	Difficulty falling or staying asleep	☐	☐
20	Describe any other issues you notice such as pain, discomfort, or unusual behaviors that appeared during this period. Any other comments?		

Study ID _____ Date _____ Time recorded _____ am/pm

D. 24 hours after start of study treatment.

	At any time within 16 to 24 hours since the start of the study treatment did your child show the following signs or symptoms?	**Check ☑ Yes**	**or No**
1	Does your child seem like his/her usual self?	☐	☐
2	Rash	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
3	Red/bloodshot eyes		
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
4	Eyes are sensitive to light	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
5	Swelling in hands		
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
6	Redness on hands/fingers	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
7	Swelling in feet		
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
8	Redness on feet/toes	☐	☐
	If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse		
9	Peeling on hands/fingers		
10	Peeling on feet/toes	☐	☐
11	Headache		
12	Muscle/Joint Pain	☐	☐
13	Difficulty eating or drinking		
14	Unwilling to smile	☐	☐
15	Irritability		
16	Lack of interest in playing	☐	☐
17	Lack of interest in physical activity	☐	☐
18	Lack of interest in interacting with others	☐	☐
19	Difficulty falling or staying asleep	☐	☐
20	Describe any other issues you notice such as pain, discomfort, or unusual behaviors that appeared during this period. Any other comments?		

Day __: Study ID _____ Date _____ Time recorded _____ am/pm

	At any time in the last 24 hours did your child show the following symptoms?	**Check ☑ Yes or**	**No**
1	Fever (temperature above 38° C or 100.4° F) How was temperature measured? □ Oral □ Rectal □ Axillary (Armpit)	☐	☐
2	Does your child seem like his/her usual self?	☐	☐
3	Rash If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
4	Red/bloodshot eyes If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
5	Eyes are sensitive to light If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
6	Swelling in hands If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
7	Redness on hands/fingers If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
8	Swelling in feet If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
9	Redness on feet/toes If Yes: Compared to 8 hours ago it is ☐ Better ☐ Same ☐ Worse	☐	☐
10	Peeling on hands/fingers	☐	☐
11	Peeling on feet/toes	☐	☐
12	Headache	☐	☐
13	Muscle/Joint Pain	☐	☐
14	Difficulty eating or drinking	☐	☐
15	Unwilling to smile	☐	☐
16	Irritability	☐	☐
17	Lack of interest in playing	☐	☐
18	Lack of interest in physical activity	☐	☐
19	Lack of interest in interacting with others	☐	☐
20	Difficulty falling or staying asleep	☐	☐
21	Cold symptoms (runny nose, cough, sore throat)	☐	☐
22	Vomiting	☐	☐
23	Diarrhea	☐	☐
24	Any other illnesses	☐	☐

ELIGIBILITY EVALUATION

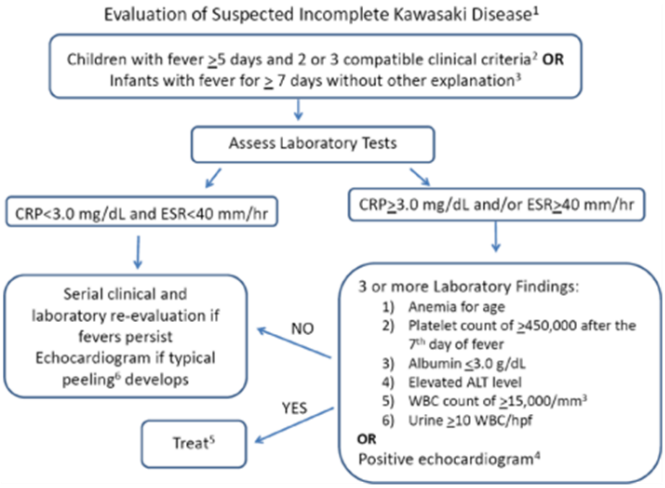
Inclusion Criteria	Yes	No
1. Is the patient at least 4 weeks to < 18 years old?		
2. Did patient have fever by parental history for 3 to 10 days prior to initial IVIG treatment?		
3. Does the patient meet AHA criteria for KD by one of the following? Please check one : ☐ Four of five clinical KD criteria (Table 1) ☐ At least 2 clinical criteria with left anterior descending /right coronary artery z-score ≥ 2.5 ☐ At least 2 clinical criteria with CRP ≥ 3 mg/dL or ESR ≥ 40 mm/hr and at least 3 supplemental laboratory criteria (Table 2)		
4. Does patient have fever (T ≥38°C orally or rectally or 37.5°C axillary) between 36 hours and 7 days after end of the first IVIG infusion <u>without other likely cause?</u>		
5. Is patient sexually active? ☐ Not applicable		
6. If patient is sexually active is he/she willing to use contraception? ☐ Not applicable		
7. Is patient, or legal representative, capable and willing to give written informed consent? Date of Informed Consent: _ _/ _ _/ _ _ _ _ (mm/dd/year) Time of Informed Consent: _____ (24-hr clock) ☐ Not applicable		

Table 1. Diagnostic criteria for KD (Adapted from American Heart Association (McCrindle et al., Circulation, 2017)):

KD standard clinical criteria :

- Erythema and cracking of lips, strawberry tongue, and/or erythema of oral and pharyngeal mucosa
- Bilateral bulbar conjunctival injection without exudate
- Rash: maculopapular, diffuse erythroderma, or erythema multiforme-like
- Erythema and edema of the hands and feet in acute phase and/or periungual desquamation in subacute phase
- Cervical lymphadenopathy (≥1.5 cm diameter), usually unilateral

Table 2. AHA Criteria for incomplete KD (McCrindle et al., Circulation, 2017)



(1) In the absence of a "gold standard" for diagnosis, this algorithm cannot be evidence based but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought any time assistance is needed. (2) Clinical findings of Kawasaki disease are listed in Table 3. Characteristics suggesting that another diagnosis should be considered include exudative conjunctivitis, exudative pharyngitis, ulcerative intraoral lesions, bullous or vesicular rash, generalized adenopathy, or splenomegaly. (3) Infants ≤6 months of age are the most likely to develop prolonged fever without other clinical criteria for Kawasaki disease; these infants are at particularly high risk of developing coronary artery abnormalities. (4) Echocardiography is considered positive for purposes of this algorithm if any of 3 conditions are met: Z score of left anterior descending coronary artery or right coronary artery ≥2.5; coronary artery aneurysm is observed; or ≥3 other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion, or Z scores in left anterior descending coronary artery or right coronary artery of 2 to 2.5. (5) If the echocardiogram is positive, treatment should be given within 10 days of fever onset or after the tenth day of fever in the presence of clinical and laboratory signs (C-reactive protein [CRP], erythrocyte sedimentation rate [ESR]) of ongoing inflammation. (6) Typical peeling begins under the nail beds of fingers and toes. ALT indicates alanine transaminase; and WBC, white blood cells

Exclusion Criteria	Yes	No
1. Has the patient been treated with infliximab or steroids for present illness (e.g. RAISE protocol)? a. Patients who received oral steroids as outpatients prior to KD diagnosis (e.g. for suspected allergic reaction) but who otherwise qualify for the study are not excluded		
2. Does the patient have any chronic disease, except asthma, atopic dermatitis, autism or controlled seizure disorder?		
3. Does the patient have a known prior infection with tuberculosis, coccidiomycosis, or histoplasmosis?		
4. Has the patient used of a TNFα blocker within the 3 months prior to enrollment?		
5. Does the patient have a history of hypersensitivity to infliximab?		
6. Does the patient have a household member with active TB?		

In order to qualify for the study, the following inclusion criteria must be met:

Inclusion criteria questions 1-2, 4, and 7 must be marked "yes".

Inclusion criteria question 3, one of the choices must be chosen.

If Inclusion criteria question 5 is "no" or "not applicable" then patient is eligible.

If Inclusion criteria question 5 is "yes" then question 6 needs to also be "yes" for the patient to be eligible.

In order to qualify for the study, exclusion criteria questions 1-6 must be marked "no"

Does the patient qualify for the study? ☐ YES ☐ NO

Trial Arms Form

Is the patient eligible for study?	☐ Yes ☐ No
Date of Randomization	_____ (MM-DD-YYYY)
Site Number	_____ (01-40)
Sex:	☐ Male ☐ Female
Age Group	☐ Less than or equal to 12 months ☐ Greater than 12 months

Subject then randomized to receive either Infliximab (10mg/kg) or Second IVIG (2g/kg)

TEMPERATURE (1st Study Drug)

Temperature recorded is the temperature-qualifying patient for study enrollment. Patient needs to have a fever T ≥38.0°C orally or rectally or T ≥37.5°C axillary/ T ≥100.4°F orally or rectally or ≥ 99.5°F axillary

	Date (mm/dd/yyyy)	Time (24 hour clock)	Temperature (indicate Centigrade or Fahrenheit)	Route			
				Oral	Rectal	Axillary	Other, Please Specify:
Aspirin (before temp measured)			N/A	N/A	N/A	N/A	N/A
Temperature qualifying subject for study enrollment							

STUDY DRUG ADMINISTRATION

Subject weight _____ kg

Subject randomized to:

☐ 2nd IVIG

☐ Infliximab

Complete appropriate table below:

2nd IVIG

Start Date:	(mm/dd/year)
Start Time:	(24-hr clock)
Stop Date:	(mm/dd/year)
Stop Time:	(24-hr clock)
Total grams administered: *Dosing protocol: 2g/kg over 8-10hr	grams
Brand:	
Lot #	

IVIG INFUSION REACTION: ☐ **Yes** ☐ **No**

If yes, complete AE form

Infliximab

Start Date:	(mm/dd/year)
Start Time:	(24hr clock)
Stop Date:	(mm/dd/year)
Stop Time:	(24-hr clock)
Total milligrams administered: *Dosing protocol: 10mg/kg over a min 2hr	mg
Brand:	

INFLIXIMAB INFUSION REACTION: ☐ **Yes** ☐ **No** **If yes, complete AE form**

TEMPERATURE (1st Study Drug)

	Date (mm/dd/yyyy)	Time (24 hour clock)	Temperature (indicate Centigrade or Fahrenheit)	Route			
				Oral	Rectal	Axillary	Other, Please Specify:
Aspirin (before temp measured)			N/A	N/A	N/A	N/A	N/A
24 hours(± 2h) from **initiation** of study treatment							

PRIMARY OUTCOME:
Was subject afebrile (<38°C rectally or orally or 37.5°C axillary/ T <100.4°F orally or rectally or < 99.5°F axillary) 24h after initiation of study treatment:

☐ **Yes** ☐ **No**

TEMPERATURE (1st Study Drug)

	Date (mm/dd/yyyy)	Time (24 hour clock)	Temperature (indicate Centigrade or Fahrenheit)	Route			
				Oral	Rectal	Axillary	Other, Please Specify:
Aspirin (before temp measured)			N/A	N/A	N/A	N/A	N/A
24 hours (± 2h) from **completion** of study treatment							

SECONDARY OUTCOME:
Was subject afebrile (<38°C rectally or orally or 37.5°C axillary /T <100.4°F orally or rectally or < 99.5°F axillary) 24h after completion of study treatment and remained afebrile until discharge:

☐ **Yes** ☐ **No**

If no, then complete Crossover Temperature Measurement Form

LABORATORY RESULTS

Please check one study visit:

☐ Baseline (pre-IVIG)
☐ 24 hours (± 2 hrs) post completion of 1st study treatment
☐ Follow up visit. 5-18 days post completion of study treatment

Hematology	Date (mm/dd/yyyy)	Time (24 hour clock)	Value	Comment
White Blood Cell Count ($X10^3$/uL)				
Hemoglobin (g/dL)				
Platelet Count ($X10^3$/uL)				
Neutrophils (%)				
Bands (%)				
Absolute Neutrophil Count (ANC)				

☐ Other (Specify) _____

Erythrocyte sedimentation rate (ESR)	Date (mm/dd/yyyy)	Time (24 hour clock)	Value	Comment
ESR (mm/hr)				
Should only be completed at enrollment and follow up visit * If ESR > 140 write in '140'				

Chemistry	Date (mm/dd/yyyy)	Time (24 hour clock)	Value	Comment
CRP (mg/dL)				

Urine pregnancy test (female patients if applicable)			☐ positive ☐ negative ☐ N/A	
***Prefer value given in mg/dL If CRP is below level of detection, write in the value of lower limit of detection of lab. e.g. if values are < 0.5 mg/dL, write in '0.5'				

CENTER ECHOCARDIOGRAM

Please check one study visit:

☐ Enrollment, Pre-IVIG (Echocardiogram at during initial hospitalization at the time of diagnosis. As soon after admission as possible)
☐ 5-18 days after completion of study treatment
☐ If coronary artery abnormalities, worst echo between enrollment and follow-up visit

Date Study Done (mm/dd/year)		
Height (cm)		
Weight (kg)		
Coronary Artery Data:		
LMCA	_____(mm)	☐ Not well seen
Proximal LAD	_____(mm)	☐ Not well seen
Circumflex	_____(mm)	☐ Not well seen
Proximal RCA	_____(mm	☐ Not well seen
Mid RCA	_____(mm	☐ Not well seen
Comments		

TEMPERATURE (Crossover)

	Date (mm/dd/yyyy)	Time (24 hour clock)	Temperature (indicate Centigrade or Fahrenheit)	Route			
				Oral	Rectal	Axillary	Other, Please Specify:
Aspirin (before temp measured)			N/A	N/A	N/A	N/A	N/A
Temperature qualifying subject for crossover							
Aspirin (before temp measured)			N/A	N/A	N/A	N/A	N/A
24 hours(± 2h) from **initiation** of study crossover treatment							
Aspirin (before temp measured)			N/A	N/A	N/A	N/A	N/A
24 hours (± 2h) from **completion** of study crossover treatment							

OUTCOME Questions:

Was subject afebrile (<38°C rectally or orally or 37.5°C axillary/ T <100.4°F orally or rectally or <99.5°F axillary) 24h after initiation of study crossover treatment:

☐ **Yes** ☐ **No**

Was subject afebrile 24h after completion of study crossover treatment and remained afebrile until discharge:

☐ **Yes** ☐ **No**

CROSSOVER LABORATORY RESULTS

Hematology	Date (mm/dd/yyyy)	Time (24 hour clock)	Value	Comment
White Blood Cell Count ($X10^3$/uL)				
Hemoglobin (g/dL)				
Platelet Count ($X10^3$/uL)				
Neutrophils (%)				
Bands (%)				
Absolute Neutrophil Count (ANC)				

Chemistry	Date (mm/dd/yyyy)	Time (24 hour clock)	Value	Comment
CRP (mg/dL)				
***Prefer value given in mg/dL If CRP is below level of detection, write in the value of lower limit of detection of lab. e.g. if values are < 0.5 mg/dL, write in '0.5'				

CROSSOVER STUDY DRUG ADMINISTRATION

Did subject have a fever (T ≥38°C orally or rectally or ≥37.5°C axillary/ T ≥100.4°F orally or rectally or ≥ 99.5°F axillary) at 24 hours after completion of 1st study treatment

☐ Yes (if yes, then complete section below) ☐ No

Which of the following treatments did the subject crossover to: (check one and complete appropriate table below):

☐ 2nd IVIG

☐ Infliximab

2nd IVIG

Start Date:	(mm/dd/year)
Start Time:	(24-hr clock)
Stop Date:	(mm/dd/year)
Stop Time:	(24-hr clock)
Total grams administered: *Dosing protocol: 2g/kg over 8-10hr	grams
Brand:	
Lot #	
Comments:	

IVIG INFUSION REACTION: ☐ **Yes** ☐ **No**

If yes, complete AE form

Infliximab

Start Date:	(mm/dd/year)
Start Time:	(24hr clock)
Stop Date:	(mm/dd/year)
Stop Time:	(24-hr clock)
Total milligrams administered: *Dosing protocol: 10mg/kg over a min 2hr	mg
Comments:	

INFLIXIMAB INFUSION REACTION: ☐ **Yes** ☐ **No** **If yes, complete AE form**

PROTOCOL DEVIATION REPORTING FORM

Date of Occurrence _____ (mm/dd/year)

1. Describe the protocol deviation: _____
_____
_____

2. Explain the reason for the protocol deviation: _____
_____
_____

3. Was the subject adversely affected by the deviation?
☐ No
☐ Yes
If "Yes", please specify: _____
If Yes, complete an AE Form
4. Describe action taken to prevent recurrence: _____
_____
_____

ADVERSE EVENT REPORTING FORM

Adverse Event Description	
Date and Time of Onset	_ _ /_ _/ _ _ _ _mm/dd/year _ _ _ _ (24-hr clock)
Outcome	☐ Ongoing ☐ Resolved, no residual effect ☐ Resolved, residual effects ☐ Unknown
Resolution Date	_ _/ _ _ / _ _ _ _mm/dd/year ☐ Continuing ☐ Unknown
Frequency	☐ Single ☐ Continuous ☐ Intermittent
Action Taken (check all that apply)	☐ No interruptions in study treatment ☐ Modified dose/rate including temporary interruptions ☐ Study drug/procedure discontinued ☐ Medication provided (complete concomitant medication form) ☐Other-please specify _____
Relationship to Study treatment?	☐ Definitely related *(The AE is clearly related to the study treatment)* ☐ Probably related (*The AE is likely related to the study treatment)* ☐ Possibly related *(The AE may be related to the study treatment)* ☐ Probably NOT related *(The AE is doubtfully related to the study treatment)* ☐ Not related
Does the Event Meet Criteria for Serious?	☐Yes ☐ No If yes, please specify. Check all that apply. ☐Fatal ☐ Life-threatening ☐ Prolong hospital admission ☐ Severely or permanently disabling ☐ Required intervention to Prevent Permanent Impairment Damage ☐The principal investigator considers it to be a serious adverse event ☐ Other-please specify_____ For an SAE, has the event been reported to IRB? ☐Yes ☐ No Date:_____
Is the Event Anticipated?	☐Yes ☐ No *** Problems/events that are unanticipated and serious should be reported to the Samantha Roberts (sroberts@ucsd.edu) within 5 working days
Comments:	

FEVER DAYS

Total number of fever days (24 hour period with a T ≥38°C orally or rectally or ≥37.5°C axillary/ T ≥100.4°F orally or rectally or ≥ 99.5°F axillary) from time of start of infusion of first study treatment: _____ days

***A day is from 12:01am to 12:00 midnight.

Example: If patient starts first study treatment at 1:00 am and becomes afebrile at 11:00 pm that night, then that is one fever day. If fever returns two days later at 1:00 am and patient receives second study treatment and becomes afebrile at 11:00pm that night, then this counts as another fever day. The total fever days this patient will have had is 2.

DURATION OF HOSPITALIZATION

Duration of hospitalization following study entry (count number of days from randomization; each 24h-period from 12:01am to 12 midnight counts as one calendar day): _____ days

CONCOMITANT MEDICATION

Provide the trade or generic name and route for all medications taken during study-specific time period. Provide the medication stop date or check "Continues".

Medication:	
Dose, specify units (ug/mg/g)	
Dosage(mg/kg):	
Frequency:	
Route:	☐ Oral ☐ Topical ☐ Subcutaneous ☐ IV ☐ Other (Specify): _____
Start Date:	_____ mm / dd / year
Start Time:	_____ (24-hr clock)
Stop Date:	_____ mm / dd / year
Stop Time:	_____ (24-hr clock)
Reason for Therapy (Diagnosis)	_____ _____

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