DIAGNOSE-CRDS STUDY SYNOPSIS

Title	**Evaluation of a Novel Diagnostic Test for Calcium Release Deficiency Syndrome**
Short Title	**A Novel Diagnostic Test for CRDS**
Investigators	Dr. Jason Roberts (Population Health Research Institute) – PI Dr. Wayne Chen (University of Calgary) – Co-PI Dr. Ziv Dadon (McMaster University) – Co-Investigator
Primary Objectives	Primary Objective: To evaluate the ability of ventricular and atrial burst pacing to serve as a diagnostic test for CRDS and distinguish affected patients from survivors of unexplained cardiac arrest (UCA) that do not possess an RyR2 loss-of-function variant, RyR2-CPVT patients, and patients with supraventricular tachycardia and structurally normal hearts.
Study Design	Primarily prospective case-control study
Study Size	It is anticipated that the study will enroll - 20-50 CRDS participants - 20-50 CPVT participants - 50-400 UCA participants - 100-500 SVT Controls
Inclusion Criteria	**For CRDS participants:** - Presence of an RyR2 variant confirmed to be loss-of-function on *in vitro* testing **For CPVT participants:** - Satisfy a clinical phenotype consistent with the Expert Consensus Statement - Presence of a confirmed or presumed pathogenic gain-of-function RyR2 variant OR homozygous or compound heterozygous for likely pathogenic/pathogenic CASQ2 variants **For survivors of UCA:** - Cardiac arrest requiring cardioversion or defibrillation that remains unexplained following an ECG, Echocardiogram, Coronary assessment, cardiac MRI, exercise treadmill test, and sodium channel blocker provocation. - Has undergone genetic testing that includes screening of RyR2 **For SVT Controls:** - Undergoing an invasive electrophysiology study - Normal baseline ECG
Exclusion Criteria	**For all participants:** - Unable to provide informed consent (unless the maneuvers had previously been performed and the patient is no longer accessible for consent) **For CPVT participants:** - Use of a QT prolonging medication aside from flecainide, at the time of the burst pacing maneuvers **For survivors of UCA**: - Use of a QT prolonging medication at the time of the burst pacing maneuvers **For SVT Controls:** - Ventricular cardiomyopathy - Ventricular pre-excitation - Long QT syndrome - Use of a QT prolonging medication at the time of the EP study - Use of Class I or Class III anti-arrhythmic drug at the time of EP study - Known obstructive coronary artery disease (existing coronary stenosis >50%)

Outcome Assessment	The co-primary outcomes of the study are comparisons of the ΔQT and ΔT-wave observed in CRDS cases relative to that observed in CPVT and UCA cases and SVT controls. Study participants will undergo burst pacing for 10 beats from both the atria and ventricles at 150bpm and 120bpm and the post-pacing QT-interval on the first return beat will be assessed on 12-lead ECG. Secondary outcomes that will be evaluated include absolute QT-interval and T-wave height values on the first post-paced beat and presence of post -pacing ventricular ectopy.
Statistical Considerations	Based on preliminary data from CRDS cases and control participants, we anticipate the mean ΔQT among CRDS cases will be 150ms (standard deviation: 40ms), whereas, we anticipate that the mean ΔQT interval in SVT controls will be 40ms (standard deviation: 20ms). Based on these assumptions, 16 CRDS cases and 16 control participants from each group are necessary to provide 90% statistical power (assuming a 2-sided alpha = 0.05). To identify a difference in mean ΔQT values between these groups, our primary objective is to identify a threshold ΔQT and/or ΔT-wave height value sufficient to make a CRDS diagnosis. In this context, it is crucial to attempt to capture the full distribution of post-pacing QT values for cases and controls in order to clarify potential overlap. This will not be achieved with such small number of cases and controls. Accordingly, we intend to enroll a sufficient volume of cases and controls that will permit a robust assessment of their full distribution of ΔQT and/or ΔT-wave height values (mean $\pm$ 2 standard deviations). This will require enrollment of all accessible CRDS cases (target goal: 50) and we anticipate enrolling a similar number of CPVT cases (enrollment will also be challenging given their relative rarity and a minority possessing implanted devices capable of pacing). We will additionally enroll ~ 200 cases of both SVT and survivors of UCA. Assuming a normal distribution of the ΔQT data and the aforementioned assumed means and standard deviations, 50 CRDS cases and 200 controls will yield a QT threshold for diagnosis with 95% confidence interval boundaries that span 11ms