TITLE:
Title: REDuce Radiation Exposure in Fluoroscopic INterventions Evaluation (REDEFINE)

NCT04404257

Approval date: 07/14/2021

Protocol and Statistical Analysis Plan

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Investigational Plan

Version 12.0

5/26/2021

IRB Approved 7/14/2021

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1.0 Protocol Summary

Title	A prospective, randomized evaluation of the ControlRad system to reduce radiation exposure during cardiac catheterization and electrophysiology procedures
Design	Prospective, randomized, single center evaluation
Procedure	40 cardiac interventional procedures and 120 pacemaker and/or ICD procedures
Objective	To determine whether the ControlRad system reduces radiation exposure to operators, staff and patients during diagnostic and interventional cardiac catheterization procedures and electrophysiology implant procedures
Enrollment	Prospective
Site(s)	Beaumont Hospital Royal Oak
Time Course	2020- 2021
Primary Outcome	Effective radiation dose to primary operator
Principal Investigator	Simon R. Dixon, MBChB
Co-Investigators	Cheryl Schultz, Scott Emerson, Nishaki Mehta Study Coordination Beaumont Hospital Royal Oak

2.0 Background

2.1 Current Approaches for Radiation Protection

Long-term radiation exposure in the cardiac catheterization laboratory is associated with an increased risk of premature cataract formation, chromosomal damage, subclinical atherosclerosis and cancer (1-4). Conventional approaches to limit radiation exposure include a) wearing lead apparel, b) positioning table and ceiling-mounted radiation shields between the operator and patient, and c) technical considerations such as reducing the fluoroscopic frame rate, minimizing fluoroscopic time and acquisition runs, maintaining the optimal table height and image intensifier position, and use of filters and collimators in the imaging chain (5,6).

Despite these approaches, physicians working in the cardiac catheterization laboratory continue to receive high doses of radiation, primarily attributable to scatter radiation from the patient. This situation has in part been compounded by the increasing complexity of therapeutic procedures, such as interventions for chronic total occlusion. Prior studies have demonstrated that the primary operator is subject to the highest radiation dose due to proximity to the primary radiation beam, but other operators and staff also receive significant occupational exposure. Because of these concerns, there

has been a clear need to develop new methods to reduce radiation exposure to physicians and staff in the cardiac catheterization laboratory.

2.2 ControlRad System

ControlRad has developed a novel technology to reduce radiation exposure during cardiac catheterization procedures. The system uses a dynamic collimator that is installed above the X-ray tube of the cath lab system (Figure 1). The collimator is composed of a partially X-ray attenuating plate with a non-attenuating aperture corresponding to the region of interest. The attenuating plate is controlled by a number of motors to support high-speed motion of the plate. The position of the aperture is controlled by the physician using a table-mounted touch pad (Figure 2). Image processing software is used to match brightness and contrast in the attenuated and non-attenuated zones. The portion of the image seen through the aperture receives normal radiation dose, whereas the portion seen through the attenuated zone receives less radiation (Figure 3). For example, during a mid-LAD intervention, the aperture can be placed to maintain normal fluoroscopic image quality over the region of interest with a lower resolution over the remainder of the screen. The ControlRad system reduces radiation exposure during fluoroscopy, but does not change the dose during cineangiography.

Figure 1: ControlRad system mounted above X-ray tube

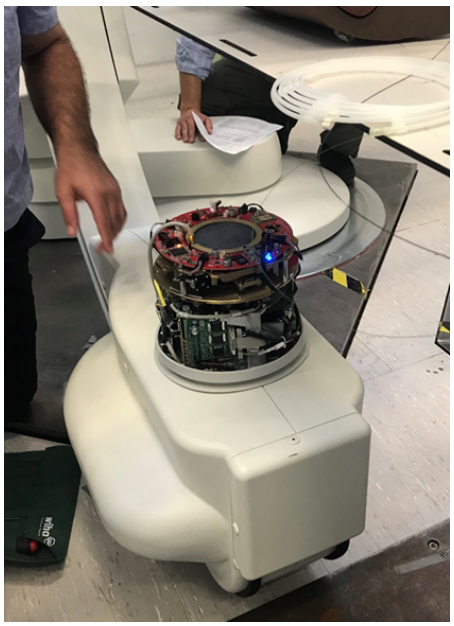
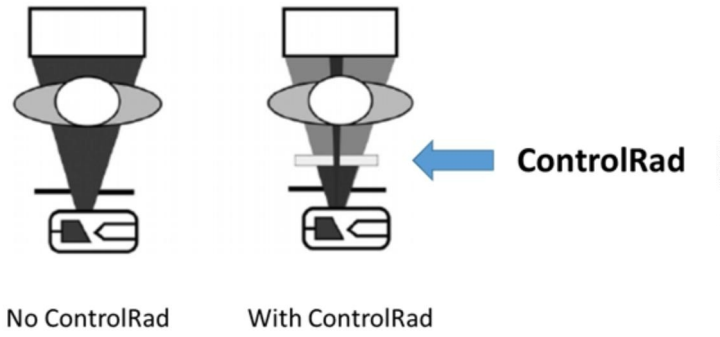


Figure 2: Table side touch pad

Figure 3: Illustration of ControlRad System



2.3 Pre-Clinical Data

The ControlRad system was evaluated in a swine model of iliac and renal artery stenting (7). Radiation dose measurements were obtained with and without the ControlRad system.

As shown below, there was a significant reduction in baseline radiation dose to both the operator and animal with the ControlRad system. The overall effect was a radiation reduction of approximately 75% relative to baseline dose.

	Without	With	p-value
Total kerma air product (μGym2)	635	124	<0.001
Total air kerma (mGy)	3394	1061	<0.001
Dosimeter (mR/h)	20.5	6.3	<0.001

3.0 Study Design

3.1 Objectives

To determine whether the ControlRad system reduces radiation dose to operators, staff and patients during diagnostic and interventional cardiac catheterization and electrophysiology (EP) implant procedures

3.2 Design

Prospective, randomized single center evaluation

3.3 Study Population

- Patients scheduled for cardiac catheterization in cath lab 5 at Beaumont Royal Oak.
- Enrolment will continue until 40 patients undergoing intervention have been recruited. (The total patient population is estimated to be 200 given the current diagnostic cardiac catheterization to interventional cardiac catheterization case ration is 2:1 which may fluctuate more participants are enrolled.)
- EP patients scheduled for a Pacemaker or ICD in cath lab 5 at Beaumont Royal Oak Hospital. Enrollment will continue until 30 patients undergo a complex procedure in the EP lab. (The current patient population is estimated to be 120 given the simple to complex case ratio which may fluctuate as more participants are enrolled.)
- Physicians and staff
    - For each procedure, 3 staff members will be study subjects: a) the primary operator, b) the secondary operator, c) the nurse/tech who circulates in the room
    - Different operators and staff may participate in each case depending on cath lab scheduling. The cath lab has 20 cardiology fellows, 35 interventional cardiologists and 56 staff, all of whom may participate in the study

3.4 Inclusion Criteria

Subjects will be eligible to participate if the following criteria are met:

- Patient
    - Scheduled to undergo left heart catheterization with angiography, and/or percutaneous coronary intervention
    - Scheduled to undergo pacemaker or ICD implant
    - EP device upgrade
    - Able to provide written informed consent prior to the procedure
    - Age ≥18 years
- Physicians and Staff
    - Able to provide consent for the study

3.5 Exclusion Criteria

Subjects will not be eligible to participate if any of the following criteria are met:

- Patient
    - Cardiogenic shock

  - Reason for cath procedure is pericardiocentesis
  - Subcutaneous ICDs
  - Lead revisions
  - Inability to provide informed consent
  - Pregnant
- Physicians and Staff
  - Those who are not willing to participate in the study

3.6 Study Endpoints

Primary Endpoint

- Mean effective radiation dose (µSv) to the primary operator

Secondary Endpoints

- Mean effective radiation dose (µSv) to the secondary operator
- Mean effective radiation dose (µSv) to the circulating nurse
- Mean radiation dose to the patient (dose-area product, DAP)
- Mean radiation dose (µSv) at a standard location on the wall of the cath lab

3.7 Definitions

- Primary operator is the physician who usually stands nearest to the C-arm. This is generally the attending physician in the EP cases and a fellow in cath lab
- Secondary operator is the physician or scrub assistant (nurse or technician) who typically stands to the right of the primary operator and in most cases is the attending physician in the cath lab.
- Nurse or Anesthesia team typically circulates in the room and is responsible for monitoring the patient, administering medications and obtaining equipment for the procedure

4.0 Conduct of Study

4.1 Screening

Patient

- All patients who are scheduled for cardiac catheterization in Cath Lab 5 will be considered for inclusion in the study.

Physicians and Staff

- Physicians and staff who work in Cath Lab 5 will be considered for participation in the study.

4.2 Informed Consent

Patient

- Written informed consent will be obtained from the patient by the research coordinator or investigator.

Physician and Staff

- Physicians and staff who work in Cath Lab 5 will be provided an information sheet regarding the study. The principal investigator will assist in informing the physicians and staff about the study, but will not participate in the consent process. Consent will be obtained by the research coordinator and will continue for the duration of the study. A physician or staff member may withdraw consent at any time during the study. Scheduling of procedures and staff will be determined by the cath lab manager/scheduler according to usual schedules and lab availability. If a patient, physician or staff member declines participation, the procedure will be scheduled in another cath lab.

4.3 Randomization

Procedures will be randomized 1:1 using sealed envelopes provided by the study statistician to either cardiac catheterization without ControlRad or cardiac catheterization with the ControlRad system. The same 1:1 randomization process will be applied to the EP patient population. Patients will be blinded to the randomization.

4.4 Measurement of Radiation Dose

Two methods will be used to measure radiation dose during the catheterization procedure:

A. Real-time Dosimeter Badge (RaySafe)

Real-time radiation exposure data will be collected using the commercially available RaySafe dosimetry system (RaySafe i3, Billdal, Sweden). This dosimeter provides the ability to measure radiation dose *per case*.

B. Landauer Luxel Aluminium Oxide Dosimeter Badges

The Landauer dosimeter badge will provide a *cumulative* radiation dose for each anatomic location. One set of badges will be used for cases performed with ControlRad, and one set for catheterization cases without ControlRad.

C. Dosimeter Badge Positions

Prior to each catheterization procedure the radiation badges will be placed at each location by the research coordinator, radiation safety officer, or trained cath lab staff member. The dosimeter badges will be removed at the end of each case. The location of the badges is shown below:

	RaySafe *(Dose Per Case)*	Landauer *(Cumulative Dose)*
Primary Operator	Thyroid Knee	Thyroid (2) Inner (2)
Secondary Operator	Thyroid Knee	Thyroid (2) Inner (2)
Nurse	Thyroid Knee	Thyroid (2) Inner (2)

Cath Lab	Wall	Wall (2)

The outer dosimeter badges will be placed on the left anterior side of the thyroid collar and the left ankle. The knee badge is affixed to the lower seam of the lead apron.
The inner badges will be placed underneath the lead apparel over the left anterior chest.
The cath lab dosimeters will be placed at standard location on the wall at the foot end of the cath lab table.
For the Landauer dosimeters, two badges will be placed at each location (one badge as a backup). 28 badges will be required (14 with and 14 without ControlRad)

4.5 Radiation Settings in Lab

The frame rate for fluoroscopy will be 7.5 frames per second (fps) and 15 fps for cineangiography (these settings are currently the default in Lab 5).

4.6 Catheterization Procedure and EP procedure

Cardiac catheterization, percutaneous coronary intervention, pacemaker and ICD implantation will be performed according to standard guidelines and clinical practice. The ControlRad is only used during fluoroscopy (the device is not used during “cine” acquisition runs). In the event use of the ControlRad device is felt to significantly diminish imaging quality outside the region of interest the device can be turned off. Standard of care views (typically orthogonal) will be performed after PCI to ensure there is no vessel injury.

Each attending physician may perform 1-2 “roll-in” cases to train on the ControlRad system before randomizing patients in the study.

4.7 Follow-Up

No clinical follow-up will be performed after the hospital stay since the primary endpoint is radiation dose measured in the cath lab.

5.0 Data Management

5.1 Data Collection

Data will be collected in case report forms in the REDCap database.

5.2 Effective Radiation Dose

The effective radiation dose per case (E) will be calculated using a single dosimeter method (8).

5.3 Power Analysis

In 2017, the median total air kerma dose (TAK) for a diagnostic and PCI in Cath Lab 5 was 460 mGy and 1577 mGy respectively. Approximately 50% of the TAK for a diagnostic or PCI procedure is from fluoroscopy and 50% from cineangiography. In pre-clinical studies the ControlRad system reduced radiation dose by 75% during fluoroscopy.
Using PASS 14 Power Analysis and Sample Size Software (2015). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass, we found that 9 diagnostic patients and 6 PCI patients per arm would give us 80% power to detect that absolute difference of 20% with a 0.05 significance level. Allowing for some variation in the actual frequencies in this higher risk group of patients or any drop outs, we intend to enroll 30 patients per arm.

5.4 Blinding

The physicians and nurses will be blinded to the radiation dose received in each case. The radiation dose to each operator and nurse will be recorded after every case by the study coordinator or radiation safety operator.

5.5 Statistical Analysis

Data will be analyzed on an intent-to-treat basis. Continuous variables will be reported as mean ± standard deviation, and where appropriate as median ± interquartile range. Analyses will be performed by a biostatistician using with SAS software for Windows version 9.3 (or higher).

6.0 Risk Analysis

6.1 Risks/Benefits to Physicians and Staff

In the standard of care arm of the study there is no additional risk or benefit to the physicians or staff. In the ControlRad arm there is no risk to the physician or staff however both may benefit from reduced radiation exposure.

6.2 Risks/Benefits to Patient

The decision how to treat the patient is at the discretion of the attending physician. The technical approach used for the cardiac catheterization procedure will not be affected by the ControlRad system. In the standard of care arm of the study there is no additional risk or benefit to the patient. In the ControlRad arm there the patient may benefit from reduced radiation exposure. In the ControlRad arm there may be slightly diminished visualization of surrounding structures (outside the region of interest) when the device is used during fluoroscopy.

7.0 References

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8.0 Tables

Table 1. Patient and Procedural Characteristics

	Total N= 60	ControlRad N=	No ControlRad N=	p-value
Age				
Weight				
Height				
BMI				
BSA				
Diagnostic				
PCI				
Radial				
Femoral				
Brachial				
Procedure time (mins)				
Fluoro time (min)				
Detector size				
SID				
Fluoro frame rate				
Flouro air kerma				
Fluoro kVP				
Fluoro mA				
Cine frame rate				
Cine magn size				
Cine kVp				
Cine mA				
Total air kerma				
DAP				

Table 2. Cumulative Radiation Dose Measured with *Aluminum Oxide* dosimeter badges (mrem)

	Location	ControlRad N=	No ControlRad N=	p-value
Operator 1	Thyroid			
	Inner			
Operator 2	Thyroid			
	Inner			
Anesthesia/Nurse	Thyroid			
	Inner			
Cath Lab Fixed	Wall			

Table 3. Mean Radiation Dose to Physicians and Nurse Measured with *RaySafe Dosimeters* (mrem)

		ControlRad N=	No ControlRad N=	p-value
Operator 1	Thyroid			
	Knee			
Operator 2	Thyroid			
	Knee			
Anesthesia/Nurse	Thyroid			
	Knee			