DURABLE-I STUDY PROTOCOL

SIGNATURE PAGE

AUTHORIZATION			
	NAME	SIGNATURE	DATE
Issued by:	**Yitzhack Schwartz, MD Chief Medical Director**	Y. Schwartz	18.9.2016
Approved by:	**Itzik Shmaayahoo, Director of System Architecture & SW**		18.9.2016
	Micha Nisani, General Manager		18.9.2016

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1	First Issue	14/09/2016
2	Up rev. following general review	18.9.2016

MASTER

DURABLE-I STUDY:

DIELECTRIC UNRAVELLING OF RADIOFREQUENCY ABLATION EFFECTIVENESS

Study Purpose

The purpose of this study is to evaluate real-time gap detection using EPD D700 dielectric sensing compared with customary electrical isolation tests and Adenosine infusion at the end of the procedure. Furthermore, safety, usability and clinical applicability of the system for guided AF ablation will be confirmed.

Study Design

Prospective, single-center, non-randomized, non-blinded, open label, and single arm study.

All procedures will be performed under CARTO 3 guidance for the treatment of atrial fibrillation (AF). The EPD D700 system will be used interchangably, to record pre-, during and immediate post-ablation tissue characteristics and compute likelihood of lesion transmurality and permanency. Additionally, D700 system safety, feasibility, usability and clinical applicability will be documented.

The entire procedure will be conducted as customary, using standard and approved off-the-shelf equipment (body surface electrodes, diagnostic and irrigated ablation catheters, RF generator and recording system), in a completely clinically independent manner from the EPD D700 system. The physician will neither use nor rely on any of the D700 system output for clinical decision making and will be blinded to the D700 lesion assessment forecasts. One month following the initial procedure, a repeated procedure will be performed for gap detection and its results will be correlated with the D700 predictions.

Study Population

Twenty four Paroxysmal Atrial-Fibrillation (PAF) patients, amenable to catheter-based AF ablation therapy comprising of Pulmonary Veins Isolation (PVI). We suggest that 4 will patients decline to participate. The overall number of patients in the study is twenty.

Key Inclusion Criteria

1. Male or female patients, age ≥ 18 and ≤ 80 years.
2. Paroxysmal atrial fibrillation (PAF)

3. Able to provide written informed consent form to participate in the study, prior to any study related procedures.
4. Able and willing to comply with the study protocol requirements.
5. A female subject is eligible if not of child bearing potential or has a negative pregnancy test within the previous 7 days.

Key Exclusion Criteria

1. Any planned surgical or endovascular intervention within 30 days before or after the index procedures.
2. Subject is enrolled in another drug or device study protocol that has not reached its primary endpoint.
3. Previous AF ablation therapy.
4. Clinical evidence of active coronary ischemia, significant Valvular heart disease, or hemodynamically significant congenital cardiac abnormality.
5. Patient had experienced myocardial infarction (MI), stroke (CVA) or transient ischemic attack (TIA) or other neurological disturbances.
6. Patient has a pacemaker.
7. Thrombi detected in the heart.
8. Life expectancy less than 12 months.
9. Known severe renal insufficiency.
10. Known allergy to iodine.

Baseline Assessment

- Eligibility according to inclusion and exclusion criteria.
- Obtaining signed Informed Consent Form (ICF).
- Demographics.
- Medical history.
- Concomitant medications.
- Disease oriented physical examination including vital signs.
- 12 lead ECG.
- Standard laboratory tests;
    - Complete blood count
    - Coagulation studies if appropriate
    - Serum creatinine and electrolytes
    - Liver function tests
    - CRP
- TTE or TEE.
- Pregnancy test, if applicable.

Study procedures

- **Cardiac CT** (pre-procedure imaging) **or MR.**
- **CT/MR post-processing and analysis** at EPD Research (Caesarea, Israel):
  - **Cardiac chambers' segmentation**
  - **Electrical fields computation**
  - **Optional recommended PVI ablation lines**
  - **Optional preliminary lesion forecast at the point level**
- **Forwarding the ready to use pre-planned data to the site.**
- **First AF ablation procedure** (Figure 1)**:**
  - EPD D700 system installed in the EP cath-lab.
  - Deployment of body surface electrodes (patches) by the local EP technician/nurse under supervision of EPD Research team members, to be used later by both the CARTO3 and EPD D700 system, interchangeably, according to the diagrams in Appendix 1.
  - Deployment of BWI body surface magnetic sensors according to the customary setup guidelines.
  - Connecting the ThermoCool SmartTouch ablation catheter via the commercially available extension cables to the CARTO3 system according to the diagrams in Appendix 1.
  - Connecting the Stockert RF ablation generator to the CARTO3 system according to the diagrams in Appendix 1.
  - Registration of the pre-acquired 3D CT or MR images of the Right Atrium (RA) with EPD D700, using CARTOMERGE module.
  - Registration of the pre-acquired 3D CT or MR images of the RA with EPD D700 system under fluoroscopy and or CARTO3-guidance.
  - Performance of Transseptal Procedure under fluoroscopy and/or ultrasound (TEE or ICE) guidance.
  - Registration of the pre-acquired 3D CT or MR images of the Left Atrium (LA) and Pulmonary Veins (PVs) with CARTO3 using CARTOMERGE module.
  - Registration of the pre-acquired 3D CT or MR images of the LA and PVs with EPD D700 system under fluoroscopy or CARTO3-guidance.
  - Targeted navigation inside the LA and reaching the 1st, either user-determined or computer recommended, point of the 1st preplanned PVI ablation lines.
  - Performing the specific ablation strategy while ascertaining contiguity using VISITAG module, i.e. 5-6 mm between consecutive ablation points, and moving along the PVI line systematically in preplanned continuous order. The specific ablation parameters to be used, i.e. 30 W 30 and 25W a30 sec in anterior and posterior LA wall, respectively; as well as the desired Ablation Index to be reached, will be determined solely by the operator regardless of the system's recommendation.

- Before, during and immediately after each ablation point, the EPD D700 system will record (for a few seconds) specific dielectric characteristics from the catheter tip. These readings, reflecting estimated transmurality and probability of the lesion's permanency, will be analyzed in the post-procedure phase and will not be considered by the user during the procedure.
- Thirty minutes after the completion of the full ablation plan, a formal acute electrical isolation test will be performed to identify remaining gaps.
- IV Adenosine infusion, a bolus of 12-18mg, will be performed to identify additional existing dormant conduction.
- Touch-up ablations will be added according to the two previous tests' findings.
- The procedure will be concluded only after the physician has decided there are currently no remaining identifiable gaps and the PVI is based on current knowledge, deemed durable.

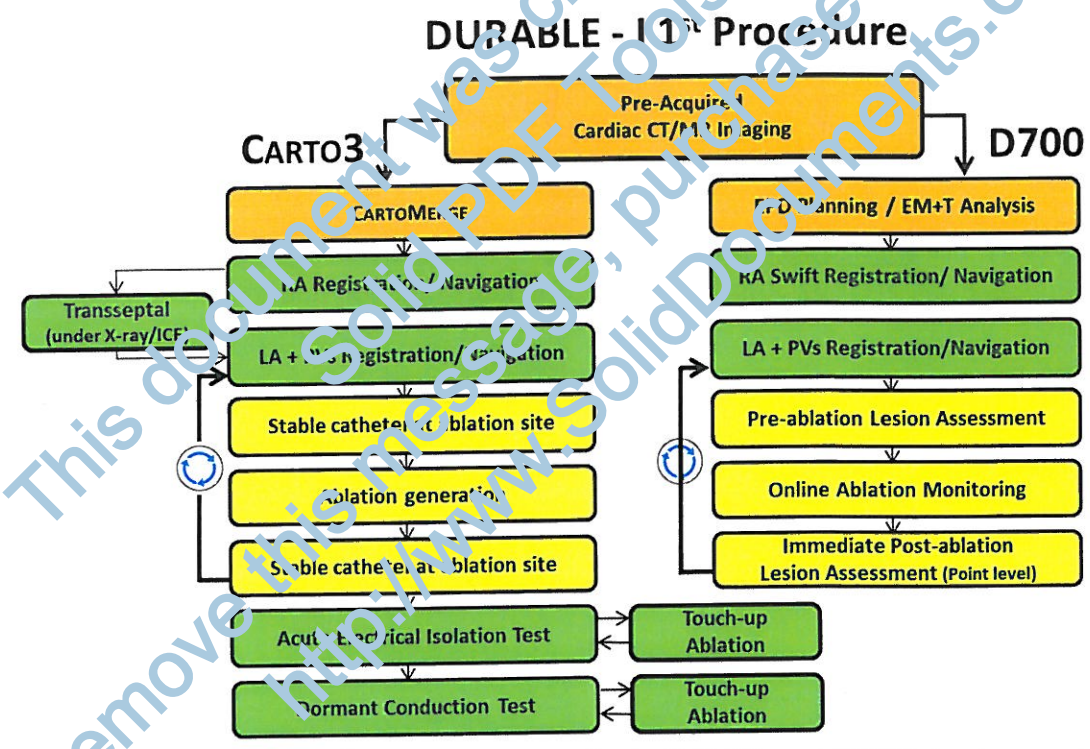

Figure 1: **Step-by-step 1st procedure**, using both CARTO3 and D700 interchangeably.

- **Second AF ablation procedure** (Figure 2):
  - The second procedure will be conducted 1 month after the initial procedure in a similar set up under CARTO3 guidance.
  - After repeated registration, with the previous pre-acquired 3D image, the LA will be remapped.
  - In order to functionally identify existing gaps, remaining gaps will be sought for by electrical functional test.

- If such gaps will be encountered, the physician will apply the customary touch-up approach.
- The location of gaps around the PVs will be reported in 8-16 segments (Figure 3).

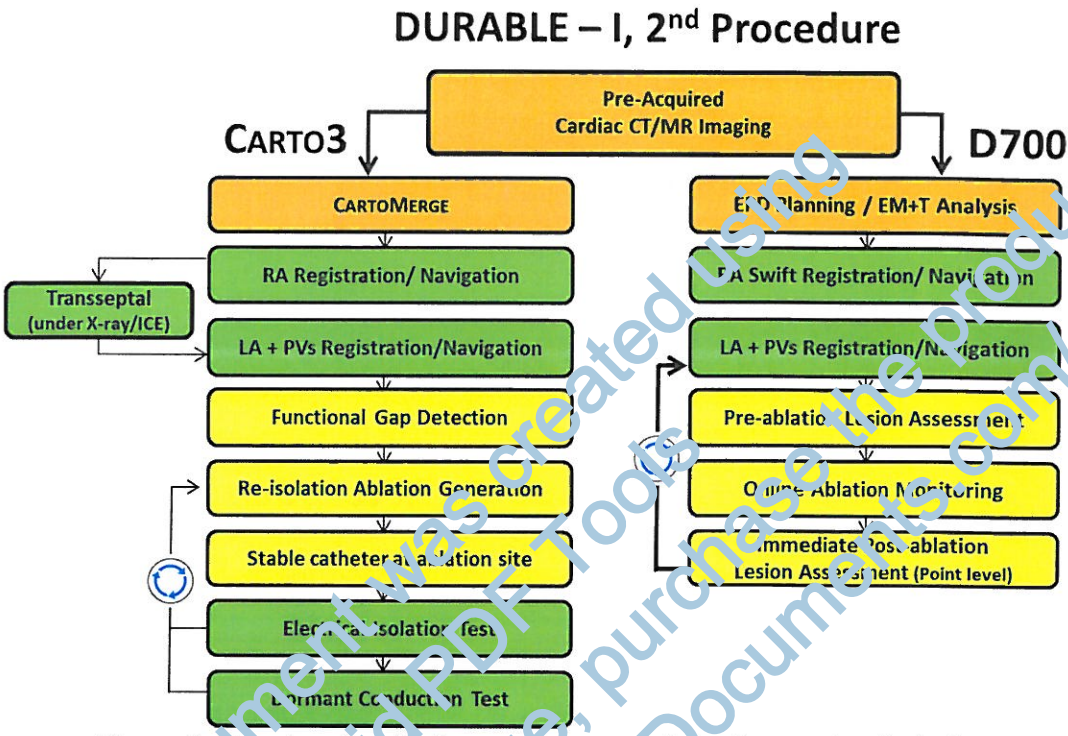

Figure 2: **Step-by-step 2nd procedure,** gap detection and re-isolation.

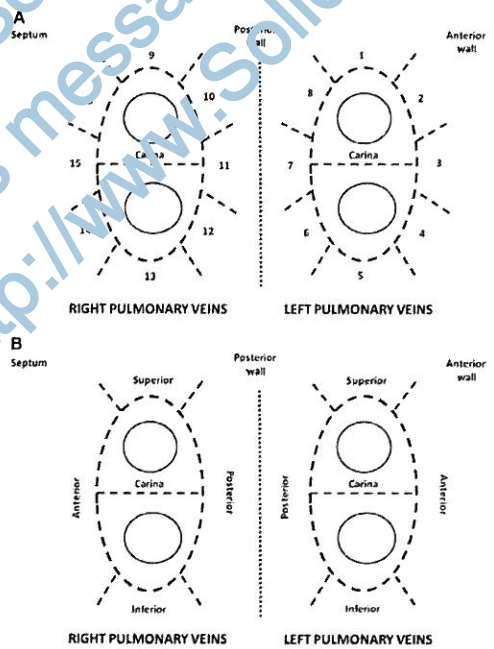

Figure 3: **Data collection around PVs**. (A) Data collection at 8 numbered sections: 1,9 – superior; 2, 16 – anterior superior; 3, 15 – anterior middle; 4, 14 – anterior inferior; 5, 13 – inferior; 6, 12 – posterior inferior; 7, 11 – posterior middle; 8, 10 – posterior

superior; (B) Sections 2, 3, 4 and 14, 15, 16 were grouped, respectively, into left and right anterior segments and 6, 7, 8 and 10, 11, 12 were grouped, respectively, into left and right posterior segments.

Data to be collected during the procedures:

- Overall procedure time.
- Overall EPD D700 set up time.
- Fluoroscopy time.
- Acute (during and immediately after the procedure) AE/SAE Evaluation.
- Full CARTO3 location data (CARTO3 export file).
- Full CARTO3 Point List and Tags.
- Pre-ablation, during and Immediate Post-ablation lesion assessment at each ablation point.
- Each ablation site location will be tagged on both CARTO3 and EPD D700 maps.
- As SmartTouch® is used, contact force data will also be recorded.
- Recording system data.

Appendix 1: CARTO3 and EPD D700 operating in-tandem

This appendix describes the connection between D700 system and CARTO3 (Biosense Webster JNJ) system that was especially developed in order to enable temporary operation of the two systems in-tandem. This is a requirement that must be met merely in the interim phase until users gain full confidence in D700's accuracy and reliability. The connection between the two systems is accomplished by two EPD external boxes:

- **EPD CARTO3 Cat** box
- **EPD CARTO3 Patch** box

There are two operational modes enabled while using these connection boxes:

a. CARTO3 mode:
   In this mode the CARTO3 is connected as standalone system and retains all its customary functionalities using both EM and Impedance-based localization.
b. D700 mode:
   In this mode the system toggles the RF generator and the body surface patches to the D700 system, while disconnecting the CARTO3 from the ablation catheter and the body surface patches. Dummy loads are connected to CARTO3 system as inputs. In this mode, although an error message might appear on CARTO screen, the CARTO3 is still using its magnetic location and the navigable catheters equipped with a magnetic sensor will still be visualized.

D700 and CARTO3 connection - Top level

Figure 1 shows the connection between the two systems.
The control cable carries voltage and control signals for the internal relay box.
The connection is made by the two connection boxes:

EPD Cart3 Cat box

The EPD Cart3 Cat box is used to connect between the ablation catheter, RF generator, and the D700 system.
Figure 2 shows the internal connections when the box is set to CARTO3 standalone mode. In CARTO3 standalone mode the RF generator is connected directly to CARTO3 and the ablation catheter electrodes C4-C1 are connected directly to CARTO3. The relay position is set by a control signal from D700. All the relays are hi-voltage enabled and defibrillation safe.
Figure 3 shows the box in the D700 mode. The 13 KHz block filter is used to block the location signals of the D700 from for RF generator low impedance output.
Dummy resistors load are connected to CARTO3 inputs.

EPD Cart3 Patch box

The EPD Cart3 patches box is used to connect between the body surface patches to CARTO3 or D700 system, interchangeably.

Figure 4 shows the internal connections when the box is set to CARTO3 mode.
Figure 5 shows the connection when the box is set to D700 mode.

Available Modes

System Mode	Description	Note
CARTO3 only	The CARTO3 is connected to all catheter electrodes, body surface patches, and RF generator	Same full performance as standalone CARTO3 system, all indwelling catheters, including SmartTouch ablation catheter, Lasso and Decapolar diagnostic catheters, and all their electrodes will be visualized on the CARTO screen
D700 + CARTO3 in EM location only	1. The CARTO3 is connected only to electromagnetic and temperature sensors, hence the ablation catheter will still be correctly localized and displayed on the CARTO screen 2. Ablation catheter C4-C1 connected to D700, CARTO3 is optionally connected to dummy load 3. RF generator is connected to C1 with a blocking filter of D700 frequencies 4. Body surface patches are connected to D700 5. CARTO3 body surface input is optionally connected to dummy load	• No RF performance degradation (energy transfer) in C1. • ECG signals of C1 to C4 transferred to recording system from D700 RS connection box. • Error message on CARTO screen due to "loss" of impedance input. • Non-navigation diagnostic catheters, whose visualization solely depends on impedance measurements (body surface patches reading the current injected from the electrodes on the catheter), will temporarily disappear from the CARTO screen • The intra-cardiac ECG will be displayed on the recording system in the channels reserved for D700 rather than the channels

		reserved for the CARTO3 • Performing an ablation under this mode will be safe and there'll be no associated new risk to the patient

Supported catheters

CARTO®3

1. NAVISTAR catheter / THERMOCOOL® SF catheter
2. THERMOCOOL SMARTTOUCH® catheter
3. LASSO catheter

External Cables used

Therapeutic CARTO® 3 System Cables:

1. CR3425CT 3 m Cable for existing NAVISTAR® Catheter, 25 pin black, 34 pin red
2. CR3434CT 3 m Cable for THERMOCOOL SMARTTOUCH® Catheter, 34 pin red, 34 pin red
3. 39E43R PIU to Stockert EP Shuttle Generator

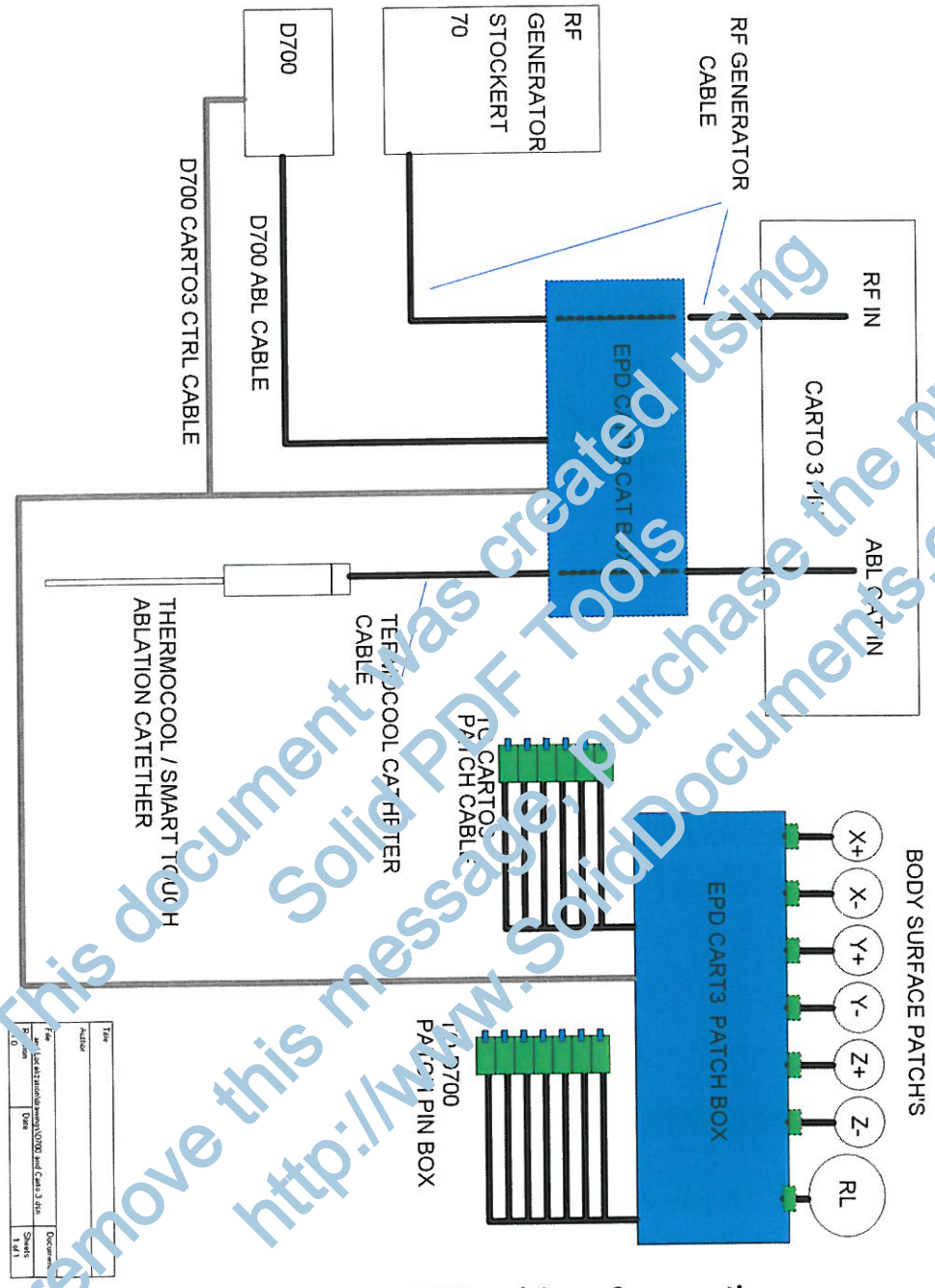

Figure 1: **D700 and CARTO3 connections**

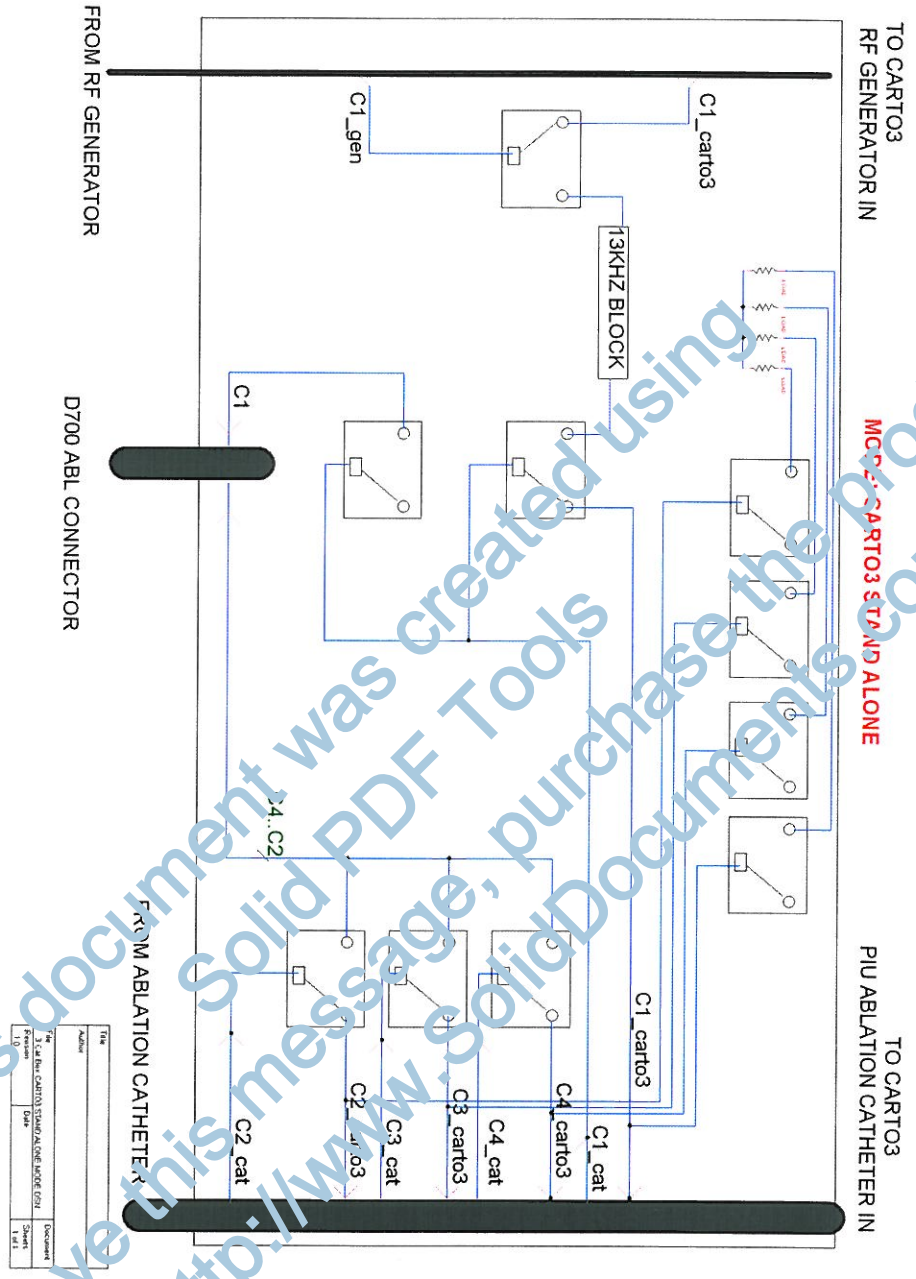

Figure 2: **Cat box in CARTO3 mode**

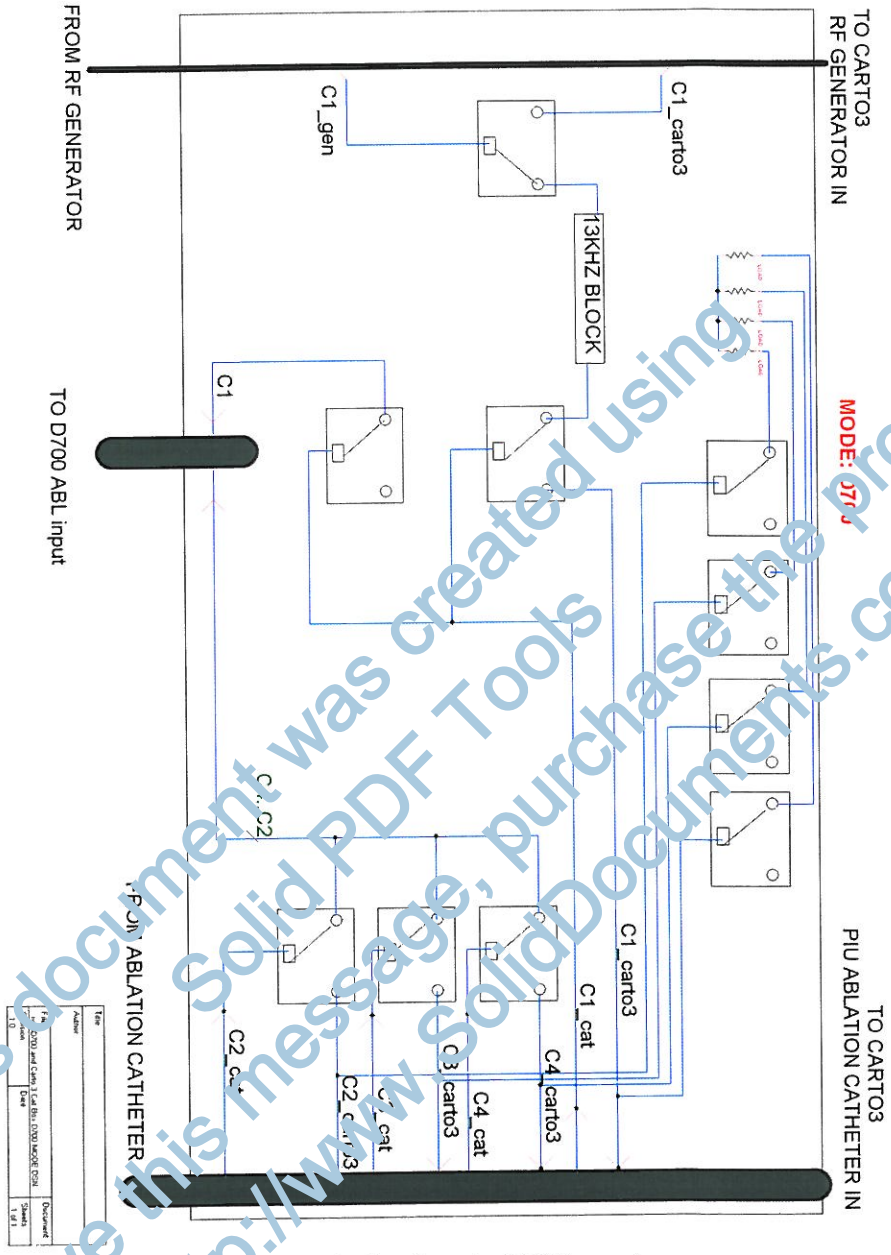

Figure 3: **Cat box in D700 mode**

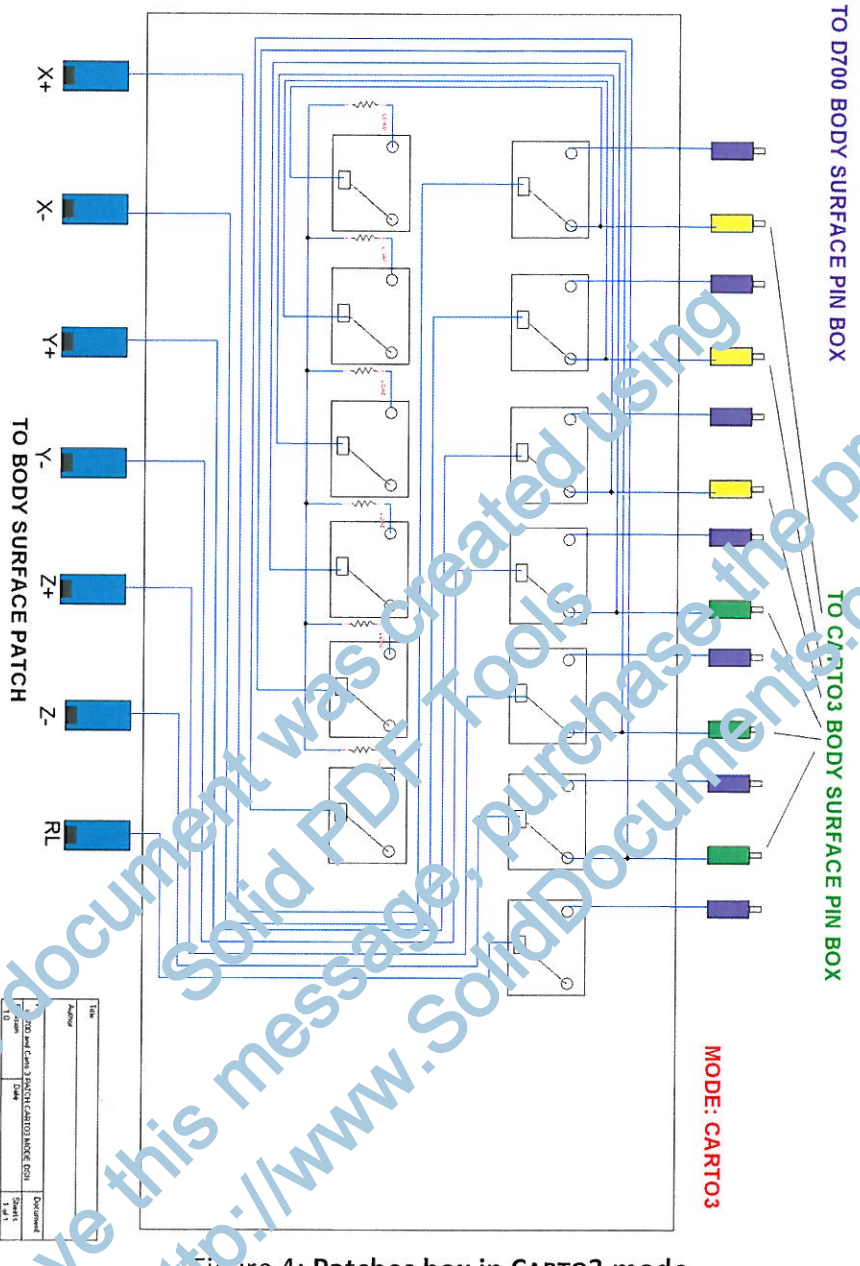

Figure 4: **Patches box in CARTO3 mode**

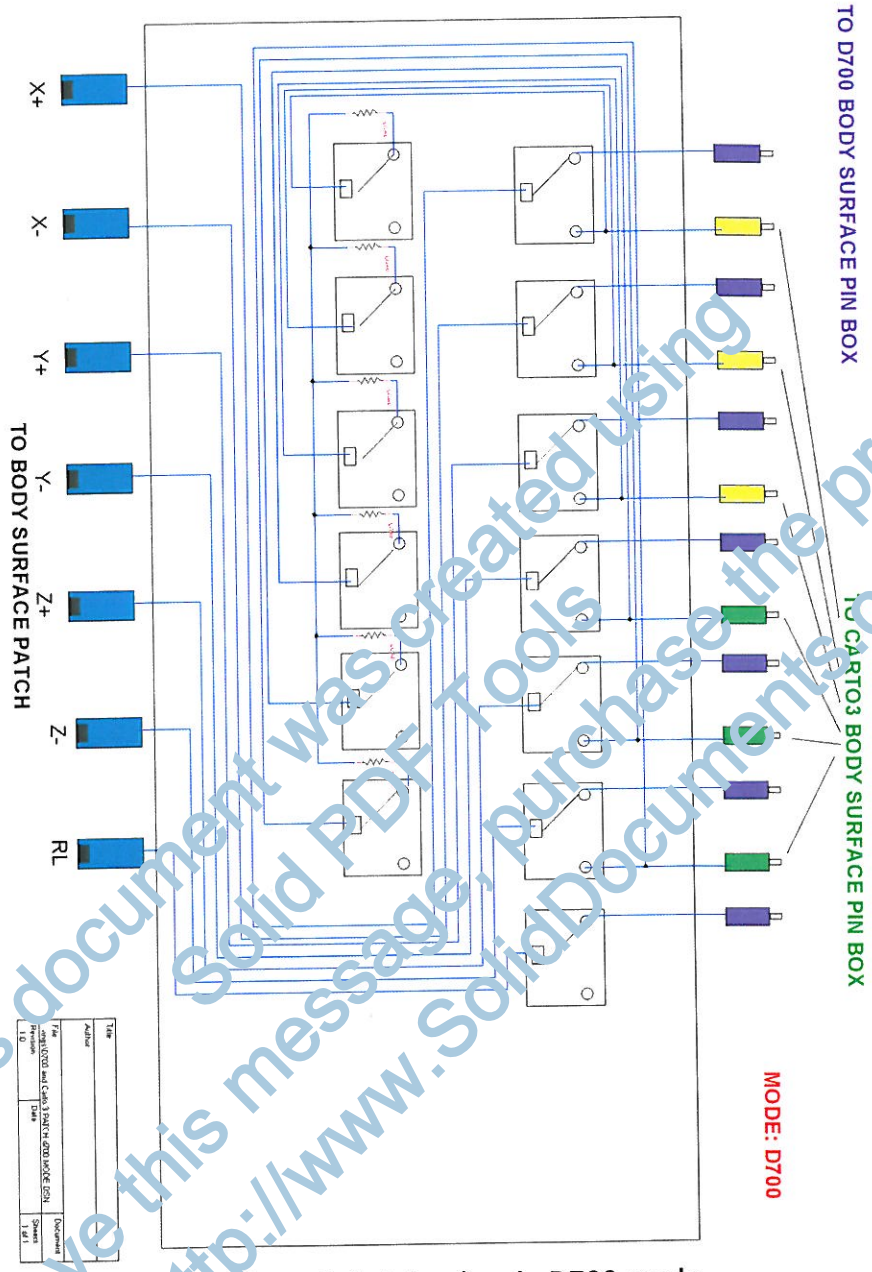

Figure 5: **Patches box in D700 mode**