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When a Clinical Trial Lasts Forever: A Reporting Solution for Post-Market Surveillance of Cardiac Rhythm Devices

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ABSTRACT

Post-market surveillance data is vital to the medical device industry for monitoring product performance, patient safety and patient outcomes. The collection and analysis of this data poses some special challenges. This paper discusses a unique post-market study of implantable cardiac rhythm and heart failure (CRHF) devices that began in 1983 and continues to this day. The study currently contains data collected for approximately 210,000 devices implanted in more than 75,000 patients at over 300 sites. These data have been collected in multiple geographies using numerous platforms under evolving data collection standards. In recent years the complexity of the data and expanding analysis needs have outpaced the scope of the existing reporting structure. A solution was needed to more effectively document reporting requirements, increase efficiency, and provide broader internal access to the data.

INTRODUCTION

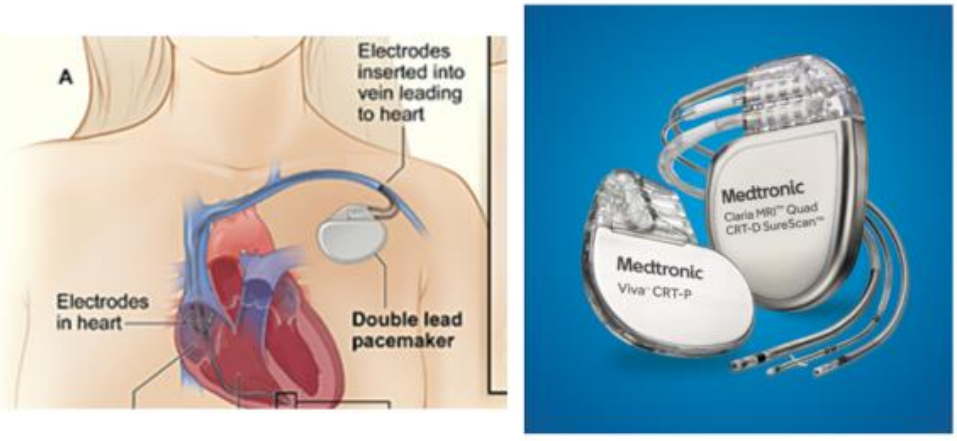
The purpose of this paper is to introduce a unique medical devices clinical trial and to discuss the challenges and solutions involved in using and analyzing the data.

BACKGROUND

THERAPY OVERVIEW

Implantable cardiac rhythm systems generally consist of two types of devices: a generator and one or more leads. A generator is basically a small computer with a battery, implanted in the chest. It monitors the heart's electrical activity and delivers therapy through one or more leads inserted through veins and into chambers of the heart.

Display 1. Therapy Overview



There are three main generator types:

- IPGs (Implantable Pulse Generators or Pacemakers)
- ICDs (Implantable Cardiac Defibrillators)
- CRTs (Cardiac Resynchronization Therapy)

There are three main lead types:

- RA (Right Atrial, Pacing Therapy)
- RV (Right Ventricular, Pacing or Defibrillation Therapy)
- LV (Left Ventricular, Cardiac Resynchronization Therapy)

Dozens of models of each of these devices have been released over time to meet different patient needs and to incorporate new features. Both before and after approval they need to be monitored for safety and efficacy.

STUDY OVERVIEW

Patients are enrolled in the Surveillance Registry (SR) when implanted with an eligible device model and may be exited from the study when analysis needs for a device model have been met. A patient will generally have more than one device model of interest at a time and may have a system comprised of devices from more than one manufacturer. Generator batteries generally last from 5-10 years at which time the generator needs to be replaced. A generator or lead may also need to be replaced if it becomes ineffective or if a patient's therapy needs change; therefore, a patient can also have more than one model of a device type over time. A sample patient in the study could look like this:

Table 1. Sample Patient

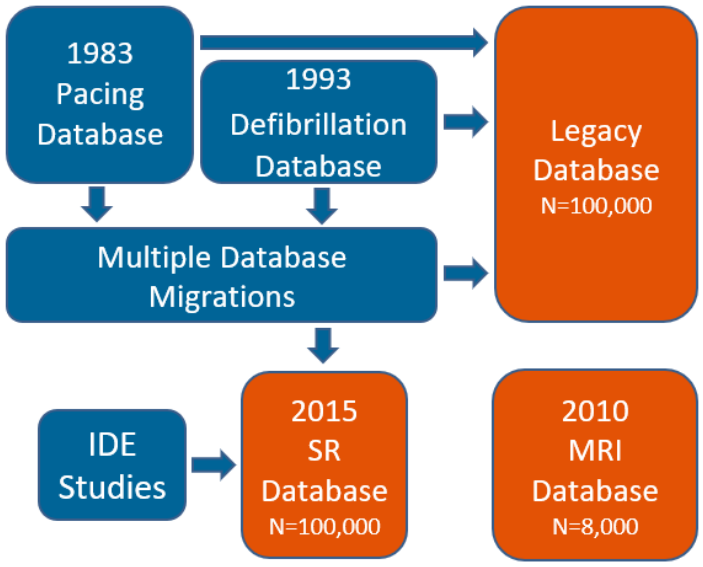
Implant Date	Device Type	Device Model
7/21/1998	IPG	7964i
7/21/1998	RV Lead	4023
7/21/1998	RA Lead	4068
7/13/2005	CRT	7298
7/13/2005	LV Lead	4193
7/13/2005	RV Lead	6949
6/28/2006	RV Lead	6931
11/2/2010	CRT	D354TRG
11/2/2010	RA Lead	4076
11/2/2010	RV Lead	6935
10/26/2015	CRT	DTBC2D1

DATA COLLECTION OVERVIEW

Data collection practices and technology have obviously evolved over time. Over the course of the study, there have been multiple database migrations. In some cases, data was migrated forward and in other cases it was archived to a Legacy database. In 2010 a separate database was needed for a study of MRI-conditional devices. The net result today is 3 main database sources: Legacy, SR and MRI. Future changes are likely as new products become commercially available after their Investigational Device Exemption studies (IDEs) are approved. Only the SR database has been conformed to SDTM. There were early attempts to conform Legacy and MRI to SDTM, but since the three sources are so different

and since none of them were based on CDASH-compliant data collection instruments this approach was not ideal. Here is an overview of the data collection history:

Display 2. Data Collection Overview



REPORTING OVERVIEW

Reporting needs have also evolved over time. In 1983 the primary analysis focus was the structural integrity of the leads. A lead sits in a physically challenging environment in the body and some of the complications possible for a lead are for it to dislodge, fracture, or to have electrical issues. To monitor these complications, it was the practice to create survival curves every 6 months for each lead model of interest and to disseminate these survival curves and complication counts to health care providers.

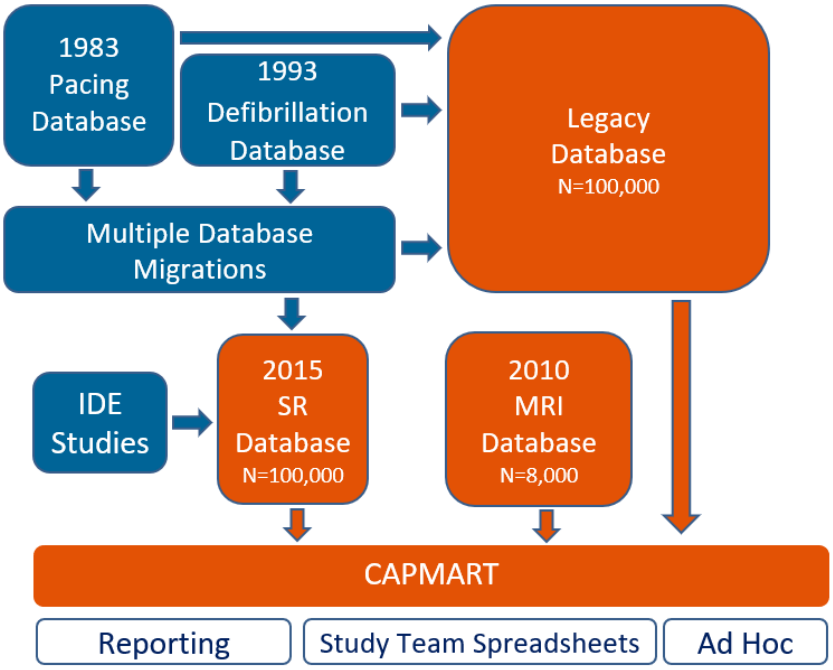
More recently two distinct types of reporting needs have evolved. One need is for regulatory reporting. After approval a regulatory agency may request post-approval reporting. Rather than having to set up a unique clinical study for each post-approval request it is much more efficient to use the existing surveillance protocol and database to gather the data. Approximately 20 regulatory reports are now produced each year from this data specific to a device model or feature. These reports are very targeted in scope and only use the SR data source. They use SDTM data sets and we are in the process of transitioning our existing analysis data sets to ADaM data sets for these reports.

The other need is to use the entire cohort of enrollments for additional non-regulatory reporting and research. Signal detection activities for identification of emerging patient safety or performance issues are still of high priority, but the richness of this data also leads to many requests for both formal and ad hoc reporting from various groups like Marketing, Regulatory, R&D and Quality. These requests use data from all three data sources and this is the reporting need we will address.

REPORTING SOLUTION

The solution for this non-regulatory reporting was to develop a CRHF Analysis Plan DataMart (CAPMART). Instead of creating analysis data sets at the report level, for the first time analysis data sets were implemented upstream at the study level. The goal was to standardize across data sources, centralize complex computations, minimize documentation and provide the data in a format useful to the study team.

Display 3. CAPMART



REQUIREMENTS

Analysis Data Set Metadata

A major advantage was being able to work backwards from known outputs and analysis data sets. A well-documented history of ad hoc requests was also available to anticipate future needs. The first step was to leverage these legacy reporting activities to begin documentation. This led to the following high-level design of seven analysis data sets:

Table 2. Analysis Data Set Metadata

Data Set Name	Data Set Description	Data Set Structure
A_LEAD_COHORT	Basic information about each lead. Includes consistent handling of duplicate entries over time[1] and re-enrollments[2].	One row per patient per lead serial number
A_GENR_COHORT	Basic information about each generator. Includes consistent handling of duplicate entries over time[1] and re-enrollments[2].	One row per patient per generator serial number
A_EVENTS	Information for each event. If an event is product-related, then information about the product is also included. Patient-level information and adjudication information are also included.	One row per patient per event per relatedness
A_VISITS	This intermediate data set identifies all dates of patient contact.	One row per patient per patient contact
A_LEAD_SURVIVAL	Uses the other data sets to compute lead survival.	One row per patient per lead serial number
A_GENR_SURVIVAL	Uses the other data sets to compute generator survival.	One row per patient per generator serial number

A_PATIENTS	Basic information about each patient. Also uses the other data sets to compute flags like whether the patient ever had an event or whether the patient ever had a pacing lead.	One row per patient

[1]The case report forms are designed so that each device in a system is documented at every implant procedure whether it is newly implanted or chronic. This is helpful for ensuring all system modifications have been properly documented but the existence of duplicate data also complicates the retrieval of data for analysis and requires a consistent approach to retrieval.

[2]Patients are allowed to exit the study and re-enroll at a later date. This also adds a layer of complexity to the retrieval of data.

Analysis Variable Metadata

The next step was to create detailed requirements for each variable for each data set for each data source. The priority was to create business requirements that non-technical people could understand and to only create technical requirements in the case of ambiguity or complexity. In order to minimize the impact to downstream code, legacy variables names were maintained wherever possible. Descriptive labels were added and special attention was paid to traceability so that the sources of derived variables were available. These requirements were reviewed with the study team so their feedback could be incorporated.

RACE is a straightforward example. The collection of race was different for each data source and only needed to be standardized. This is not hard to do but is not something we want to do each time we get an ad hoc request. For example:

Table 3. Race

NAME	Source: SR	Source: Legacy	Source: MRI
RACE	BASELINE & MEDICAL HISTORY form 'Race as determined by patient or family'	set to 'DATA NOT COLLECTED IN LEGACY SYSTEM'	ENROLLMENT form 'Race/Ethnic origin' map for case report form (CRF) differences as follows 'Asian' to 'Other Asian' 'Black or African American' to 'Black' 'Hispanic or Latino' to null 'Other race' to 'Other' 'Subject/physician chose not to provide information' to 'Patient/physician chose not to provide information' otherwise keep the original value

Device model is more complicated. On some of the CRFs model was collected as free text and on others it was a dropdown list. The dropdown lists changed over time and thus various values could have been migrated forward to the ‘Other, specify’ field in the SR database. For the Legacy data we continue to use the free text value to preserve historical precedent. But for the SR data source we have defined an algorithm. It first looks at the serial number prefix of the device that was entered on the CRF, then considers the model number entered on the CRF and then handles special cases. Here is an example of the result for one lead model. Note that we keep the original CRF value. Note also the derived model number maintains the legacy MDLSHRTDESC variable name so that all downstream legacy code does not need to be modified:

Table 4. Device Model

CRF Serial Number Prefix	CRF Model Number	Derived Model Number (MDLSHRTDESC)	Derived Model Number Source
LDW	10366	4968	SN Prefix
LDW	OTHER, SPECIFY:10366	4968	SN Prefix
LEN	4968	4968	SN Prefix
LEN	4968-35	4968	SN Prefix
LEN	496835	4968	SN Prefix
LEN	OTHER, SPECIFY:4968	4968	SN Prefix
LEN	OTHER, SPECIFY:4968 - CAPSURE EPI (EPICARDIAL)	4968	SN Prefix
LEN	OTHER, SPECIFY:4968 CAP SURE EPI	4968	SN Prefix
LEN	OTHER, SPECIFY:4968 CAPSURE EPI	4968	SN Prefix
YY0	10366	4968	CRF Model Specify
YY0	OTHER, SPECIFY:10366	4968	CRF Model Specify

IMPLEMENTATION

The CAPMART was implemented as a clinical study report to be generated quarterly on a data snapshot. Later a daily refresh of the report was added.

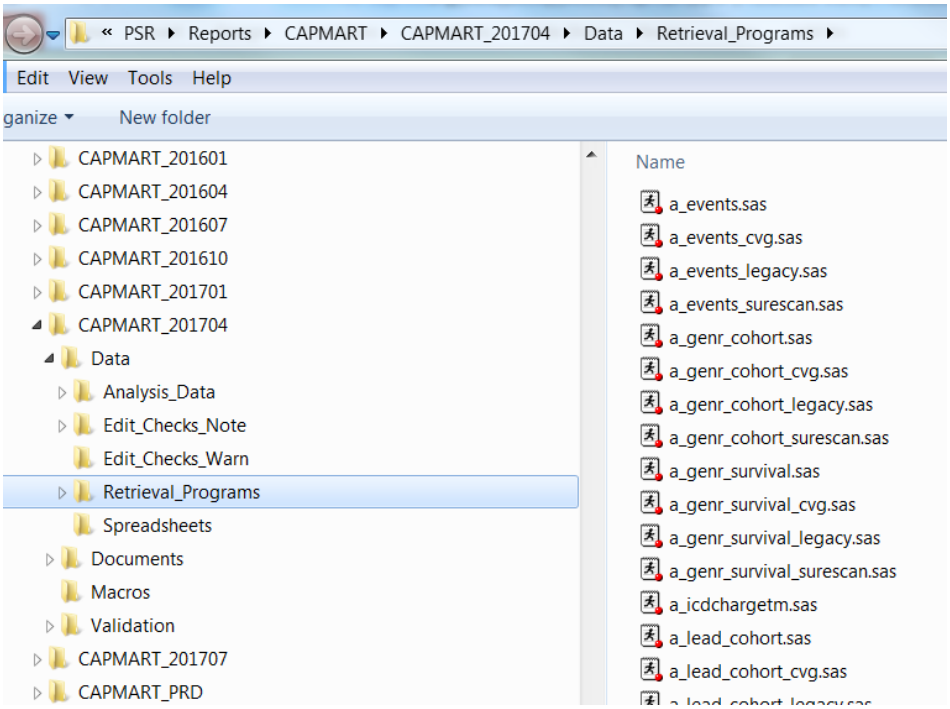
Environment

SAS® programs were developed in the PC environment. Production is generally executed in the Linux environment. Utilizing Linux greatly improves processing time and allows the daily refresh to be automated.

Programs

Four SAS programs were created for each analysis data set: one program for each of the three data sources and one program to combine the sources and handle any re-enrollment issues. The programs dynamically derive the source and target paths from the location of the code. This allows the programs to be copied from one folder to the next without modification. Here is a screen capture of the folder and file structure:

Display 4. Programs



The program code contains a lot of “data traps”. These were useful during development to catch errors and misunderstandings early. In production they are a safety net for catching new data values or situations that may come with adding new products over time. For example:

```
data _null_;
   set mydata;
   by pt form formdt;
   if not (first.formdt and last.formdt) then do;
     put "WARN" "ING: unexpected data " pt= form= formdt=;
   end;
run;
```

Validation

Most of the validation is done by independent programming but some of the Legacy and MRI programs were validated by peer review.

Output

SAS datasets are of course generated for analysis. In addition, Excel files are generated for study team review. The creation of these files proved to be an additional tool for catching issues early. Reviewing the filters for each column revealed unexpected values and resulted in improved requirements. These files are now used frequently by the study team. Sometimes the team members can answer their own questions, and other times the files enable the team to better formulate their ad hoc requests before requesting programming assistance.

Below is an example of the EVENTS file. Note that is shows the original database source of the event form. Note also the assignment of event date. In the early days of the study there was no ‘Onset Date’ on the CRF so a different date needed to be used for this. With a surveillance study data cleaning can sometimes be a challenge and in an example below ‘Center Aware Date’ is used as a proxy for ‘Event Date’ until the data can be cleaned.

Table 5. Sample Output

Snapshot Date [SNAPSHOT_DATE]	Surveillance Patient Number [PT_MASTER]	AE Number [EVENT_ID]	AE Original Source [X_FORMID_SOURCE]	Event Type [EVENT_TYPE]	Standardized Serial Number [SN_UPPER]	PPR Event Date [X_EVENTDT_PPR]	PPR Event Date Type [X_EVENTDT_PPR_TYPE]
20180131	M101100874	0	Migrated Study	Procedure Related		11/25/2013	Onset Date
20180131	M109100383	0	SR Study	Procedure Related		6/29/2016	Center Aware Date
20180131	M109100383	1	SR Study	Relatedness Pending		3/9/2016	Onset Date
20180131	S105400014	0	MRI Study	MRI Related		4/26/2012	Onset Date
20180131	L100030011	1	Legacy Study	Lead Related	QRS037247V	10/8/2004	First Clinical Action Date

CONCLUSION

Data from three primary databases now resides in one unified structure with one comprehensive set of requirements. A substantial learning curve is still required to master the therapy knowledge; however, it is now easier as all complex derivations, special cases, and historical changes are documented in one place. The CAPMART has been generated quarterly on frozen data for the last eight quarters and has produced eight Safety Trending Reports, four Product Performance Reports, one regulatory report, and multiple ad hoc reports. Each of these activities requires less documentation, coding and validation since the work has been pushed upstream to the CAPMART. The CAPMART is also refreshed daily allowing users to access and interpret their current data without waiting for a programming resource to pull the data for them.

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CONTACT INFORMATION

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