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Pacemaker Guy: De-Mystifying a Business Use Case for SDTM and Medical Device Domains

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# Pacemaker Guy: De-Mystifying a Business Use Case for SDTM and Medical Device Domains

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# Agenda

1. The Need
2. The Solution
3. Implementation
4. Conclusion

# The Need

# The Need

- In 2014 a CDRH statistician did a presentation in 2014 at an AdvaMed Statistical Issues conference (Nair 2014).

- The statistician listed six areas where CDRH was having issues with medical device submissions:
  1. Hard to identify and determine the impact of protocol deviations
  2. Lack of data traceability
  3. The impact of missing data
  4. Lack of accountability for all subjects in a clinical trial
  5. Lack of code lists for variables
  6. Lack of standards for electronic data

# The Need

| | CDRH Issue | CDRH Reviewer Request |
|---|---|---|
| Data Traceability | Lack of data traceability; Means cannot assess data validity | • Provide mechanism to trace each data point from the study report back to the CRF |
| Trial Data Issues | | • Include electronic datasets in PMA submission<br>• AE listings for medical reviewers<br>• Analysis dataset(s) and raw data to validate results<br>• Analysis datasets to support key effectiveness/safety analyses<br>• Basic demographic variables and important covariates in analysis datasets<br>• Define/README file for datasets and program files<br>• Document datasets and code sufficiently |

# The Solution

# The Solution

- The CDISC Medical Device team took the presentation by the CDRH statistician and annotated it with all of the ways that CDISC standards could solve the problems that CDRH is experiencing with data submitted to them.
- The annotated solutions was presented as a poster at the CDISC International Interchange in 2015 (Nair et al 2015).

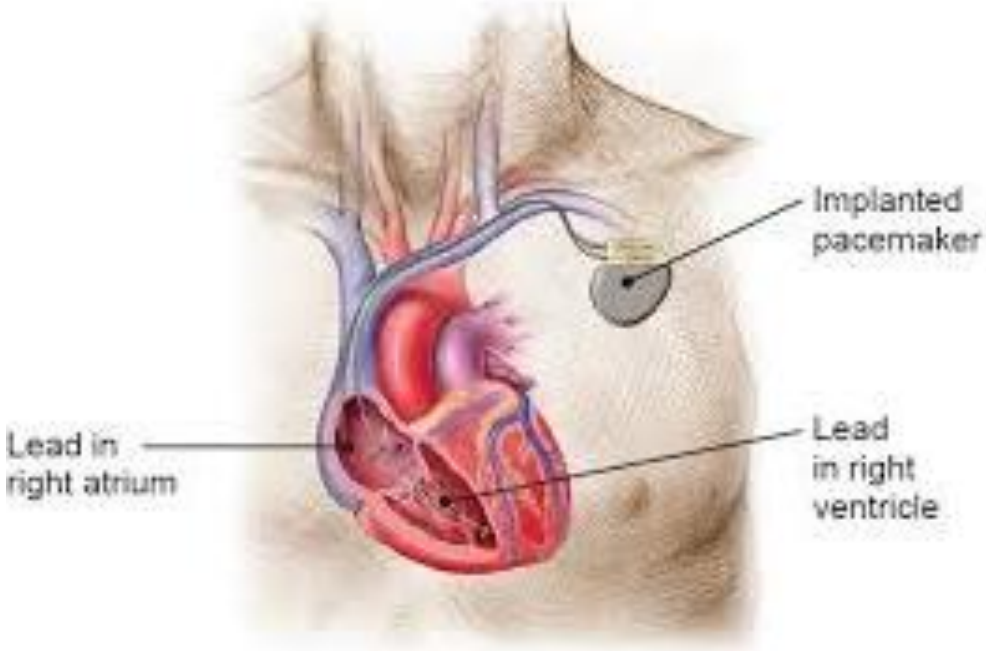
# The Solution

| | CDRH Reviewer Request | CDISC Solution |
|---|---|---|
| Data Traceability | • Provide mechanism to trace each data point from the study report back to the CRF | • ADaM, SDTM, associated define-xml and CDASH-conformant CRFs are specifically designed for this: hyperlink each variable to associated algorithm(s), source dataset(s), controlled terms and annotated CRF(s) |
| Trial Data Issues | • Include electronic datasets in PMA submission<br>• AE listings for medical reviewers<br>• Analysis dataset(s) and raw data to validate results<br>• Analysis datasets to support key effectiveness/safety analyses<br>• Basic demographic variables and important covariates in analysis datasets<br>• Define/README file for datasets and program files<br>• Document datasets and code sufficiently | • SDTM and ADaM provide subject- and device-level tabulation and analysis datasets<br>• Data transmitted in SAS transport files<br>• Standardized AE data support listings from data visualization tools<br>• ADaM defines key effectiveness / safety analyses and datasets, and permits inclusion of any/all relevant variables<br>• ADaM datasets are “one proc away” from running analyses<br>• Define-xml provides structure to document all datasets |

# Implementation

# Pacemaker


Artificial cardiac
pacemaker


Implanted
pacemaker
Lead in
right atrium
Lead
in right
ventricle

# Implementation

- Pacemaker Guy
  - “Pacemaker Guy”, was randomized to a single blind study (STUDYID= CDISCLWO), testing the new design “Right Ventricle Pacing Lead.”
  - The marketed pacemaker has a stable generator of a cardiac pacemaker with 2 leads (right atrium and right ventricle).
  - Surgery to implant the pacemaker went as planned.
  - On Day 8, subject complains of fatigue. EKG and examination detects bradycardia.
    - Further testing detects the “study” lead has migrated.
  - The next day the subject is admitted for an unscheduled hospitalization and surgery to reposition the lead.
  - During the replacement surgery, the surgeon replaces the lead.

# Implementation

- Pacemaker Guy (continued)
  - The clinical site should return the lead that was replaced to manufacturer for engineering review to determine if it malfunctioned.
  - On Day 10, the subject was discharged, and examinations are satisfactory.
  - Returns on Day 18 and all is fine.

# Implementation

- The paper that accompanies this presentation shows how to implement the SDTM Medical Device and Core domains.
  - SDTM Medical Device Domains implemented include:
    - DI, DO, DU, DX, DR, DE and DT
  - SDTM Core Domains implemented include:
    - DM, DS, AE, PR, CE, HO, HE, EG

# Implementation

## Schedule of Events

| | | Visit 1 | Visit 2 |
|---|---|---|---|
| | | Screening | Implant Procedure |
| | | Day -1 > 1 | Day 2 |
| **SDTM Domain** | **Study Assessments** | | |
| DS | Informed Consent | X | |
| DS | Randomization | X | |
| PR | Procedure for Pacemaker | | X |
| DI/DO/DT | The device as is at the site | X | |
| DU/DX/DR/DT | The device as implanted in the subject | | X |

# Implementation

- The Device Identifiers (DI) domain identifies each device and component uniquely, and this is done by creating SPDEVID.

| SPDEVID | DIPARMCD | DIPARM | DIVAL |
|---|---|---|---|
| LWO001 | DEVTYPE | DEVICE TYPE | IMPLANTABLE PACING SYSTEM |
| LWO001 | MANUF | MANUFACTURER | RELIABLE CARDIOVASCULAR SOLUTIONS, INC. |
| LWO003-01 | DEVTYPE | DEVICE TYPE | IMPLANTABLE PACEMAKER PULSE-GENERATOR |
| LWO003-01 | MODEL | MODEL | RELIABLE PM GENERATOR |
| LWO002-01 | DEVTYPE | DEVICE TYPE | RV PACKING LEAD |
| LWO002-01 | MODEL | MODEL | RELIABLE RV ELECTRODE |
| LWO002-02 | DEVTYPE | DEVICE TYPE | RA PACKING LEAD |
| LWO002-02 | MODEL | MODEL | RELIABLE RA ELECTRODE |
| LWO002-03 | DEVTYPE | DEVICE TYPE | RV PACKING LEAD |
| LWO002-03 | MODEL | MODEL | RELIABLE RV ELECTRODE |

# Implementation

- The Device In-Use (DU) domain contains data describing settings for devices as used with individual subjects.

| USUBJID | SPDEVID | DUTESTCD | DUTEST | DUORRES | DUORRESU | DULOC |
|---|---|---|---|---|---|---|
| CDISCLWO-018-03 | LWO002-01 | SIGW | ELECTRICAL SIGNAL WIDTH | 0.3 | MS | HEART, VENTRICLE |
| CDISCLWO-018-03 | LWO002-01 | SIGAMP | ELECTRICAL SIGNAL AMPLITUDE | 1.5 | VOLTS | HEART, VENTRICLE |

# Implementation

- The Device Exposure (DX) domain details a subject's exposure to a medical device under study

| USUBJID | SPDEVID | DXTRT | DXLOC | DXSTDTC | DXENDTC |
|---|---|---|---|---|---|
| CDISCLWO-018-03 | LWO003-01 | IMPLANTABLE PACEMAKER PULSE-GENERATOR | CHEST | 6/9/2015 | |
| CDISCLWO-018-03 | LWO002-01 | RV PACING LEAD | HEART, VENTRICLE | 6/9/2015 | 6/16/2015 |
| CDISCLWO-018-03 | LWO002-02 | RA LEAD | HEART, ATRIUM | 6/9/2015 | |
| CDISCLWO-018-03 | LWO002-03 | RV PACING LEAD | HEART, VENTRICLE | 6/16/2015 | |

# Implementation

- The Device Event (DE) domain details a medical device malfunction and may or may not be related to an adverse event in a subject.

| USUBJID | SPDEVID | DETERM | DECAT | DEACNDEV | DESTDTC |
|---|---|---|---|---|---|
| CDISCLWO-018-03 | LWO002-01 | LOW IMPEDANCE | EQUIPMENT FAILURE | EXPLANTED | 6/16/2015 |
| CDISCLWO-018-03 | LWO002-01 | INSULATION ABRASION | EQUIPMENT FAILURE | EXPLANTED | 6/16/2015 |
| CDISCLWO-018-03 | LWO002-01 | LEAD DISLODGEMENT | EQUIPMENT FAILURE | EXPLANTED | 6/16/2015 |

# Implementation – Disposition (DS) records

This data capture the status of the subject's study participation at various pre-defined time points, as well as the timing of pre-defined protocol milestones. In this example, the dates of the informed consent and randomization milestones are captured, as well as the subject's participation at the end of each epoch.

| USUBJID | DSTERM | DSDECOD | DSCAT | DSSTDTC | EPOCH |
|---|---|---|---|---|---|
| CDISCLWO-018-03 | INFORMED CONSENT OBTAINED | COMPLETED | PROTOCOL MILESTONE | 2015-06-02 | |
| CDISCLWO-018-03 | COMPLETED | COMPLETED | DISPOSITION EVENT | 2015-06-02 | SCREENING |
| CDISCLWO-018-03 | RANDOMIZED | RANDOMIZED | PROTOCOL MILESTONE | 2015-06-02 | |
| CDISCLWO-018-03 | COMPLETED | COMPLETED | DISPOSITION EVENT | 2015-06-09 | PROCEDURE |
| CDISCLWO-018-03 | COMPLETED | COMPLETED | DISPOSITION EVENT | 2015-06-023 | FOLLOW-UP |

# Implementation - Procedures (PR) records

The procedures domain captures data about any medical procedures conducted during the study. In this use case, the surgeries that implant and explant the pacemaker go into the PR domain as well as the radiograph.

| USUBJID | SPDEVID | PRTRT | PRDECOD | PRINDC | PRLOC | VISIT |
|---|---|---|---|---|---|---|
| CDISCLWO-018-03 | LWO001 | IMPLANTATION | IMPLANTATION | ATRIAL FIBRILLATION | | PROCEDURE |
| CDISCLWO-018-03 | | RADIOGRAPH | RADIOGRAPHY | BRADYCARDIA | CHEST | UNSCHEDULED |
| CDISCLWO-018-03 | LWO002-01 | EXPLANTED | EXPLANTATION | LEAD ABRASION | | UNSCHEDULED |
| CDISCLWO-018-03 | LWO002-03 | IMPLANTED | IMPLANTATION | IMPLANT REPLACEMENT LEAD | | UNSCHEDULED |

# Implementation – Adverse Events (AE) records

- After surgery is performed, subject develops a systemic infection. He returns to the site for the Day 8 follow-up visit, where fatigue, bradycardia, systemic infection and incision site pain are recorded as AEs. The subject is returned to surgery where the lead is replaced.  No further AEs reported.

| USUBJID | AETERM | AEDECOD | AESEV | AEOUT | AESTDTC | AEENDTC |
|---|---|---|---|---|---|---|
| CDISCLWO-018-03 | INCISION SITE PAIN | INCISION SITE PAIN | MODERATE | RECOVERED/ RESOLVED | 2015-06-11 | 2015-06-13 |
| CDISCLWO-018-03 | FATIGUE | FATIGUE | MILD | RECOVERED/ RESOLVED | 2015-06-13 | 2015-06-17 |
| CDISCLWO-018-03 | BRADYCARDIA | BRADYCARDIA | MODERATE | RECOVERED/ RESOLVED | 2015-06-13 | 2015-06-17 |
| CDISCLWO-018-03 | SYSTEMIC INFECTION | SYSTEMIC INFECTION | MODERATE | RECOVERED/ RESOLVED | 2015-06-13 | 2015-06-30 |

# Conclusion

# Conclusion

- This presentation has demonstrated the need for implementing CDISC standards for Medical Device submissions to CDRH.
- We have shown that CDISC standards can provide solutions to problems that occur with Medical Device submissions to CDRH.
- We have illustrated using Pacemaker Guy how to implement SDTM for Medical Device submissions.
- Currently, the Center for Devices and Radiologic Health (CDRH) encourages (but does not requires) sponsors to submit data in CDISC conforming standards
  - https://www.fda.gov/medicaldevices/deviceregulationandguidance/datastandardsmedicaldevices/default.htm.
- This webpage lists the following reason for encouraging sponsors to submit CDISC conforming data:
  - https://www.cdisc.org/system/files/all/article/PDF/2014%20Business%20Case_Executive%20Summary.pdf

# Thank You!

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