# Evolution or Revolution:

## Transitioning from a long history of internal standards and SAS computing environment to CDISC and an off-the-shelf SCE

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# Disclaimer and preface

- Views are my own
- My career spans only 2 life sciences companies
- Feel free to shout out during presentation if I'm not making sense
- Definition of evolution versus revolution
  - *Evolution*: a process of continuous change from a lower, simpler, or worse to a higher, more complex, or better state
  - *Revolution*: a sudden, radical, or complete change

# Company History

- Cetus 

- Chiron 

- Novartis 

# Global organization – most functions

- BCDM is geographically dispersed, global orientation
- Data managers in Amsterdam and India
- Statisticians and programmers in 5 countries
- Clinical operations mirrors this structure
  - Key decision makers and departments in Cambridge and Italy
  - Trials run by regional teams
- Bottom line:
  - Systems, processes, interactions need to support and take into account these factors

# History of internal BCDM standards

- When, why and how did standards start
  - Chiron - 1993
  - Standards-oriented director – executive support
  - Less project load, strong design/programming skills
  - GCP, ICH influences
- Both data and standard SAS programs for reporting
- Home grown tools
- Lots of accompanying processes and documentation, however ...
  - No coding standards, no system usage standards – remarkably few SOPs in the programming group

# Standard demographics CRF and dataset

demog.sas7bdat

| | Variable | Type | Len | DLen | Format | InFormat | Label |
|---|---|---|---|---|---|---|---|
| 1 | AGED | Num | 8 | 12 | 12. | . | AGED |
| 2 | BIRTHDT | Num | 8 | 7 | DATE7. | . | BIRTHDT Derived from BIRTHDY, BIRTHMO |
| 3 | BIRTHDT_CRF | Char | 12 | 12 | $12. | . | BIRTHDT_CRF in text format Derived fro |
| 4 | BIRTHDY | Num | 8 | 12 | 12. | . | BIRTHDY |
| 5 | BIRTHMO | Char | 3 | 21 | $21. | $21. | BIRTHMO |
| 6 | BIRTHYR | Num | 8 | 12 | 12. | . | BIRTHYR |
| 7 | BLOCKREP | Char | 40 | 40 | $40. | $40. | BLOCKREP |
| 8 | BMI | Num | 8 | 12 | 12. | . | BMI |
| 9 | CENTER | Char | 3 | 3 | $3. | $3. | CENTER |
| 10 | CRI | Char | 3 | 3 | $3. | $3. | CRI |
| 11 | CRISP | Char | 200 | 15 | $200. | $200. | CRISP |
| 12 | CRIW | Char | 16 | 15 | $16. | . | CRIW |
| 13 | CTRECID | Char | 40 | 15 | $40. | $40. | CT field: UNIQUE RECORD IDENTIFIER |
| 14 | EDCBLOCK | Char | 40 | 15 | $40. | $40. | EDCBLOCK |
| 15 | EDCPAGE | Char | 40 | 15 | $40. | $40. | EDCPAGE |
| 16 | ENTDTIME | Num | 8 | 15 | DATETIME2 | DATETIME20. | CT field: ENTRY DATE TIME |
| 17 | ENTID | Char | 20 | 20 | $20. | $20. | CT field: ENTERER ID |
| 18 | EXT | Num | 8 | 12 | 12. | . | EXT |
| 19 | FORMDT | Num | 8 | 7 | DATE7. | . | FORMDT Derived from FORMDY, FORMMO and |
| 20 | FORMDT_CRF | Char | 12 | 12 | $12. | . | FORMDT_CRF in text format Derived from |
| 21 | FORMDY | Num | 8 | 12 | 12. | . | VISIT DAY |
| 22 | FORMMO | Char | 3 | 21 | $21. | $21. | VISIT MONTH |
| 23 | FORMYR | Num | 8 | 12 | 12. | . | VISIT YEAR |
| 24 | HT | Num | 8 | 12 | 12. | . | HT |
| 25 | HTD | Num | 8 | 12 | 12. | . | HTD |
| 26 | HTUNIT | Char | 3 | 3 | $3. | $3. | HTUNIT |
| 27 | HTUNK | Char | 3 | 3 | $3. | $3. | HTUNK |
| 28 | HTUNKW | Char | 7 | 7 | $7. | . | HTUNKW |
| 29 | LASTPG | Char | 1 | 1 | $1. | $1. | LASTPG |
| 30 | MRGDTIME | Num | 8 | 15 | DATETIME2 | DATETIME20. | CT field: MERGE DATE TIME |
| 31 | PAGE | Num | 8 | 12 | 12. | . | PAGE |
| 32 | PROT | Char | 18 | 18 | $18. | $18. | PROT |
| 33 | PRVPN | Char | 3 | 3 | $3 | $3 | PRVPN |

Vaccines Standard

## DEMOGRAPHICS

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CHIRON | VACCINES

Protocol Information is Inserted Here

| PROTOCOL NUMBER | SITE NUMBER | SUBJECT NUMBER | SUBJECT INITIALS (First, Middle, Last) |
|---|---|---|---|
| V-0-P-0 | 0 0 | 0 0 _ _ _ _ | _ _ _ |

| VISIT DATE (dd-mm-yyyy) | VISIT NUMBER |
|---|---|
| _ _ - _ _ - _ _ _ _ | 1 |

Screen Number: 9 _ _ _ _ _

Date of Birth: _ _ - _ _ - _ _ _ _ (dd mm yyyy)

Sex:
- ☐ 1 Male
- ☐ 2 Female

Ethnic Origin: (check one only)
- ☐ 1 Asian
- ☐ 2 Black
- ☐ 3 Caucasian
- ☐ 4 Hispanic
- ☐ 5 Other, Specify: _____

Weight: ☐☐☐.☐ kg

Height: ☐☐☐ cm

Did the subject meet all study entry criteria specified in the protocol?

☐ 1 Yes ☐ 2 No

If No, describe: _____

After the subject had signed the informed consent form, I performed a physical examination and assessed subject's in- and exclusion criteria as specified in the study protocol.

_____ Investigator's Signature

_____ Date

INVESTIGATOR RETAINS YELLOW COPY

Oct-03

# The benefits of adopting data standards

- Common understanding across projects/teams/people
- Pooling
- Standardized reporting
- Decreased costs in printing CRFs
- More trials, less staff
- Other examples of standards and benefits
  - Programming standards enhance compliance, consistency, maintainability
  - Documentation standards facilitate historical review, audit readiness

# Success factors for standards

- Dedicated staff
- Governance structure
- Standing ground in the face of criticism
  - Not yielding to whims of clinical colleagues
  - Convincing clinical colleagues of benefits
  - Involving clinical colleagues in shaping and maintaining standards
  - Articulating the value of standards

# Maintaining a standards-based environment

- Needless to say, a challenge in its own right
  - Governance
  - Metadata and more metadata – becomes the focus
  - Backward compatibility
  - Impact analyses for changes become more complex when you have more studies, across increasing projects
  - Turnover in personnel and skill set
- How to avoid getting trapped into a closed frame of mind
  - Still seeing the big picture – don't force something to fit into a model which can't hold it
  - Analogy: oncology units tend to branch out on their own

# Emergence of CDISC data standards

- Internal standards help people within a company
- External standards help people across an industry
- FDA acceptance the key motivator for adoption
  - CBER has been slower than CDER
- Some auxilliary questions
  - Do reviews go faster with CDISC?
  - How stable are CDISC standards?
  - Does it mean programmers and data managers become commodity items?  Can they move interchangably between companies?
  - etc.

# Statistical computing environments (SCE)

- Infrastructure (toolset and processes) with which SAS programmers work
- Think and you will see/hear about various types of environments defined by a few characteristics
  - Central versus workstation
  - Validated versus non-validated
  - Management by IT versus management by biostats
  - Process orientation versus technical orientation

Central Server

Distributed PCs

# Programming in a non-structured environment

- PC SAS
- Other tools –freeware or home-grown
- Lack of standard folder structure
- No formalized review of code
- Absence of defined workflows and processes
- Undisciplined, e.g. full admin privilege to computer

# Our statistical computing environment

- Central SAS server
  - Windows Terminal Server
  - Evolved from a more informal central model to a more controlled central model
- Driven by compliance needs
  - 21 CFR Part 11
  - Maturation of computer systems validation requirements – IQ, OQ, PQ (even led SAS to adopt supportive tools)
  - Audit
  - Information security

# What makes a SCE “structured and disciplined”?

- Formal access procedure
- Standard folder structure
- An infrastructure to support change control
  - SUGI 31: *SAS® AND VMWARE® TO CREATE AN ENVIRONMENT FOR COMPUTER. SYSTEMS VALIDATION IN A PHARMACEUTICAL COMPANY*
- Support for programming lifecycle
  - Dev, test, prod
  - Check in, check out
  - Versioning
  - Developer checklists and peer review forms

# The Project

- Decision to migrate all legacy data to CDISC SDTM
  - 250+ studies
- Move our SCE to off-the-shelf product
  - Including standard reporting utilities (macro library)
- Do it all in less than 1 year – no pilot phase
- Future
  - Migrate the EDC data standard to CDASH conventions
  - ADaM for analysis

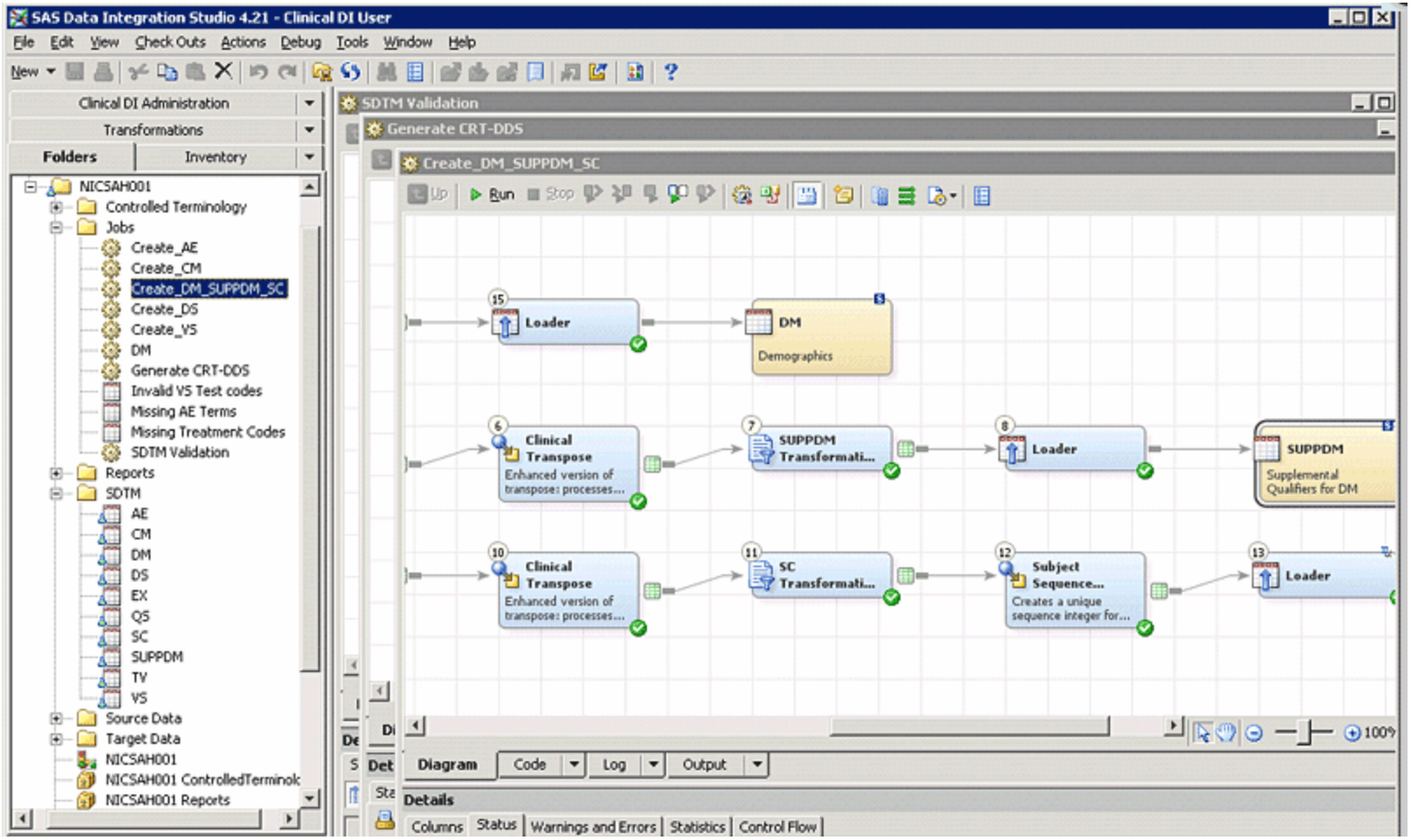
# Motivations for change

- CDISC submission requirement
- Ability to respond quickly to pooled analysis questions from health authorities
- Hosting by third-party; transfer risks for validation, support, and disaster recovery to vendor
- Lack of skill set and resources to refine current SCE
- Leverage off-the-shelf tool for adhoc data exploration (Jreview)
- Emphasis on control, compliance and audit-proofing

# Leveraging CDI for data standards management

- CDI = Clinical Data Integration
  - Product that helps process raw data and map them to a standard
- Using CDI
  - Legacy data migration from current standard datasets to SDTM
  - Steady-state ETL from EDC source to SDTM datasets for reporting
  - Modelling data flows
- Prerequisites
  - Defining the company SDTM+ and other data standards

# CDI Screenshot (from SAS website)



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# SDD and its evolution

- Started with PH-CLINICAL
  - A self-contained clinical reporting environment for multiple audiences
- Now at 3.5
  - Progress toward programmer friendliness
- Next generation is 4.x
  - SAS listens to customers in their development

# Off-the-shelf SCE – Features

- Controlled access (logged)
- Standard folder structures
- Role-based security
- Workflows – controlled programming (dev/test/prod)
- Process orientation – traceability
- Auditing, versions, roll-back, check-in/check-out
- E-signatures and documentation
- Program using metadata

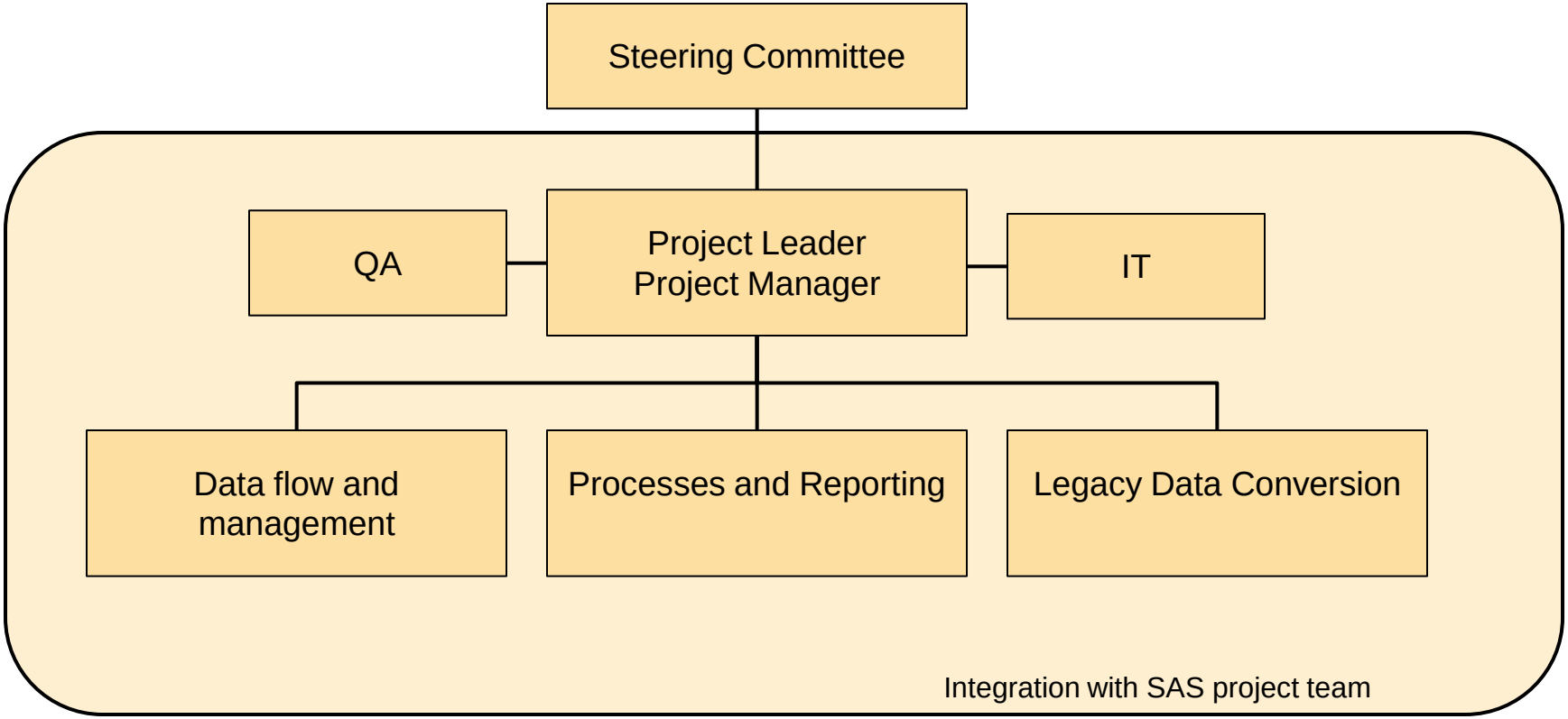
# Off-the-shelf SCE – Features (cont'd)

- Metrics – progress reports
- Messaging and notification
- Support for extending capabilities using an API
- Interface for non-biostat (QA, IT, external collaborators)
- Standardized IT infrastructure
- System qualification / change control / utility validation

# Project issues

- People
  - Inspiring them to help and adapt to change
  - How to motivate when overloaded with project workload
  - Refocusing mindset – “operational” to “creative”
  - Who to use – internal resources or contractors
- Organization
  - Stakeholders – Higher management, Steering committee
  - The project team – Leaders, QA, IT, business-driven subteams
  - 3 areas of focus – future data management, reporting, legacy data conversion
  - Understanding roles – myself included

# Project organization



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# Project issues (cont'd)

- Challenges
  - Working virtually
  - Technology hurdles – hosted solution connecting to in-house databases; replacements for familiar in-house tools
  - Competing demands and limited resources
  - Communications and transition – managing expectations
  - Available skill set
- Considerations
  - Learning from past hosted system efforts (EDC, IVRS)
  - Learn from industry (conference papers, local events)
  - Engage different parts of the organization early

# Project issues (cont'd)

- Decisions
  - Driving consensus in short time frame that will not haunt us later
  - Stakeholder buy-in
- Change
  - People aspects of change (different ways people perceive/cope)
  - Assuring a smooth transition, but how?
  - Avoid feeling helpless as people move toward something unknown
  - Training
  - Managing expectations

# Reasons to Expect Success

- Experience with standards
- Homogeneity of vaccines data
  - Facilitates migration to SDTM
- Support from top management
- Ability of CDI to serve as the migration tool
- Platform independence of std. programs
- Experience with SAS environment migration
- Support from SAS

# Concluding thought: can standards go too far?

- Coding standards
- Naming standards (files, variables)
- Standard look-and-feel to output
- Endless meetings of governance committees
- Flexibility is a casualty
  - Losing view of “big picture”
  - Loss of motivation for creativity
- Introduction of standards to govern standards
  - Some companies have an SOP on how to write and maintain SOPs

# Acknowledgments


- Pantaleo Nacci
  - Global Head, Statistical Programming
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  - Senior Programmer, original developer of many standard macros

# Questions and feedback