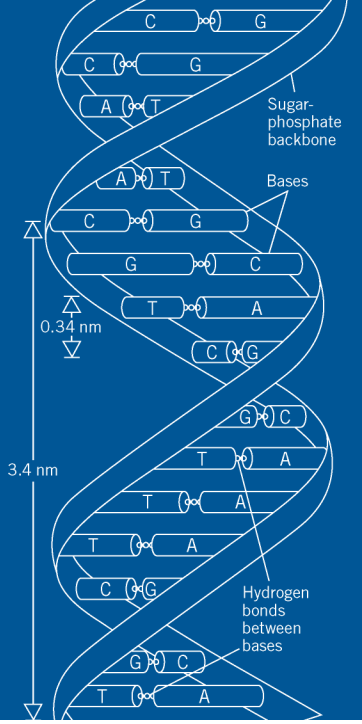


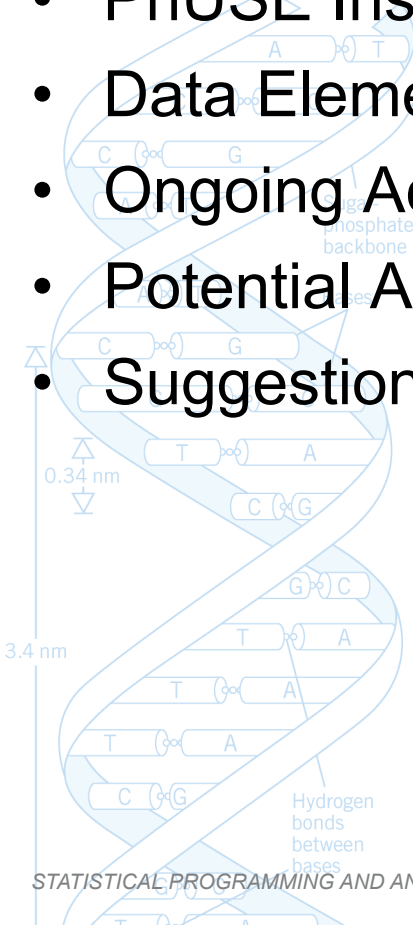
PhUSE Working Group for Inspection Site Selection Data Standards

Patricia L. Gerend
Genentech, Inc., A Member of the Roche Group
2 December 2015

Genentech
A Member of the Roche Group

Agenda

- PhUSE Working Groups (WGs)
- Inspection Site Selection Processes
- PhUSE Inspection Site Selection WG
- Data Elements and CDISC Applicability
- Ongoing Activities and Next Steps
- Potential Approaches for Sponsor Companies
- Suggestions / Questions



Introduction to PhUSE Working Groups (WGs)

FDA/PhUSE Computational Science Symposium (CSS) occurs annually with the goal of increasing efficiency of health product development and regulatory review via presentations at the annual event and longer-term working groups (WGs).

Participants in CSS and WGs:

- Industry
- FDA
- CDISC
- Vendors
- Academia

See this web site for details:
http://www.phuse.eu/cs-working-groups.aspx

Introduction to PhUSE Working Groups (WGs)

Managing Volunteer Teams

Challenges with volunteerism:

- Good intentions but little available time
- No direct authority

Potential approaches:

- *Dictatorial:*
  Tell team what to do and make own decisions if they don't participate
- *Collaborative leadership*:
  Persevere and nudge respectfully
- *Laissez faire:*
  Wait for team members to get it together
- *Combination of above*

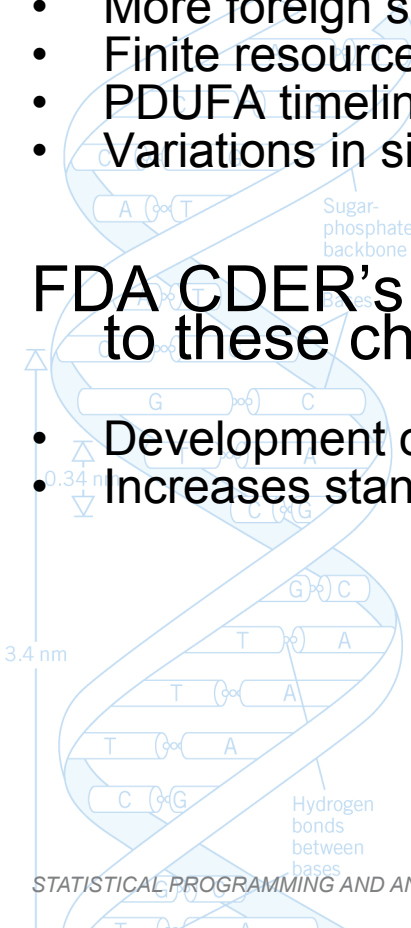
Background on FDA's Inspection Site Selection Methodology

Increase in size and complexity of clinical trials is challenging for inspection site selection:

- More sites per trial
- More foreign sites
- Finite resources for site inspection
- PDUFA timelines and resulting need for more efficiency
- Variations in site selection approaches

FDA CDER's Office of Scientific Investigations (OSI) response to these challenges:

- Development of risk-based inspection site selection tool
- Increases standardization and resulting efficiency of process



Inspection Site Selection Dilemma

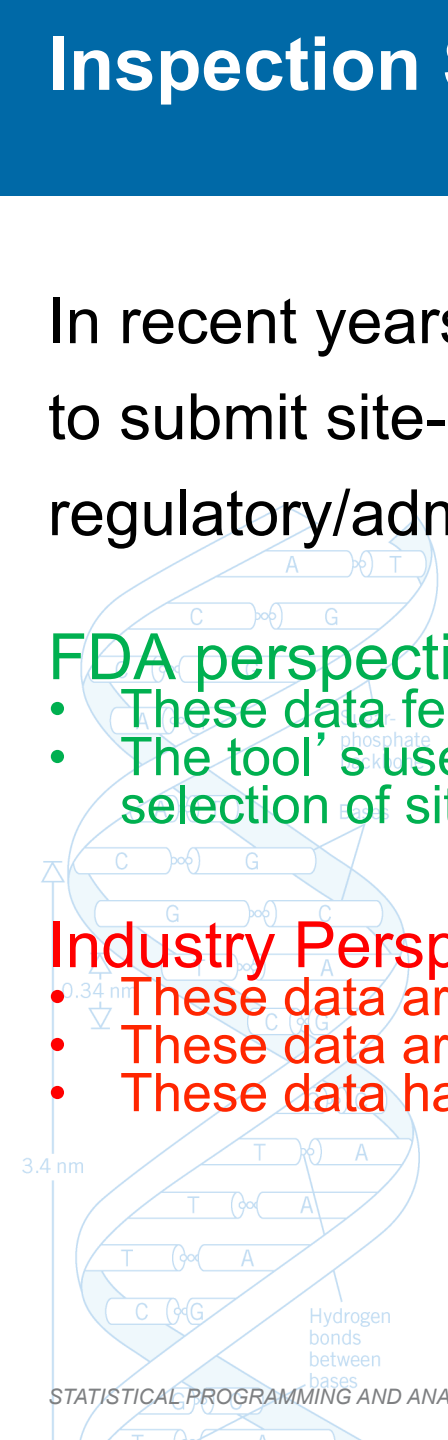
In recent years, FDA-CDER began asking companies to submit site-level datasets (safety/efficacy results, regulatory/admin info) to aid in selection of sites for inspection.

FDA perspective:

- These data feed into the new tool developed by OSI
- The tool's use of these data improve the quality and efficiency of selection of sites for audit

Industry Perspective:

- These data are rarely used by sponsor companies
- These data are difficult to produce due to diverse sources
- These data have few current CDISC standards



PhUSE Inspection Site Selection WG Overview

Inspection Site Selection WG formed to address situation

- Began March 2012
- Changed original remit to eliminate business process recommendations
- Developed draft gap analysis on what OSI needs and what CDISC provides
- Went on hiatus due to job changes
- Re-formed April 2015
  - *Lead: Patty Gerend*
  - *FDA Co-Lead: Jean Mulinde*
  - *CDSIC Co-Lead: Nate Freimark*

Remit:

- Complete gap analysis between what OSI needs and what CDISC provides
- Submit gap analysis to CDISC for consideration of developing site-level domains and other new standards

Timeline:

- Complete activities in 2015

FDA Draft Guidance

While WG was deliberating…..

In 12/2012 FDA issued:

- Draft Guidance "*Summary Level Clinical Site Data for CDER's Inspection Planning*"
- "*Specifications for Preparing and Submitting Summary Level Clinical Site Data for CDER's Inspection Planning*"

Summary of site dataset guidance and specs:

- Site inspections needed to safeguard patients
- Site dataset needed to assist in selection of sites for inspection
- Needed for pivotal studies
- Should be submitted before filing if possible, else with filing
- Include in Module 5
- Includes regulatory, site-level safety / efficacy, investigator information ***by clinical site and treatment arm***

Data Elements and CDISC Applicability, Current Overview

39 variables requested:

- 7 (18%) are explicitly represented by current CDISC standards
- 5 (13%) could be incorporated into SDTM.TS.TSPARM by extending existing Controlled Terminology
- **27 (70%) have no current CDISC standards**

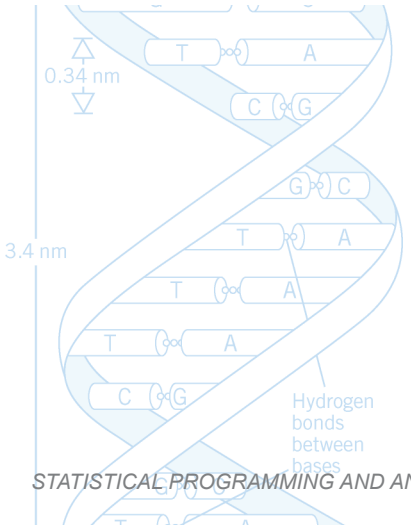
With some effort, the following could occur:

- 1 (3%) could be assigned by the sponsor company
- 9 (23%) could be derived from existing SDTM and/or ADaM

NOTE: Some variables could theoretically be extracted from the backbone of the xml submission but a process would be needed.

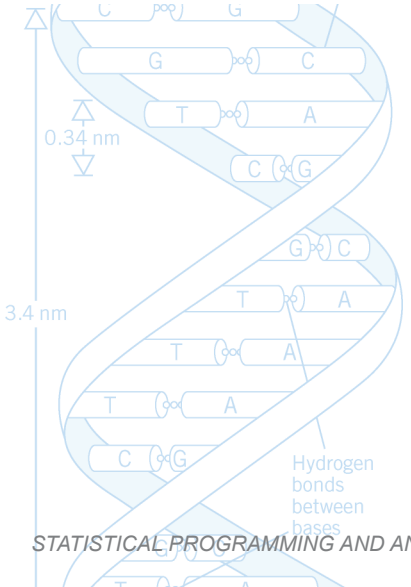
Data Elements and CDISC Applicability, SUBMISSION-Level Variables

Variable	CDISC Std
IND Number	
NDA Number	
BLA Number	
Supplement Number	
Sponsor Name	SDTM.TS.TSPARMCD='SPONSOR'
Sponsor Count	



Data Elements and CDISC Applicability, STUDY-Level Variables

Variable	CDISC Std
Study Number	SDTM.TS.STUDYID
Study Title	SDTM.TS.TSPARMCD='TITLE'
Arm	SDTM.TA.ARM
Primary Endpoint	SDTM.TS.TSPARMCD='OBJPRIM'
Endpoint Type	

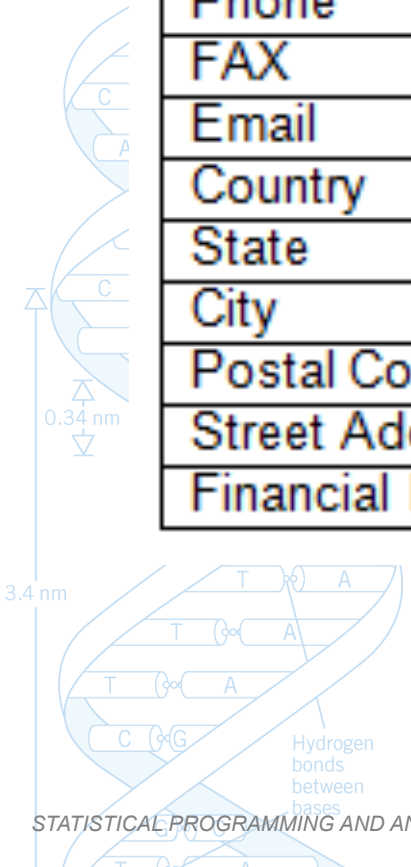


Data Elements and CDISC Applicability, SITE-Level Variables – Part 1

Variable	CDISC Std
Domain	
Site Identifier	SDTM.DM.SITEID
Under IND	
Number Subjects Screened	
Number Subjects Enrolled in Safety Population	
Number Subjects Discontinued	
Treatment Efficacy Result	
Treatment Efficacy Results Standard Deviation	
Site-Specific Efficacy Effect Size	
Site-Specific Efficacy Effect Size Standard Deviation	
Censored Observations	
Number Non-Serious AEs	
Number Serious AEs	
Number of Deaths	
Number of Protocol Violations	
Maximum Financial Disclosure Amt	

Data Elements and CDISC Applicability, SITE-Level Variables – Part 2

Variable	CDISC Std
Last Name	
First Name	
Middle Initial	
Phone	
FAX	
Email	
Country	SDTM.DM.COUNTRY
State	
City	
Postal Code	
Street Address	
Financial Disclosure Amount	



Changes Planned to 12/2012 Draft FDA Specs

- Clarifications to meaning/content of some variables
- Variable name changes:
  - STUDY -> STUDYID (to conform to CDISC standard name)
  - DISCONT -> DISCSTUD (to accommodate addition of treatment discontinuations)
  - ENROLL -> SAFPOP (to clarify expected content)
- New variables:
  - DISCTRT (No. of treatment discontinuations)
  - STREET2 (Second line for site address)
- Removed variable:
  - FINLMAX (Maximum financial disclosure amount for any investigator at the site)

Ongoing Activities and Next Steps

- WG wrapping up gap analysis between OSI request and CDISC standards
- WG providing input to FDA on revision of draft guidance and specs
- WG will submit gap analysis to CDISC organization, who will
  - Consider site-level domain(s)
  - Consider other additional standards
  - Consider database design
  - Consider idea of extracting some of this info from filing's xml backbone
- FDA to further develop programming tools to utilize data in new standard structures provided by CDISC (if this happens)

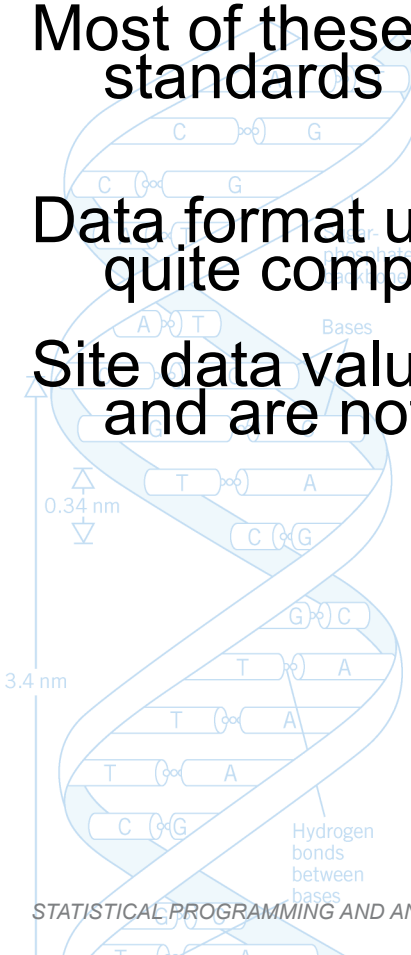
Summary of Investigator Data Situation

Lots of data points needed that are scattered across sponsor systems / paperwork

Most of these data points do not have accompanying CDISC standards

Data format used in OSI's tool is not in 3rd normal form and is quite complex

Site data values are generally produced only for submissions and are not normally used by sponsors



Potential Approaches for Sponsor Companies

Until final decisions are made about FDA requirements, here are some approaches that have worked across companies:

- Discuss with FDA before submission what is needed
- If FDA reviewers request information by site, consider:
  - First choice: Producing a dataset that meets FDA's 12/2012 draft specs (once FDA's tools changes to match PhUSE WG's revised specs, aim for these specs)
  - Second choice: Providing only a listing of the information requested in the FDA's 12/2012 draft specs. This may or may not save time for sponsor and can still be useful by FDA, although not as useful as the dataset (Note that FDA does not key this info into their tool, so must peruse it visually)

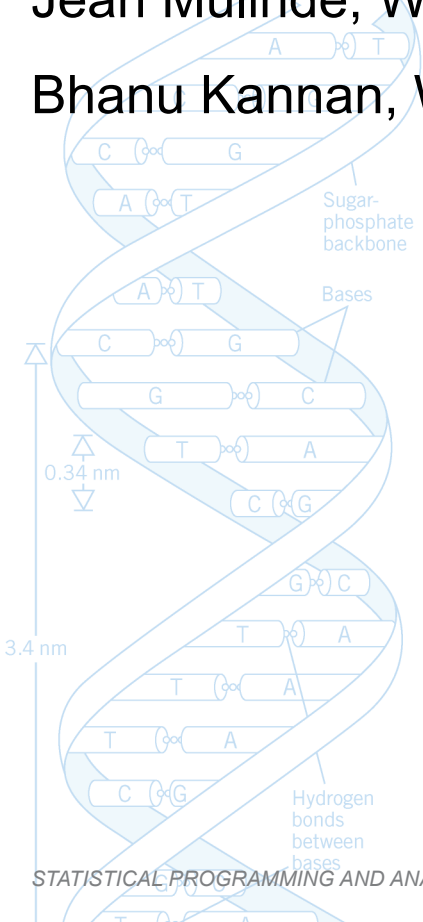
Acknowledgements

Michael Brennan, original WG lead

Nate Freimark, WG co-lead, CDISC

Jean Mulinde, WG co-lead, FDA

Bhanu Kannan, WG team member, FDA



Suggestions / Questions

Thoughts on including site-level domain and other new site-level standards in CDISC?

Thoughts on including financial / admin info in CDISC?

Thoughts on what site level approaches have worked for your company?

Other thoughts?