

Abstract:

While the standards used in clinical and nonclinical have the same foundation, the requirements, procedures, practices and workflows for data collection and reporting of nonclinical safety studies are significantly different from those in clinical. Thus while some of the challenges of data standardization and submission may be similar, most solutions and best practices for addressing these challenges in nonclinical are unique to that discipline. This presentation provides a survey of some key past and present challenges in nonclinical data standardization, along with approaches used by industry experts to address these challenges. The presentation will also highlight some key differences in clinical and nonclinical practices, thus providing a foundation for all attendees to relate the challenges presented to their own activities.

A Nonclinical Perspective

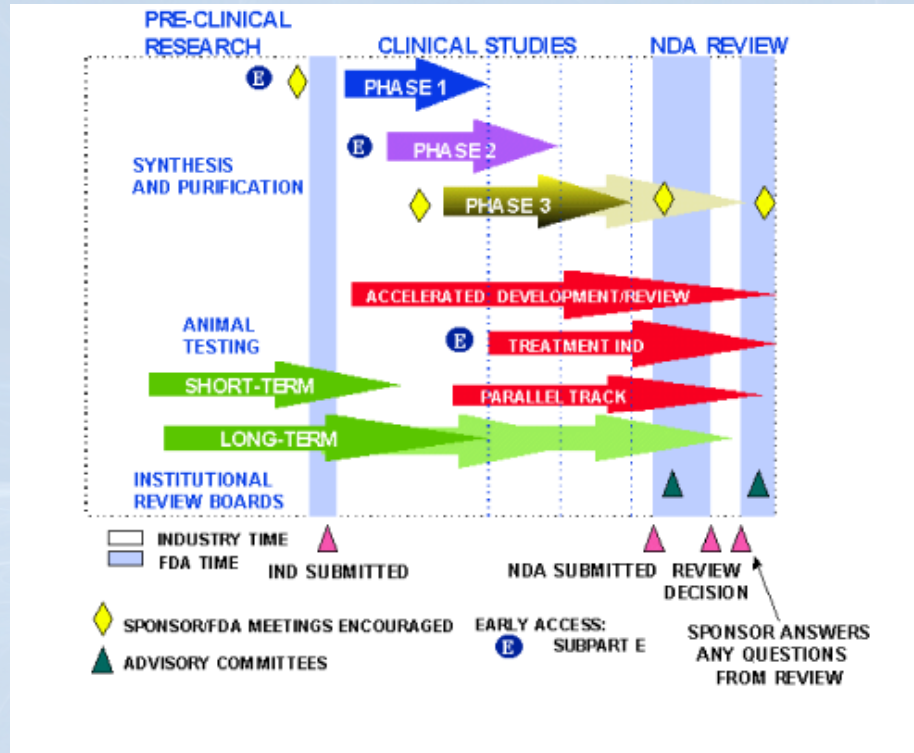
Can clinical and nonclinical learn from one another's standardization practices?

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Nonclinical Safety Assessment Studies

Not just clinical studies with animals....



New Drug Development and Review Process

FDA CDER SBIA

Nonclinical Safety Assessment

- Most testing is *in-vivo*; *in-vitro*, *ex-vivo* testing also performed
- Animals on a study differ only by sex and dosing regimen
- Control group present on study, no drug administered
- Dose groups each get a different dosing regimen
- All factors on the study controlled
- Group results (means, incidences) used for analysis
- Drug effect is based on group differences from control, generally identified based on well-established, published comparative statistics

ICH Safety Guidelines set the framework

Safety Guidelines / ICH Guidelines / Work Products /

ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

[Zip file with all ICH Safety Guidelines in Word format](#)

Stakeholders are invited to report Safety Guideline issues at safety@ich.org.

S1A - S1C Carcinogenicity Studies



S2 Genotoxicity Studies



S3A - S3B Toxicokinetics and Pharmacokinetics



S4 Toxicity Testing



S5 Reproductive Toxicology

S6 Biotechnological Products

S7A - S7B Pharmacology Studies

S8 Immunotoxicology Studies

S9 Nonclinical Evaluation for Anticancer Pharmaceuticals

S10 Photosafety Evaluation

S11 Nonclinical Safety Testing

Cross-cutting Topics

4. GUIDANCE ON DURATION OF CHRONIC TOXICITY TESTING FOR TRIPARTITE DEVELOPMENT PLAN

Arising from the extensive analysis and review of the above mentioned data in non-rodents and based upon the achievements of ICH1 for testing in rodents, and so as to avoid duplication and follow a single development plan for chronic toxicity testing of new medicinal products, the following studies are considered acceptable for submission in the 3 Regions:

1) Rodents:

a study of 6 months duration;

2) Non-rodents:

a study of nine months duration.

Regulatory Framework

- Since 1979, FDA requires researchers to use **21 CFR Part 58.1: Good Laboratory Practice for Nonclinical Laboratory Studies** (GLP) for preclinical laboratory studies. These regulations set the minimum basic requirements for:
 - study conduct
 - personnel
 - facilities
 - equipment
 - written protocols
 - operating procedures
 - study reports
 - and a system of quality assurance oversight for each study to help assure the safety of FDA-regulated product
- Collection and use of electronic data in a GLP study must follow **21 CFR Part 11: Electronic Records, Electronic Signatures**

Standardization Framework

➤ SEND Study Dataset

- Domain, record and variable data organization following SDTM (model)
- SENDIG Version 3.0 published 19 May 2011 and accepted by the FDA
- SENDIG Version 3.1 published 27 June 2016, not in the FDA data standards catalog
- SENDIG-DART Version 1.0 published as a provisional guide, not in the FDA data standards catalog

➤ Controlled Terminology (CT)

- Terminology required for regulatory submission
- Updated quarterly, managed by the NCI EVS at <http://evs.nci.nih.gov>

➤ Define.xml

- CRT-DDS Version 1.0 published 5 Feb 2005 and accepted by the FDA until 15 March 2018
- Define-xml Version 2.0 published 5 March 2013 and accepted by the FDA
- Define-xml Version 2.1 in public review, comments accepted through 5 May 2017

➤ Nonclinical Study Data Reviewers Guide (nSDRG)

- Overview for the study electronic data – template and user guide available from PhUSE
- FDA public comment period on draft closed 3 May, can still comment through PhUSE

Comparison of SDTMIG 3.2 & SENDIG 3.0

Domains (SDTMIG)	SENDIG
• Comments (CO)	Y
• Demographics (DM)	Y
• Subject Elements (SE)	Y
• Subject Visits (SV)	
• Concomitant Medications (CM)	
• Exposure as Collected (EC)	
• Exposure (EX)	Y
• Substance Use (SU)	
• Procedures (PR)	
• Adverse Events (AE)	
• Clinical Events (CE)	
• Disposition (DS)	Y
• Protocol Deviations (DV)	
• Healthcare Encounters (HO)	
• Medical History (MH)	
• Drug Accountability (DA)	

Domains (SDTMIG)	SENDIG
• Death Details (DD)	Y
• ECG Test Results (EG)	Y
• Inclusion/Exclusion Criterion Not Met (IE)	
• Immunogenicity Specimen Assessments (IS)	
• Laboratory Test Results (LB)	Y
• Microbiology Specimen (MB)	
• Microscopic Findings (MI)	Y
• Morphology (MO)	
• Microbiology Susceptibility Test (MS)	
• PK Concentrations (PC)	Y
• PK Parameters (PP)	Y
• Physical Examination (PE)	
• Questionnaires (QS)	
• Reproductive System Findings (RP)	

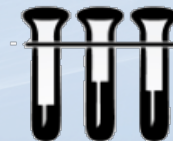
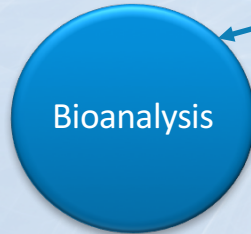
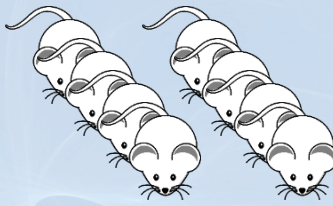
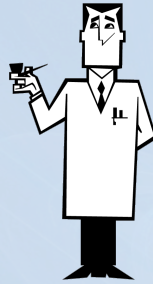
Domains (SDTMIG)	SENDIG
• Disease Response (RS)	
• Subject Characteristics (SC)	Y
• Subject Status (SS)	
• Tumor Identification (TU)	
• Tumor Results (TR)	
• Vital Signs (VS)	Y
• Findings About (FA)	
• Skin Response (SR)	
• Trial Arms (TA)	Y
• Trial Disease Assessment (TD)	
• Trial Elements (TE)	Y
• Trial Visits (TV)	
• Trial Inclusion/Exclusion Criteria (TI)	
• Trial Summary (TS)	Y
• Supplemental Qualifiers (SUPP--)	Y
• Related Records (RELREC)	Y

Impact on Standardization

- **Data Quality:** GLPs ensure the uniformity, completeness, reliability, reproducibility, quality, and integrity of nonclinical safety testing
- **Data Reporting and Analysis:** Validated “Push button” capabilities
- **SEND Processes:** Limited variability in study designs allow repeatable processes to be defined for standardization
- **Alignment with Clinical**
 - Study designs significantly different; nonclinical has adopted trial domains for alignment
 - Good alignment for clinical pathology, bioanalysis, PK
 - Alignment with some in-life, histopathology
 - Organ collection, weights, observations only in nonclinical; align with findings concepts
 - No precedence for in-vitro study data
 - No precedence for many DART (developmental and reproductive toxicity) concepts

Nonclinical Study Conduct

Location, location, location....



Multi Site Standardization

➤ Test Facility Responsible for Study SEND Package

- Aligns with study reporting responsibility
- Test sites must provide data to the test facility for integration
- Test facility integrates data from other test sites with their own data
- Test facility creates the define.xml and nSDRG with information from the test sites
- Test facility transmits study report and study SEND package to sponsor
- Sponsor includes SEND study packages in their submissions

➤ Challenges

- Test sites must integrate test facility information into their SEND domains
- If test sites provide SEND, they must integrate test facility information
- If test sites provide non-SEND files, test facility must transform test site data
- Both create concerns related to data ownership and responsibility

One Row can contain information from multiple parties:

- Requires clear lines of responsibility, exchange of information, verification by all parties

Key	
Study Animal Information	
Dosing Documentation	
Sample Collection	
Sample Analysis results	
TK Analysis	
Derived or assigned for SEND	

More than data to consider

- SEND Version
 - All dataset files must be the same SEND version
- Controlled Terminology (CT)
 - Terminology version used must be the same for all study datasets
- Define.xml must contain information from all contributors
 - Study-specific origins, derivations, terminologies, comments
- Study data Reviewers Guide (nSDRG) must contain information from all contributors
 - How SEND files were created
 - Definition of nonstandard controlled terminology extensions
 - Description of differences between SEND and the study report

Optimizing Standardization

- Test Facility provides details to test site with samples for analysis:
 - SEND Trial domains, demographics, dosing (EX) associated with sample collection
 - Partial SEND findings domain (LB, PC) with **sample details**
 - Template spreadsheet for information needed for define.xml
 - Template document for information needed for nSDRG
- Test Site creates SEND findings domain, associated CO, SUPP–
 - Test site merges analysis results with test facility sample details based in sample ID in –REFID
 - Same SEND Version and CT version in test facility TS domain
 - Information for define.xml and nSDRG added to test facility template
- Test Facility merges test site domain, define.xml and nSDRG into final SEND
- Automation available at nearly all phases

Nonclinical Collection, Reporting and SEND

Systems' impact on standardization...

Data Collection and Reporting Systems

➤ Commercial systems

- Available since late 1970s (initiated when GLPs became required)
- Validated for use with GLP submission studies
- All study designs in a single database, supporting a variety of company SOPs
- Studies can be instantiated in minutes using templates
- No CRFs – input screens driven by protocol design and standard operating procedures

➤ Real-time collection and reporting

- Tox LIMS - In-life, clinical pathology, post mortem, DART and CNS Safety Pharmacology
- Respiratory and cardiovascular tests that collect and analyze real-time continuous data
- Genetic toxicity testing
- Bioanalysis – frequently shared with clinical
- TK/PK calculations - frequently shared with clinical

➤ Individual and Summary Reporting is an embedded feature

Standardization Challenges

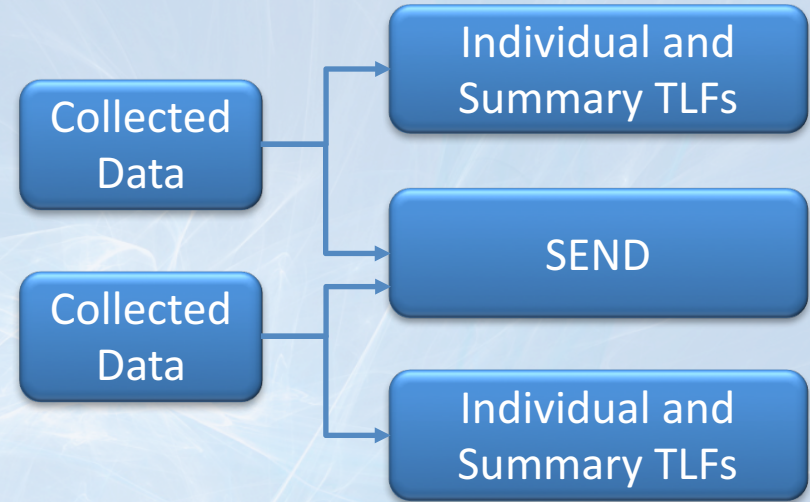
- Commercial Systems Predate CDISC standards
 - Built for maximum flexibility and efficiency
 - Wholesale modification to systems to "collect in the standard" are not practical
 - CDISC standards are not designed for data collection
- Some expected information not previously reported
 - Study protocol details only in PDF
 - Individual dose values
 - Baseline flags
 - Sample collection times
 - Timing Variables
- Common mismatch between system configuration and CDISC standards
 - Single tissue name vs. SPEC, ANTREG, DIR, LAT, PORTOT
 - Single measurement name vs. TEST, CAT, SCAT, SPEC, METHOD
 - Pathology tumor finding + tumor class vs. single MISTRESC entry
 - Study day, session name and date/time collected vs a plethora of timing variables
 - Controlled Terminology

Optimizing Standardization

- Encourage vendors to move commercial systems toward CDISC standards where practical
- Changes to best practice use of commercial systems can result in closer alignment with standards
 - Adoption of more rigid collection procedures
 - Implementation of CT in collection dictionaries when feasible
- Automated Algorithms during SEND Domain Creation
 - Translation from custom to published CT
 - For Splitting and Merging of Terms
 - For Removing Field Entries or Entire Records
 - For Creating Field Entries from Related Data
 - Lookup into EX for RFTDTC and TPTREF
 - Identifying baseline value
 - Calculating body weight gains, organ weight ratios
- Automated Findings Domain Merging
 - New –SEQ entries
 - Retain CO, RELREC SUPP– finding references

Analysis, Reporting and SEND Standardization

- › Individual Animal and Group Summary Tables, Listings and Figures for study report are created from collected data
- › SEND is created from collected data
- › Systems used for SEND and for TLFs may be different
- › Study report and SEND must match
 - Differences reported in nSDRG



Use of SEND in Analysis and Reporting

- Brings SEND into GLP use
- Would ensure that SEND and study TLFs are consistent
- Current collection system reporting capabilities are very complex
- SEND based visualization and analysis capabilities growing
- Would be a big change for nonclinical
- Some interest building



Final Study Preparations for Submission

This should be easier....

Optimizing Final Steps in SEND Preparation

➤ Final SAS files

- Generally created by SEND vendor tools, including tracked edits
- SAS not typically used in nonclinical

➤ Define.xml

- Created from completed SEND datasets
- No case for making define.xml in advance in nonclinical
- Integrate information as needed from test sites
- Clinical tools are sufficient for creation of define.xml
- Now SEND Representation on CDISC Define-xml team

➤ Package Verification

- Multiple checkers needed to get full coverage

Improved Collaboration

Is it possible? Is it worthwhile?

Barriers

- CDISC and PhUSE working groups largely separated
 - Even when working on same topic (although this is improving in PhUSE)
- Nonclinical is in the initial implementation phase
 - Advanced topics are a distraction
 - Small group of implementers, educators, volunteers
- SEND packages created within safety assessment
 - That is where core understanding of the data is, but...
 - Practices are then not shared in a company's clinical group
- Lack of understanding of one another's basic practices
 - Quickly leads to miscommunication
 - Few natural communication channels cross nonclinical/clinical

What Can Be Gained?

- Fewer stumbles when working in new areas
- Potential for sharing tools and techniques
- Potential for more innovation
- Potential for expanding use of standards
- Some obvious areas of collaboration
 - Bioanalysis, PK/TK



Questions