

Software Validation in Clinical Trial Reporting: Experiences from the Biostatistical & Data Sciences Department

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Introduction

- This presentation will provide an overview of validation and how validation processes can be applied to clinical trial reporting software and will include:
 - Why validate?
 - What is validation?
 - What validation isn't
 - What does validation involve?
 - Implementing a validation process
 - Conclusions/Considerations

Why Validate

“The FDA’s acceptance of data from clinical trials for decision making purposes is dependent upon its ability to verify the quality and integrity of such data during its onsite inspections and audits”



Why Validate?

What is Validation?

What Validation isn't (Validation vs Quality Control of Output)

What Does Validation Involve?

Implementing a Validation Process

Conclusions/Considerations

- FDA/Regulatory Requirement
- Improve Quality
- Ensure that standard reporting programs consistently meet their specifications
- Demonstrate that a quality set of programs have been produced and that changes are well controlled

What is

Why Validate?

➔ What is Validation?

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Implementing a Validation Process

Conclusions/Considerations

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Com

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- Per FDA G

Principles of

- Per ACDM

Validation in CIRM Research A

Practical Guide.

“Software Validation means confirmation by examination and provision of objective evidence that software specifications conform to user needs and intended uses and that the particular requirements implemented through the software can be consistently fulfilled.”

“Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product that conforms to specific requirements.”

“Validation encompasses the entire system development life cycle from initiation through development, testing and production use to decommissioning. It is a process which demonstrates that a system is developed, used, maintained, evolves and is eventually decommissioned in a controlled, documented manner.”

What Validation isn't (Validation vs Quality Control of Output)

Why Validate?

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➔ What Validation isn't (Validation vs Quality Control of Output)

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Table 10.9
Demographic Characteristics - Summary of Gender, Race and Age
Analysis Population

Demographic Characteristics		N (%) (N=52)
Sex	Female	43 (82.7%)
	Male	9 (17.3%)
Race	Caucasian	52 (100.0%)
Age Interval	18-25 years	6 (11.5%)
	26-35 years	7 (13.5%)
	36-45 years	20 (38.5%)
	46-55 years	9 (17.3%)
	56-65 years	7 (13.5%)
	66 years	3 (5.8%)
Age	N	52
	MEAN	43.6
	SD	14.2
	MIN	18
	MAX	81
	MISSING	0



- Within the Biostatistics & Data Sciences department of GSK, Quality Control (QC) of output is performed at various stages during the reporting process.
- QC involves:
 - reviewing the results to ensure that the information is complete and consistent.
 - ensuring the output accurately reflects the input.
 - ensuring the output format matches the table and listing templates
 - ensuring all algorithms have been derived and calculated correctly
 - checking that SAS® logs are free of errors, warnings etc.

What Validation isn't (Validation vs Quality Control of Output)

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“The output should be **validated** by regenerating them programmatically from the original data using independent code”

- Common misconceptions:

“I **validated** that program for this data review, but I need to **validate** it again when the new data arrives”

- These are examples of QC. QC is all about data, validation is all about software. QC is a subset of validation, whilst validation encompasses the whole system development life cycle.

What Validation isn't (Validation vs Quality Control of Output)

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- QC will ensure that a particular set of data being utilised is accurately recorded and reported. Validation will ensure that the software being used to report the data will consistently produce specified results on all instances of data.
- QC may form part of the validation process. It isn't by itself validation and shouldn't take the place of validation.

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Age	N	52
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	MISSING	0



What Does Validation Involve?

Why Validate?

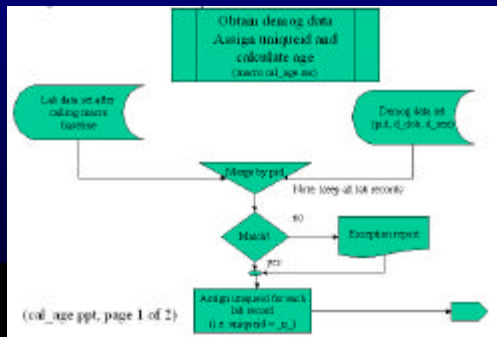
What is Validation?

What Validation isn't (Validation vs Quality Control of Output)

➔ What Does Validation Involve?

Implementing a Validation Process

Conclusions/Considerations



Validation should follow the phases of a Software Development Life Cycle (SDLC)



What Does Validation Involve?

Why Validate?

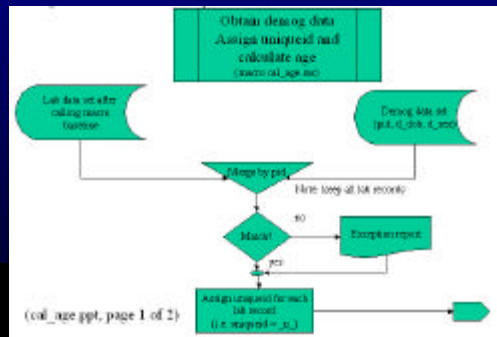
What is Validation?

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For each stage of the SDLC, associated documentation needs to be produced

Validation Protocol

➔ To provide detailed descriptions of the procedures to be followed to validate the software.

User Requirement Specifications

➔ Describe the requirements of the software in general terms.

Functional Specifications

➔ Describe how user requirements will be met and those that will not be met.

Design Specification

➔ Describe the software in sufficient detail to allow it to be programmed.

What Does Validation Involve?

Why Validate?

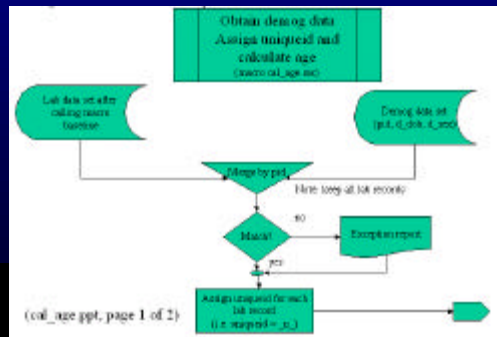
What is Validation?

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Source code programs

Source code review
documentation

Module testing results

End user documentation

To ensure the code is accurate,
clear and adheres to
programming standards

To ensure that each individual
module provides the correct
outputs for a given set of inputs

Describe comprehensively how
the software should be used.

Integration test results

System test results

To ensure that all individual
modules work together as one
unit

To ensure that the software
interfaces correctly with other
systems in the computing
environment

What Does Validation Involve?

Why Validate?

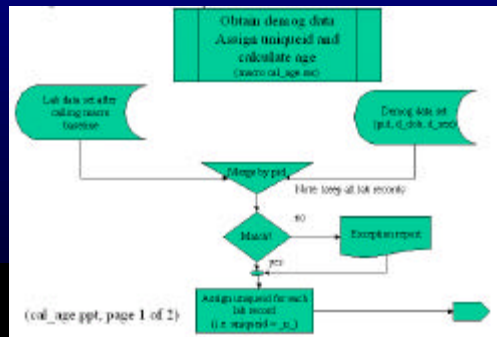
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Installation
Qualification

Performance
Qualification

To demonstrate the system has been installed according to the developers specifications

➔ A review of the systems performance in the production environment

Change control/problem reporting documentation

Periodic review documentation

To track problems reported and maintain a history of any changes made.

➔ To ensure that the validated system is functioning correctly at pre-defined time points.

Once all the validation documentation is in place and has been reviewed and signed off, the system is considered validated

Implementing a Validation Process

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Conclusions/Considerations

Biostatistics &
Data
Sciences

Biometrics
Validation
Guide

Document Revision
1.1

- Set of company computer system validation guidelines existed
- Formed a validation team whose remit included:
 - Defining, standardising and documenting the program validation process for the department
 - Compiling an inventory of all software that needed validating
 - Drafting generic validation guidelines for the department
 - Creating practical examples of how these guidelines could be implemented
 - Consulting with regulatory compliance for advice and feedback

Implementing a Validation Process The Guidelines

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 **Implementing a Validation
Process**

Conclusions/Considerations

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Sciences**

**Biometrics
Validation
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**Document Revision
1.1**

- **First draft of guidelines completed within 5 months.**

Executive Summary

- ▣ 2. Identification and Assessment of Systems Requiring Validation
 - 2.1. Category Validation Details
 - 2.2. Assessment of Systems that Require Validation
 - 2.3. Determination of Validation Priority
- ▣ 3. Validation Team Charter
 - 3.1. Validation Team Name
 - 3.2. Membership
 - Team Sponsor :
 - Team Leader:
 - ▣ Team Members:
 - 3.3. Role
 - 3.4. References
 - 3.5. Responsibilities
 - 3.6. Operations
 - 4. Validation Protocols
- ▣ 5. Software Development Details
 - 5.1. SDLC Documentation
 - 5.2. User Requirements Specification
 - 5.3. Design Specification
 - 5.4. Source Code Review Documentation
 - 5.5. End-User Documentation
- ▣ All UNIX shells stored in phcommon should have a corresponding MAN(ual) page.
- 6. Design Qualification
- 7. User Requirements Qualification
- 8. Installation Qualification
- ▣ 9. Performance Qualification
- 10. Audit Report
- ▣ 11. Controls and Procedures
- ▣ 12. Validation Report
- ▣ 13. Periodic Review Procedure

Implementing a Validation Process The Guidelines

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Document Revision
1.1

- Presented at a Biostatistics & Data Sciences Steering Team for review and comments.

- Mixed feedback was received:

- + General agreement with the document recommendations

For one-shot programs:

- Unrealistic to expect all steps to be followed
 - Overwhelmed by amount of additional documentation required
 - Process seemed a lot of work

Implementing a Validation Process The Guidelines

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Document Revision
1.1

- Additional resources/time required to achieve full SDLC for every piece of software

- Difficulty in determining what documentation would be needed for various levels of software

Implementing a Validation Process The Pilots

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➔ Implementing a Validation
Process

Conclusions/Considerations

```
SQL PROGRAM EDITOR - c:\msdosi\sql\...
*****
00000  list initial = validate(validation);
00001  *****
00002  * comment:
00003  * Set dataset and convert all units to standard units. Perform necessary
00004  * calculations on values. Create an exception listing for records with
00005  * invalid units.
00006  *****
00007  *
00008  *
00009  -data dataset
00010  select (keep = gid $value $unit);
00011  set dataset;
00012  select (null);
00013  *****
00014  * comment:
00015  * Convert F (Fahrenheit) to C (Celsius).
00016  *****
00017  *
00018  when ('F') do;
00019  value = round((value - 32) * 5 / 9, 1);
00020  unit = 'C';
00021  end;
00022  *****
00023  * comment:
00024  * Perform height conversions, ending up with either IS or CM
00025  * depending on value of height.
00026  *
00027  * Convert IS (inches) to CM (centimeters).
00028  *
00029  * Convert CM to IS
00030  * Round the value of IS to certain digit.
00031  *
00032  *
00033  * To 0.5 IS.
00034  *****
00035  *
00036  when ('IS') do;
```

Approval was given to go ahead with 2
validation pilots

- Pilot 1: Lab flagging software, used across reporting teams
- Pilot 2: Reporting environment programs, used across reporting teams

These were considered to be Phase I pilots.
A Phase II pilot was also set up to look at
validating within team standard reporting
macros.

Aim to complete these pilots by end of May 2001

Learnings from the the Pilots

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Implementing a Validation Process

Conclusions/Considerations

```

1:          SET PROGRAM C0715-convert.c
2:
3:main()
4:
5:    int unit = degrees(celsius);
6:
7:
8:    + comment:
9:    + Set dataset and convert all units to standard units. Perform necessary
10:   + calculations on data. Create an exception listing for invalid units.
11:   + Invalid units.
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```

- Need to perform a risk assessment/cost benefit analysis when considering software validation
- Need to account for a significant learning curve for validation activities
- Writing comprehensive user and design requirements is a challenge
- Validation must be the primary commitment of the validation team leader
- There must be adequate support from management
- There needs to be dedicated, internal validation resources available to consult, advise and train

Conclusions

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What Does Validation Involve?

Implementing a Validation Process

➔ Conclusions/Considerations



```
Command window
SAS PROGRAM EDITOR: sasv1.sas
*****
00001 *let want = %sysfunc(exist(''));
00002 *****
00003 * comment:
00004 *   get dataset and convert all units to standard units. Perform necessary
00005 *   calculations on value. Create an exception listing for records with
00006 *   invalid unit.
00007 *****
00008 *****
00009 data edataset;
00010   input (keep = pid avalue unit);
00011 *****
00012 *let dataset;
00013 select (dataset);
00014 *****
00015 *****
00016 * comment:
00017 *   Convert F to standard units (kg/m^2)
00018 *****
00019 *****
00020 *let ('F') do;
00021   avalue = round(avalue - 32) * 5 / 9,1;
00022   unit = "C";
00023 end;
00024 *****
00025 *****
00026 * comment:
00027 *   Perform height conversions - ending up with either in or cm
00028 *   depending on value of least.
00029 *   Ht - Convert in (inches) to cm (centimeters).
00030 *   Gr - Convert cm to in.
00031 *   Round the value of Ht to certain digit.
00032 *****
00033 *let Ht;
00034 *let Gr;
00035 *let Ht;
00036 *****
```

- Validation is an integral part of all clinical trial reporting, regardless of how adhoc the report.
- Implementing a validation process is initially time consuming.
- In the long-term validation should ensure that we have programs in place which are reliable and can be re-used.
- There is a need to change attitudes towards validation (part of the aim of the pilots).
- Validation is common sense, much of the process is probably being performed, but just not documented.
- **Validation is a regulatory requirement**

Considerations

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What Does Validation Involve?

Implementing a Validation Process

➔ Conclusions/Considerations



```
Command window
SAS PROGRAM EDITOR - sasv8.sas
-----
00001 *let want = %sysfunc(exist(''));
00002 *****
00003 * comment:
00004 *   The database and convert all units to standard units. Perform necessary
00005 *   calculations on value. Create an exception listing for records with
00006 *   invalid entry.
00007 *****
00008 *****
00009 data edatam;
00010   input (keep = pid svalue unit);
00011   get edatam;
00012   select (keep);
00013 *****
00014 * comment:
00015 *   Convert F to standard units (convert to cm)
00016 *****
00017 *let ('F') do;
00018   svalue = round(svalue - 32) * 5 / 9, 1;
00019   unit = "C";
00020 end;
00021 *****
00022 * comment:
00023 *   Perform height conversions - ending up with either in or cm
00024 *   depending on value of least.
00025 *   Ht - Convert in (inches) to cm (centimeters).
00026 *   Cr - Convert cm to in.
00027 *   Round the value of Ht to certain digits.
00028 *   Ht - Tot 2 cm
00029 *   Cr - Tot 2 in
00030 *****
```

- Finding a problem during an early phase of software development can save time and a validation process should ensure that this is achieved.
- Handling of validation for one-shot programs (time and resource issues to address).
- Development of a central database to store the documentation.
- How are other pharmaceutical companies handling validation of clinical trial reporting software?



Thank You



Any Questions?

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