Training Statistical Programmers on SAP Review Skills

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PhUSE annual conference Brighton

October 2011

Juan, living with restless legs syndrome

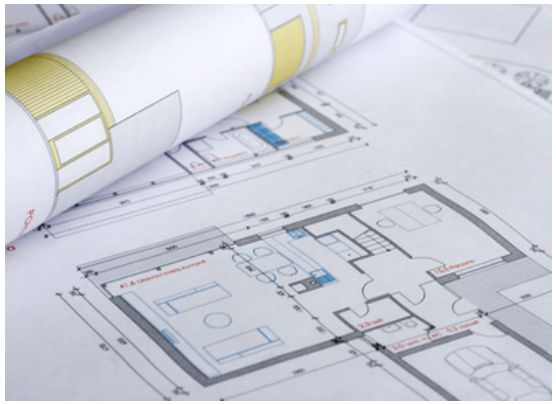
Overview

- In this presentation you will learn
  - Roles of Statistician vs. Statistical Programmer
  - Purpose of SAP
  - Importance of SAP review by Statistical Programmer
  - How to review a SAP
  - How to train Statistical Programmers on SAP review

Roles of Statistician and Statistical Programmer

- Clinical Trials need to be planned with regards to Statistics
  - Which data do we want/need to analyse?
  - How do we want to analyse the data?
  - How do we handle data if it was not collected as planned?
  - How can we ensure that observed differences between two drugs are real?
  - How do we present the analysis results?
- Responsible: Statisticians and Statistical Programmers

Roles of Statistician and Statistical Programmer

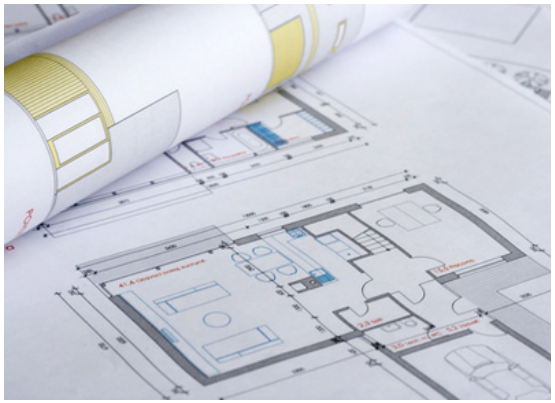


Biostatisticians
–
architect
(e.g., SAP)

Statistical Programmer
–
builder/contractor
(e.g., TFL production)

Purpose of a Statistical Analysis Plan

- Describes details for planned statistical analysis of a clinical trial
- Different types of SAPs
  - **SAP for a clinical study**
  - Interim SAP
  - Data Monitoring Committee SAP (DMC SAP)
  - Integrated Analysis Plan (ISAP)
  - Data Analysis Plan for Pop-PK (DAP + Specs)
- SAP submitted to regulatory authorities
- Creation: **Statistician**
- Review: **Statistical Programmer**



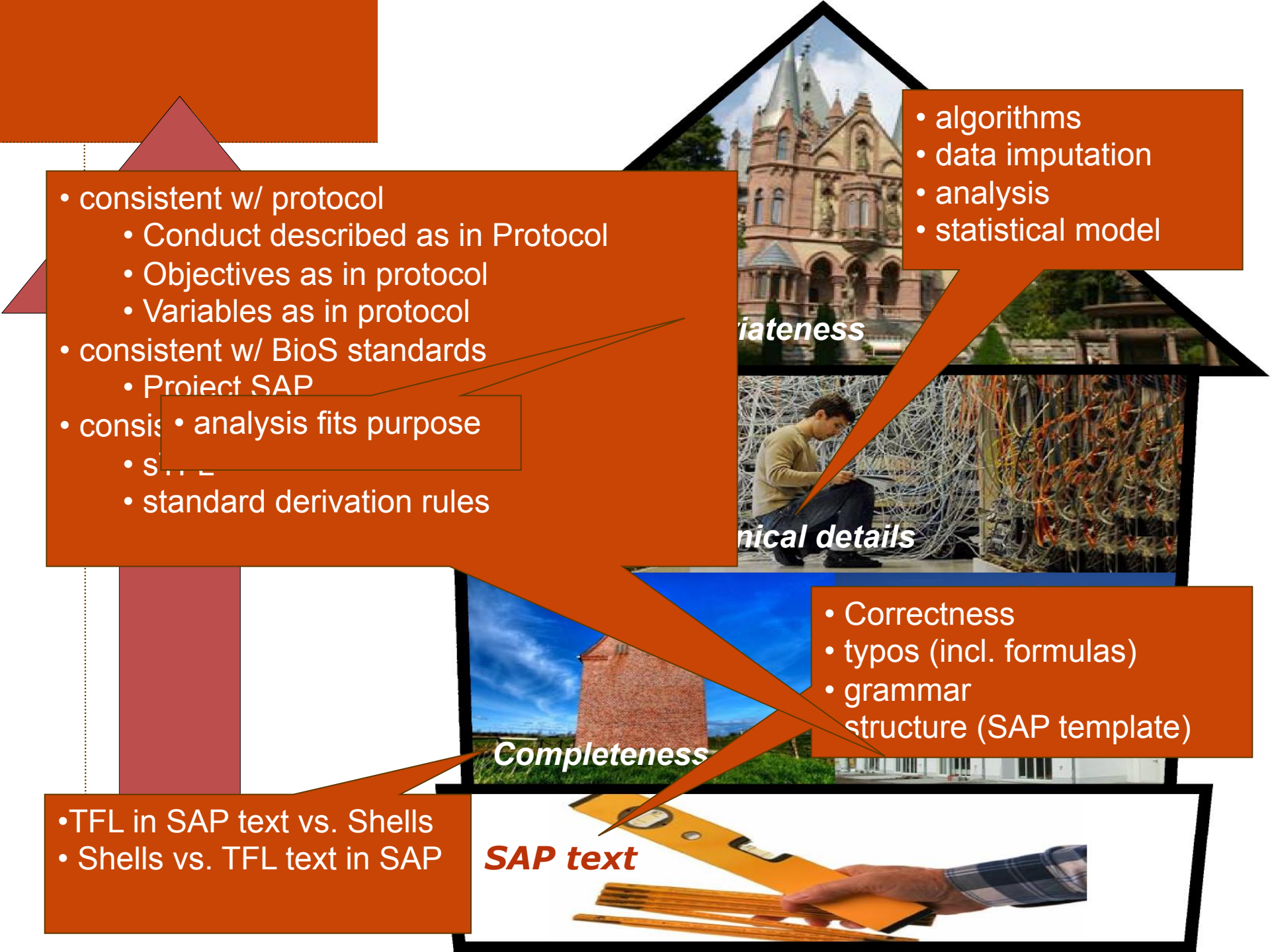
„A good plan is like a road map: it shows the final destination and usually the best way to get there.“

H.Stanley

Importance of Statistical Programming review

- SAP is technical document
  - SAP should contain technical details
  - Describes techniques used in programs by Statistical Programmers
- All statistical programming deliverables are defined in SAP
- Ensure comprehensive understanding of content relevant to statistical programming
  - Analysis populations
  - Data handling rules
  - Translation into SAS® code

Serious review will save a lot of discussions during the actual programming time and lead to higher delivery quality


• algorithms
• data imputation
• analysis
• statistical model
• consistent w/ protocol
• Conduct described as in Protocol
• Objectives as in protocol
• Variables as in protocol
• consistent w/ BioS standards
• Project SAP
• consis
• analysis fits purpose
• standard derivation rules
• Correctness
• typos (incl. formulas)
• grammar
structure (SAP template)
•TFL in SAP text vs. Shells
• Shells vs. TFL text in SAP
SAP text

Correctness

- Can be checked without statistical knowledge
- Issues that pop up at first reading
- For example:
  - Correct use of SAP template
    - High level structure unchanged?
    - TOC of TFLs within SAP text?
  - Check if statements in SAP are correct
    - E.g. ranges like 100<DBP<80
  - SAS code in SAP text
  - Typos
  - Grammar

Is everything correct?

Consistency

- Derivation rules same in project?
  - TEAE definition in Project A, Study 001

> Treatment-emergent AEs (TEAEs) are those with onset date and time at or after the very first administration of study medication. The events that emerge after the last drug administration in a treatment period, will also be considered as treatment-emergent (eg premature discontinuation, washout,…). Adverse events are assigned to a certain treatment based on the analysis phase at onset of AE. An adverse event emerging in analysis phase with treatment X and continuing in the next analysis phase with treatment Y is assigned to treatment X and not to treatment Y.

  - TEAE definition in Project A, Study 002

> An AE will be classified as TEAE if its onset date is on or after the first intake of trial medication but not later than 5 half life times after last intake of trial medication.

Can I copy and paste everything from my previous study to my next study?

- Study 001 does not have the half-time restriction
- In case different on purpose
  - Programmer needs to keep in mind to adjust programs

Completeness

SAP text

An overall summary of TEAEs will include:

- total number of AEs; ✓
- subjects with at least one AE; ✓
- subjects with AE(s) that led to permanent study drug discontinuation; ✓
- subjects with AE(s) that led to temporary study drug discontinuation; ?
- subjects with AE(s) that led to dose increased; ?
- subjects with AE(s) that led to dose decreased; ?
- subjects with AE(s) that led to hospitalization or prolongation of hospitalization; ?
- subjects with drug-related AEs; ✓
- subjects with severe AEs; ✓
- subjects with SAEs; ✓
- subjects with drug-related SAEs; ✓
- number of deaths. ?

Don‘t rely solely in the TFL shells!!!

Shell

	(N=14) n (%)
Total number of Adverse Events	17
Subjects with at least one Treatment Emergent Adverse Event (TEAE)	7 (50.0)
Subjects with TEAEs that lead to permanent study drug discontinuation	0
Subjects with drug-related TEAEs (a)	7 (50.0)
Subjects with severe TEAEs	0
Subjects with serious TEAEs	0
Subjects with drug-related serious TEAEs (a)	0

Degree of technical details

Investigators are asked to document medication that is taken within 1 month prior to entry into the study or during the study. Medication will be classified as being prior medication and/or concomitant medication and/or post treatment medication:

- Medication with a start date before the first dose of trial medication will be considered prior medication.
- Medication taken on or after the first dose of trial medication will be considered concomitant medication.
- Medication that is taken after last intake of study treatment is considered post treatment medication.
- Medication with a missing start date whose stop date is either unknown or after the date of the first dose of trial medication will be considered concomitant. Medication with a missing start date whose stop date is prior to first intake of trial medication is considered prior medication. Medication with a missing end date is considered ongoing at the end of the study.

Medication will be coded using WHO-drug reference list.

Do I have enough written technical details so that I can translate everything in SAS ® code?

vs

6.2.1 Previous, Concomitant and Post-Treatment Medication

If a partial date implies that a medication can be classified as concomitant at Baseline then this is how it should be classified. If it cannot be classified as concomitant at Baseline but can be classified as concomitant then this is how it should be classified, otherwise the dates must imply that the medication is strictly pre- or post-study and should be classified accordingly.

Appropriateness

For the assessment of bioequivalence an ANOVA will be performed for AUC_{0-tz}, $AUC_{0-\infty}$ and C_{max} primarily in order to estimate the residual error which is used to construct the confidence intervals. The ANOVA model will include treatment sequence, subject within sequence, study period and treatment as fixed effects.

- Is the described model appropriate for the analysis of a cross over study?
- Does the analysis fit the purpose?
- Statistical Programmer might ask
- Final decision Statistician

A statistical programmer should be able to understand the basic ideas of the study and the statistical model

How to train SAP review skills

Manual

Checklists

Classroom Trainings

Mentoring

Summary

- In this presentation we provided you with an introduction how to review SAPs in a structured way
  - Roles of Statistician vs. Statistical Programmer
  - Purpose of SAP
  - Importance of SAP review by Statistical Programmer
  - How to review a SAP
  - How to train Statistical Programmers on SAP review
- Good document review is essential part of our work
- Time on document review is well spent

Questions?