STUDY TAGGING FILES: THEIR VITAL ROLE IN SUBMISSIONS TO THE FDA

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Background

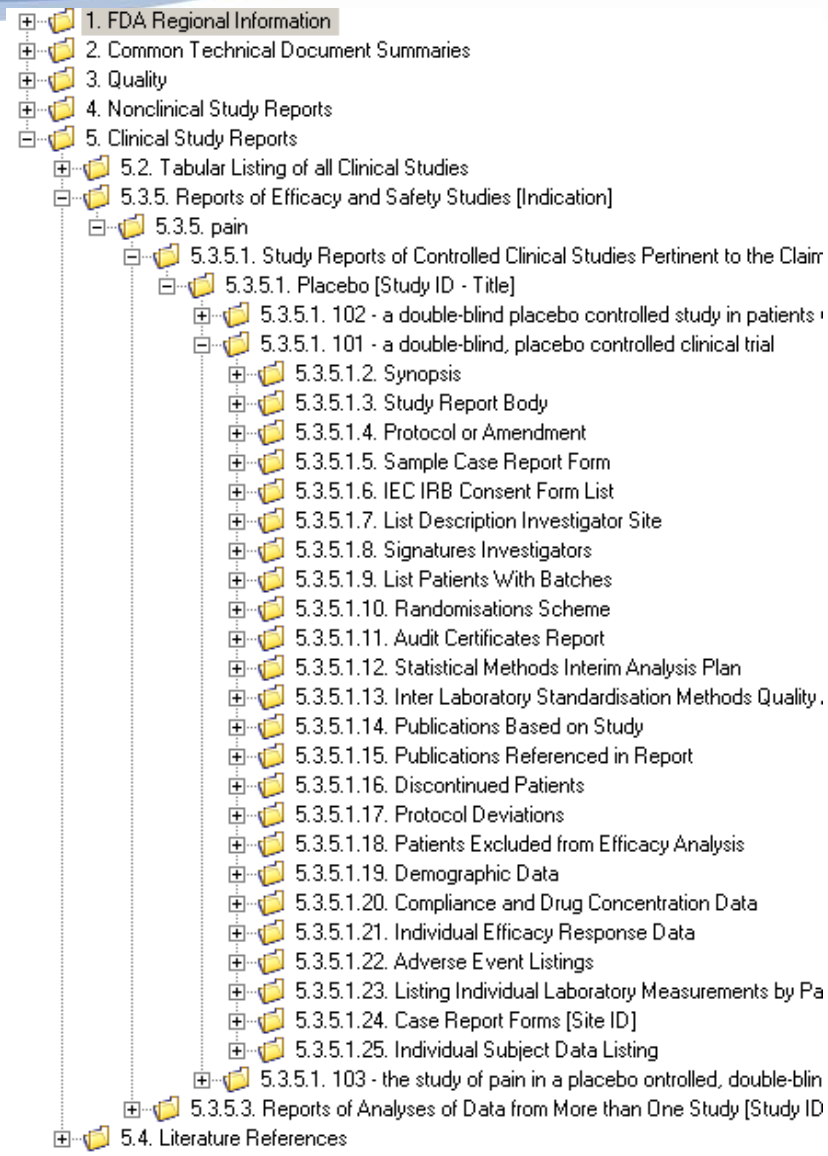
- Most eCTDs are good!
- Some recent issues reveal lack of understanding of importance of the STF
- STF can be difficult to fix after mistakes are made
- Avoiding mistakes ensures optimal viewability

Background

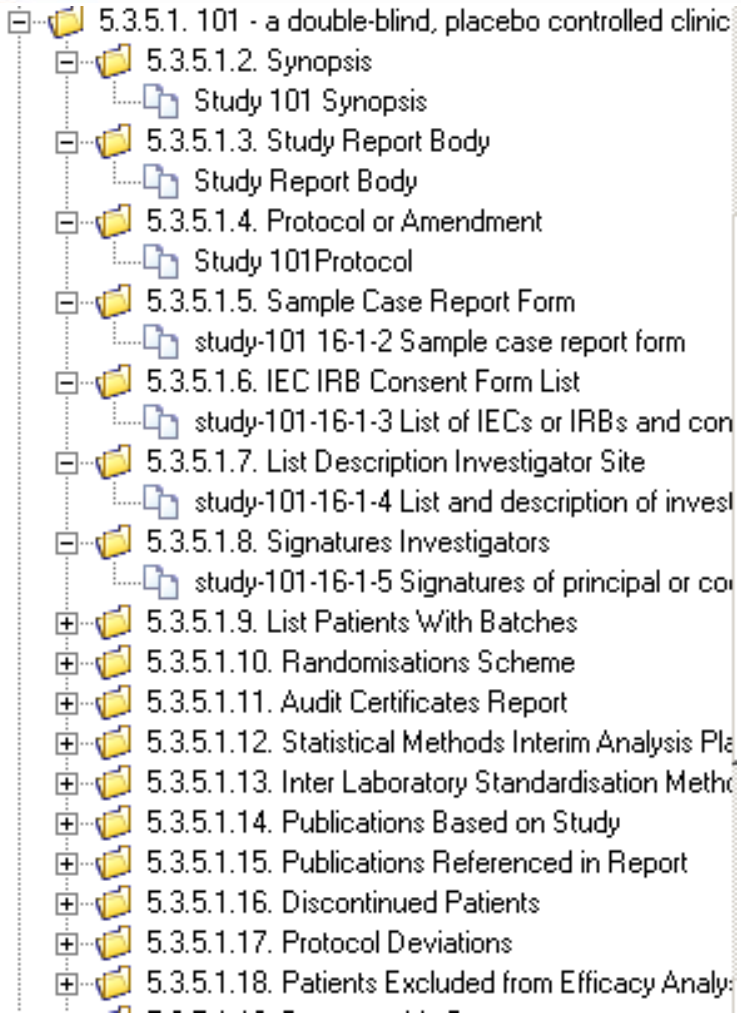
- With DTDs and stylesheets, the STF standardizes the display of study info
- Appearance is predictable and reliable
- Smooth flowing review

Role of the STF

- Organizes study information into meaningful, standardized headings
- Allows reviewer to quickly understand what has been submitted, what has not
- Helps guide reviewer to specific documents they are looking for
- Provides consistency over the lifecycle of the regulatory application


1. FDA Regional Information
2. Common Technical Document Summaries
3. Quality
4. Nonclinical Study Reports
5. Clinical Study Reports
5.2. Tabular Listing of all Clinical Studies
5.3.5. Reports of Efficacy and Safety Studies [Indication]
5.3.5. pain
5.3.5.1. Study Reports of Controlled Clinical Studies Pertinent to the Clair
5.3.5.1. Placebo [Study ID - Title]
5.3.5.1. 102 - a double-blind placebo controlled study in patients
5.3.5.1. 101 - a double-blind, placebo controlled clinical trial
5.3.5.1.2. Synopsis
5.3.5.1.3. Study Report Body
5.3.5.1.4. Protocol or Amendment
5.3.5.1.5. Sample Case Report Form
5.3.5.1.6. IEC IRB Consent Form List
5.3.5.1.7. List Description Investigator Site
5.3.5.1.8. Signatures Investigators
5.3.5.1.9. List Patients With Batches
5.3.5.1.10. Randomisations Scheme
5.3.5.1.11. Audit Certificates Report
5.3.5.1.12. Statistical Methods Interim Analysis Plan
5.3.5.1.13. Inter Laboratory Standardisation Methods Quality
5.3.5.1.14. Publications Based on Study
5.3.5.1.15. Publications Referenced in Report
5.3.5.1.16. Discontinued Patients
5.3.5.1.17. Protocol Deviations
5.3.5.1.18. Patients Excluded from Efficacy Analysis
5.3.5.1.19. Demographic Data
5.3.5.1.20. Compliance and Drug Concentration Data
5.3.5.1.21. Individual Efficacy Response Data
5.3.5.1.22. Adverse Event Listings
5.3.5.1.23. Listing Individual Laboratory Measurements by Pa
5.3.5.1.24. Case Report Forms [Site ID]
5.3.5.1.25. Individual Subject Data Listing
5.3.5.1. 103 - the study of pain in a placebo ontrolled, double-blin
5.3.5.3. Reports of Analyses of Data from More than One Study [Study ID
5.4. Literature References

Good


5.3.5.1. 101 - a double-blind, placebo controlled clinic
5.3.5.1.2. Synopsis
Study 101 Synopsis
5.3.5.1.3. Study Report Body
Study Report Body
5.3.5.1.4. Protocol or Amendment
Study 101Protocol
5.3.5.1.5. Sample Case Report Form
study-101 16-1-2 Sample case report form
5.3.5.1.6. IEC IRB Consent Form List
study-101-16-1-3 List of IECs or IRBs and con
5.3.5.1.7. List Description Investigator Site
study-101-16-1-4 List and description of invest
5.3.5.1.8. Signatures Investigators
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5.3.5.1.9. List Patients With Batches
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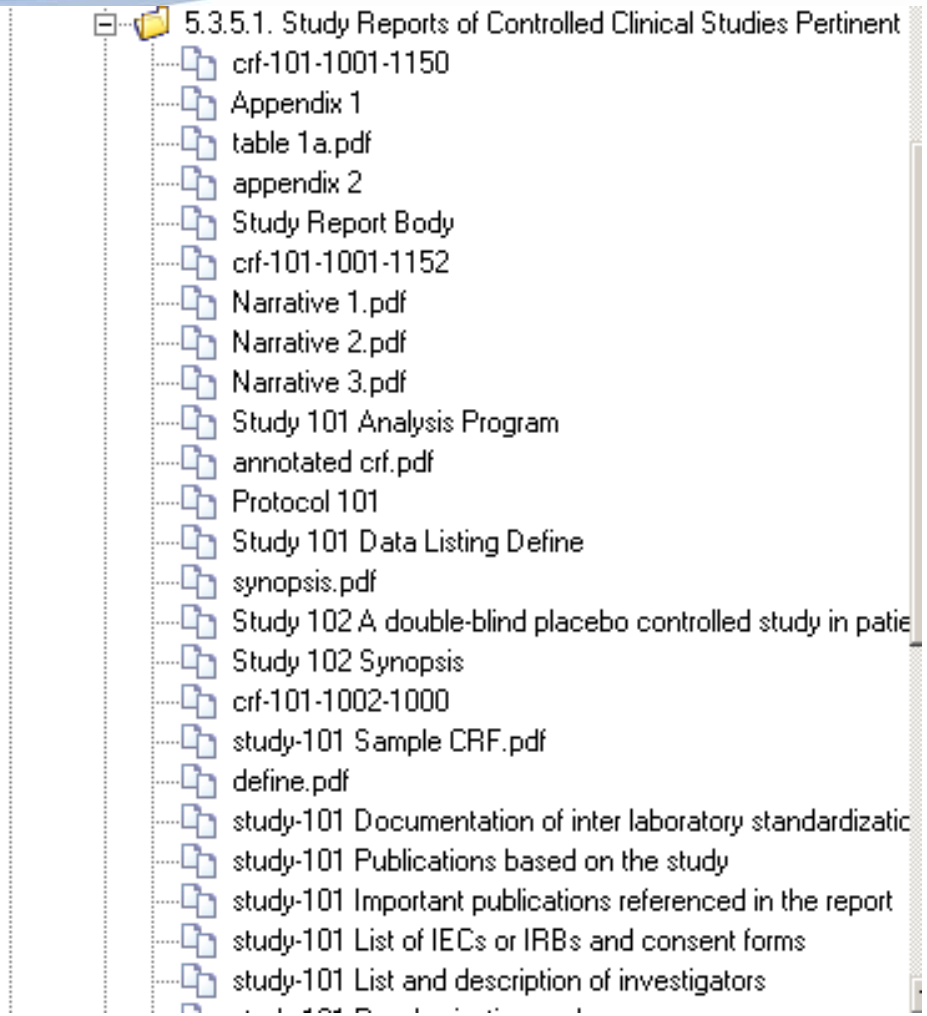

5.3.5.1. Study Reports of Controlled Clinical Studies Pertinent
crf-101-1001-1150
Appendix 1
table 1a.pdf
appendix 2
Study Report Body
crf-101-1001-1152
Narrative 1.pdf
Narrative 2.pdf
Narrative 3.pdf
Study 101 Analysis Program
annotated crf.pdf
Protocol 101
Study 101 Data Listing Define
synopsis.pdf
Study 102 A double-blind placebo controlled study in patie
Study 102 Synopsis
crf-101-1002-1000
study-101 Sample CRF.pdf
define.pdf
study-101 Documentation of inter laboratory standardizatic
study-101 Publications based on the study
study-101 Important publications referenced in the report
study-101 List of IECs or IRBs and consent forms
study-101 List and description of investigators

Bad

Background

- Not using STFs
- Using STFs for only some of the study documents, and not all
- Modifying the study title results in additional study structures (even if the study ID remains the same)
- Using same study tag for all documents or tagging document with incorrect tag

When should I use an STF?

- Anytime you are including docs in Modules 4 or 5, except 5.2 Tabular Listings, and 4.3 or 5.4 Literature references
- **So, DO include STFs for any documents submitted under 4.2 or 5.3**
  - Everything under these headings needs an STF (datasets, protocols, 1572's, ISS, ISE)

Case Study

- Original NDA (0000) was submitted in May ‘09
- Sponsor used no STFs
- eCTD was unreviewable – review clock was stopped
- Sponsor submitted their correction in June
- Sponsor’s correction did not resolve the problem – eCTD was not reviewable
- Sponsor submitted a third sequence as “original” in late August
- Sponsor lost 2 ½ months due to this issue
- This issue required numerous communications between the FDA PM, ESUB and the company

We Can Help

- Communicate with us if there is a problem
- ESUB@fda.hhs.gov
- Email account closely monitored

Examples of What Can Go Wrong

- Study under wrong heading element
- Created wrong indication under 5.3.5.1
- Multiple study structures for one study
- You referenced documents in the wrong STF

Study under wrong heading element

- Problem: You placed a pivotal study under 5.3.1.1, and now you realize it needs to be under 5.3.5.1
- Solution:
  - Delete out all the leaf IDs that were referenced in the STF under the wrong heading element. This deletes the STF.
  - Create a new STF referencing all the same files, but use new leaf IDs.
  - Submit in new submission sequence.
  - Resubmission of files shouldn't be necessary since you should be able to make the href links (path and file name) go to documents in the previous sequence

Created wrong indication under 5.3.5.1

Problem: You created the wrong indication under 5.3.5.1

Solution: See next slide

Remove incorrect STF – Submit with correct STF

- PREFACE: Don't simply delete or append the STF file in the index.xml – these approaches do not work
- Delete all documents referenced in that STF (just submit the index.xml with a "delete" operation for all documents that were referenced in the bad STF)
- Then, create an STF (with a new title) and submit as NEW (not append) and resubmit all files with new leaf IDs (resubmission of files may or may not be necessary depending on your tool)
- Do not reference existing files with existing leaf IDs
- If resubmitting documents, include a statement in your cover letter stating that no files have changed, so reviewers will not need to re-review files or make href links go to previously submitted documents
- Send as a stand-alone amendment, don't mix in with another type of submission

Multiple Study Structures for One Study

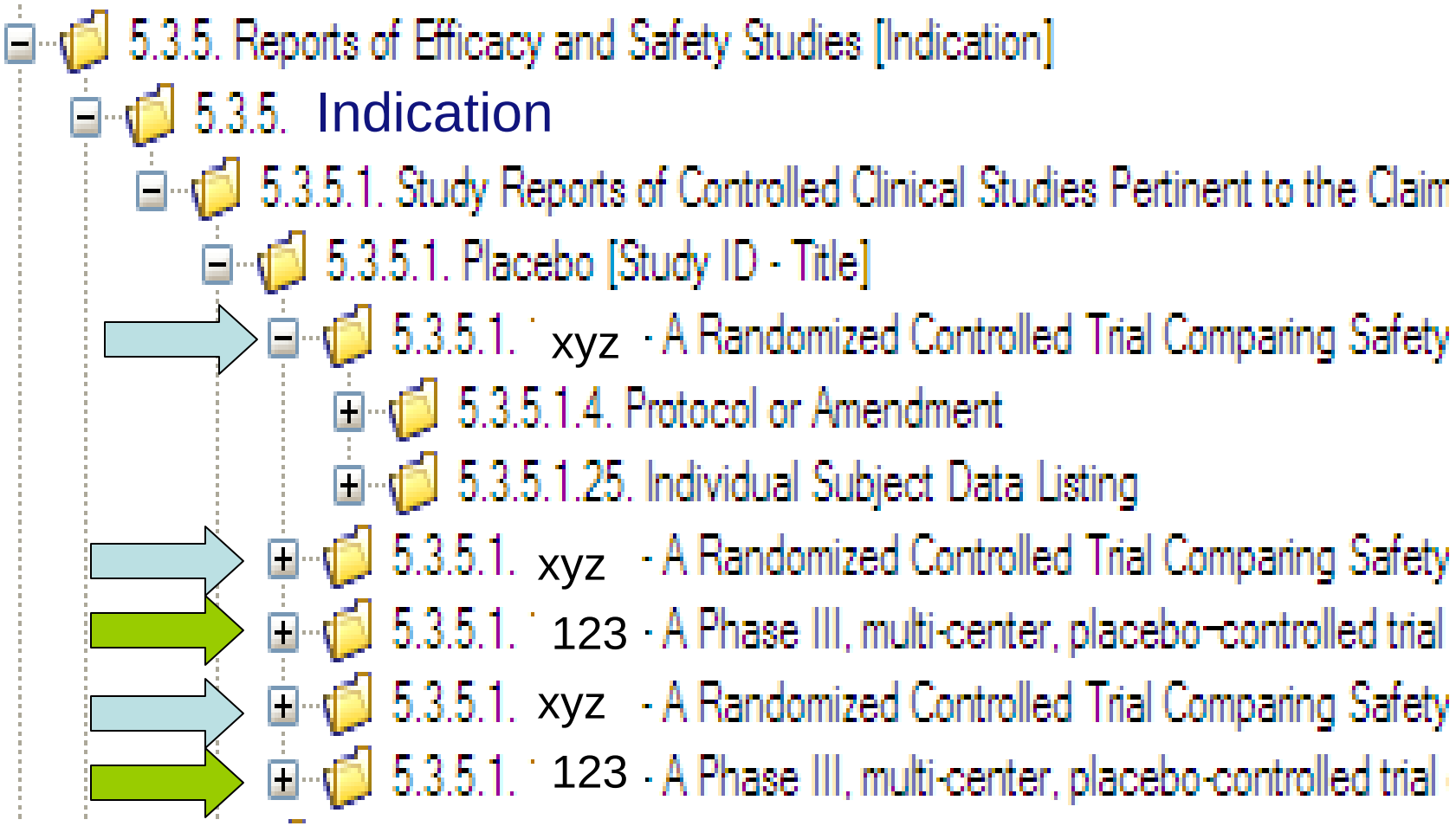
Problem: You have realized that you have multiple study Structures for one Study

Solution: See next slides

How does this happen?

- When you modify the study title, even slightly
- Many people submitting to the same NDA: each person enters the study slightly differently
- You might have an older version of a tool that prompts you to enter new study name
- Use current versions of supported tools

Example of Multiple Study Structures for One Study



How to fix - multiple study structures for one study

- Delete references in the index.xml that were referenced in the study files (STFs) you want to remove from the eCTD
- Then add the references as new to the index.xml and STF for the study that should remain
- Make sure the leaf IDs are new and different than those referenced in the old STF
- The files themselves do not need to be resubmitted but the href links should reference those files in the old sequences
- In the index.xml, do not submit an STF file with append or delete for the study structures you are trying to remove, since this will not correct the issue and can lead to more problems

Documents referenced in the wrong STF

Problem: You put docs under the wrong study

Solution:

- Delete leaf IDs from wrong STF (follow instructions on page 13 of the STF spec)
- Submit new STF with new leaf IDs
  - If STF already exists, append to existing STF with new leaf IDs referenced

When to use replace vs. append

- Don’t use append to replace things
- 4 protocols, incremental appends – instead use replace
- Safety reports – follow-up to initial safety report – use replace
- 1572s – updated – use replace
- Replace doesn’t mean “mistake”
- (draft labels – use replace, not append)
- Use append when you are adding a little more information to an existing document, not resubmitting all the same info, plus a little more

5.3.7

- FDA does not use 5.3.7 for CRFs
  - reviewers can't tell which CRFs go to a study
- Instead, CRFs should be referenced in each study's STF and tagged "case report form"
- Do not use 5.3.7

Non-IND Safety Reports

- Non-IND safety reports – create an STF
  - Safety reports related to the drug but not that specific IND
  - Compound with 3 open INDs related to it
  - Each IND opened for a separate indication, going to separate divisions
  - Safety reports must be submitted to all open INDs

Create an STF, under 5.3.5.4 – call it “Non-IND Safety Reports”

What to do if you realize your STF is in error

- Contact ESUB@fda.hhs.gov
- Please follow ESUB's technical advice for fixing
- If unable to follow ESUB's advice on your own, get professional help
- Do not attempt multiple fixes that are unproven – this can make a bad situation worse

Thank you

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