10 things you need to know for a successful e-submission

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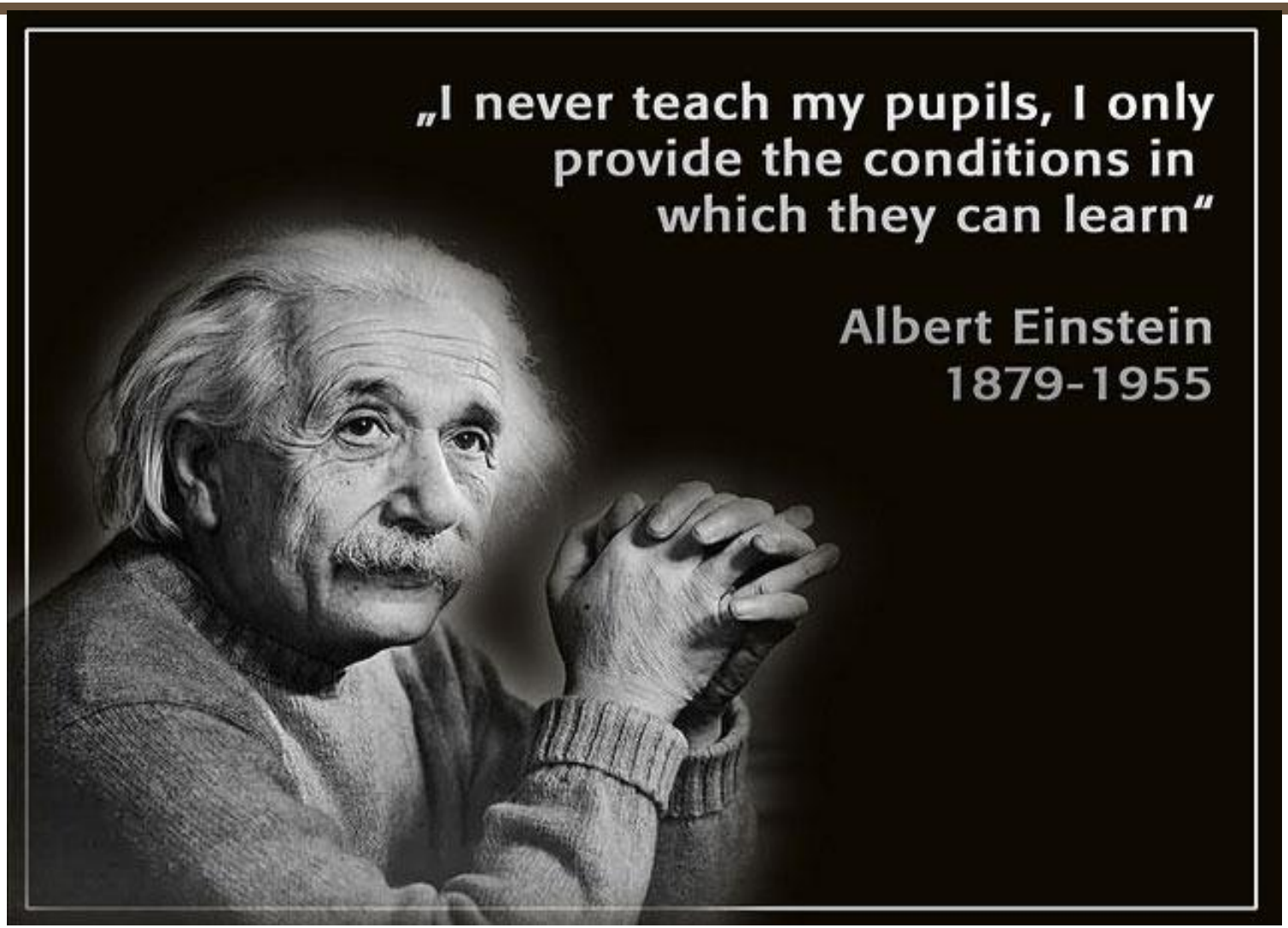
„I never teach my pupils, I only provide the conditions in which they can learn“
Albert Einstein
1879-1955

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E-Submission process-10 things you need to know

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2. Are there any approved templates for Reviewer's guides? Where do I find them?
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4. How do I start planning timelines for creation of SDTM/ADAM xpt's/defines?
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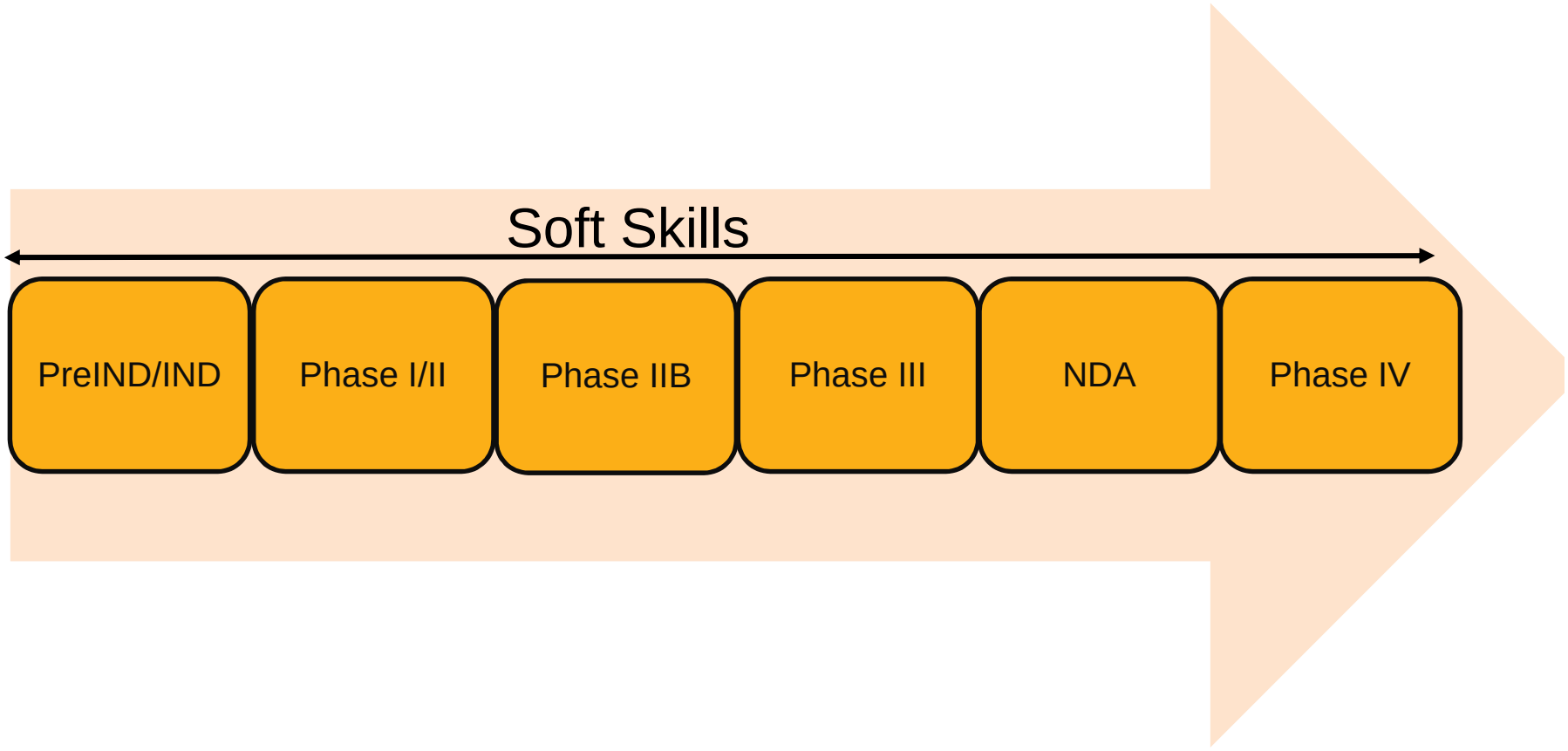
Clinical Drug Development Process Overview



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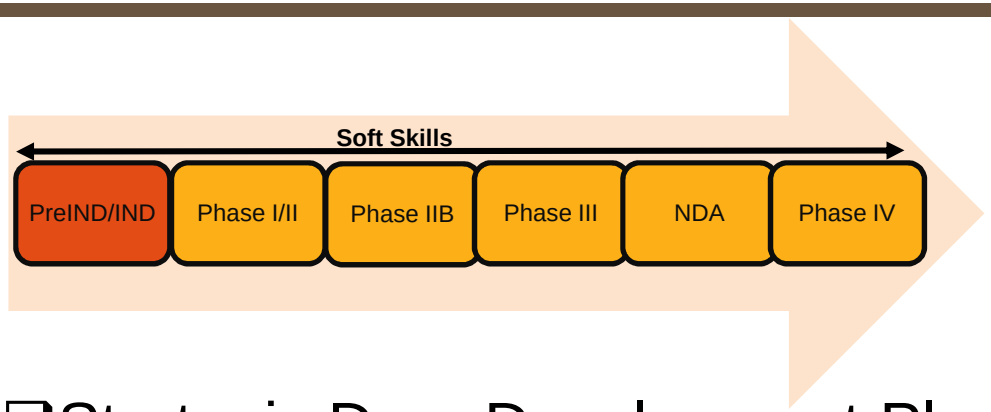
PreIND/IND



- ❑Strategic Drug Development Plan
- ❑Liaise with FDA
- ❑Target Product Profile
- ❑Pre-IND FDA Meeting

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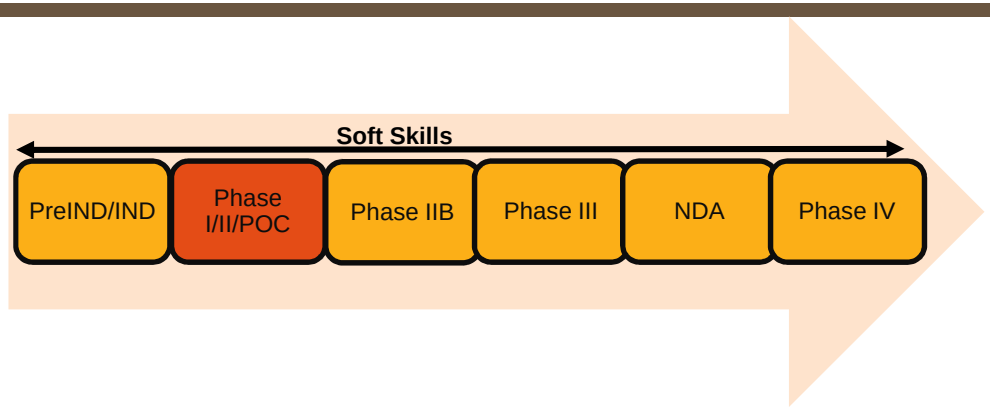
Phase 1/II/POC Studies



- Safety & Tolerability
  - TLF's for CSR's
- End of Phase I meeting
  - Fast Track Applications
- Proof of Concept Study reporting
- Decision Point Go/No go

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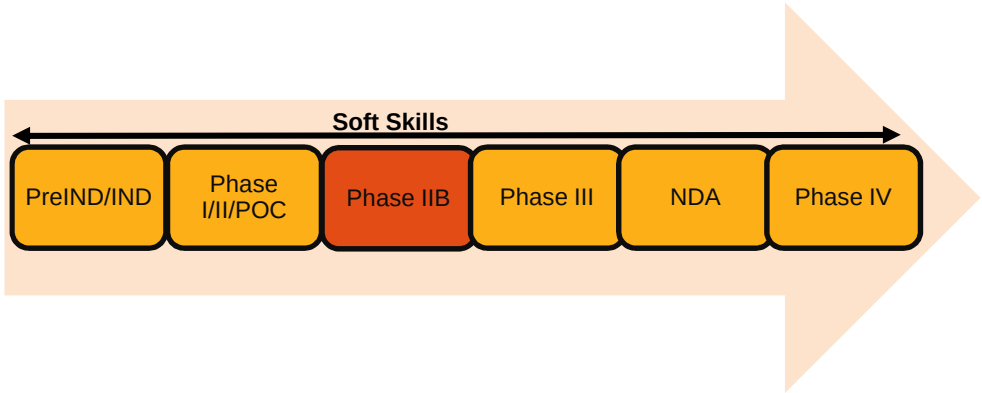
Phase IIB



- IND updates (if 1year after original IND)
- End of Phase II FDA Meetings
- Pivotal trial design
- Scientific advice meeting
- Fast track applications

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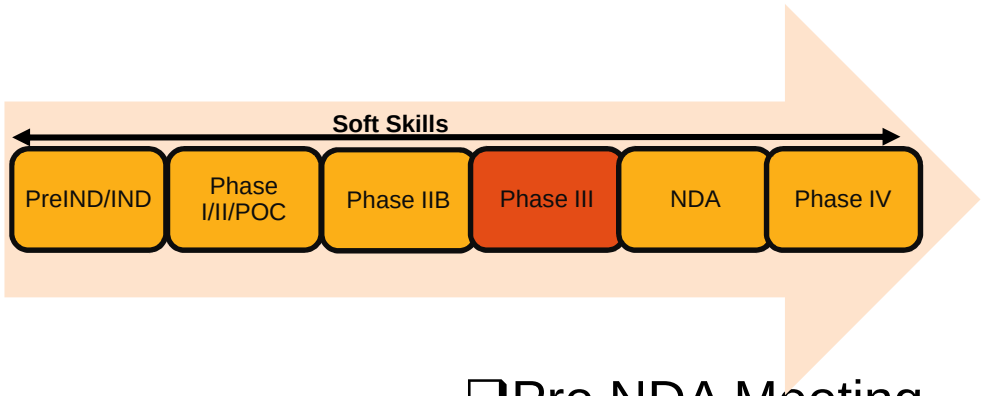
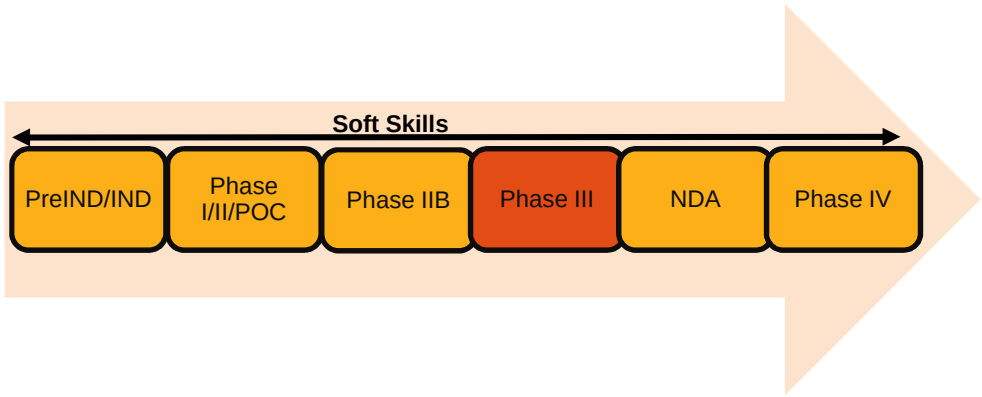
Phase III Pivotal Studies/SCS/SCE



- Pre NDA Meeting
  - Reporting of pivotal study/studies
  - Briefing Book
    - Questions for the Agency
    - Pooling Plan including lists of studies in the submission(for SCS/SCE)
    - Plan for data standards and submissions
    - Pilot define package
- Clinical Submission Plan Document

Resources/ Pre-Submission



You must submit electronic submissions using the version of eCTD currently supported by FDA. The version of eCTD currently supported is specified in the Data Standards Catalog (available @ http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM340684.xls)

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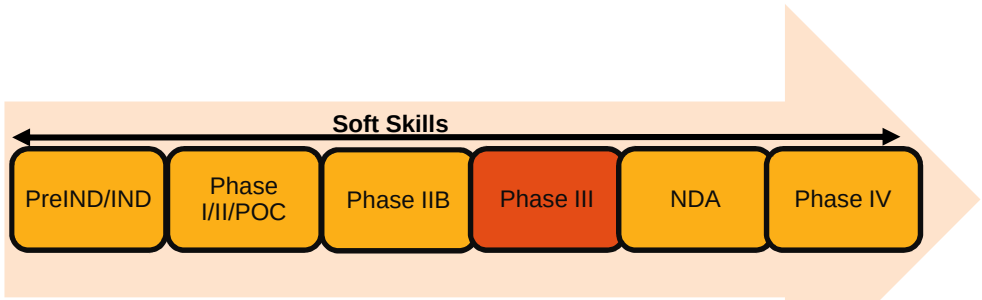
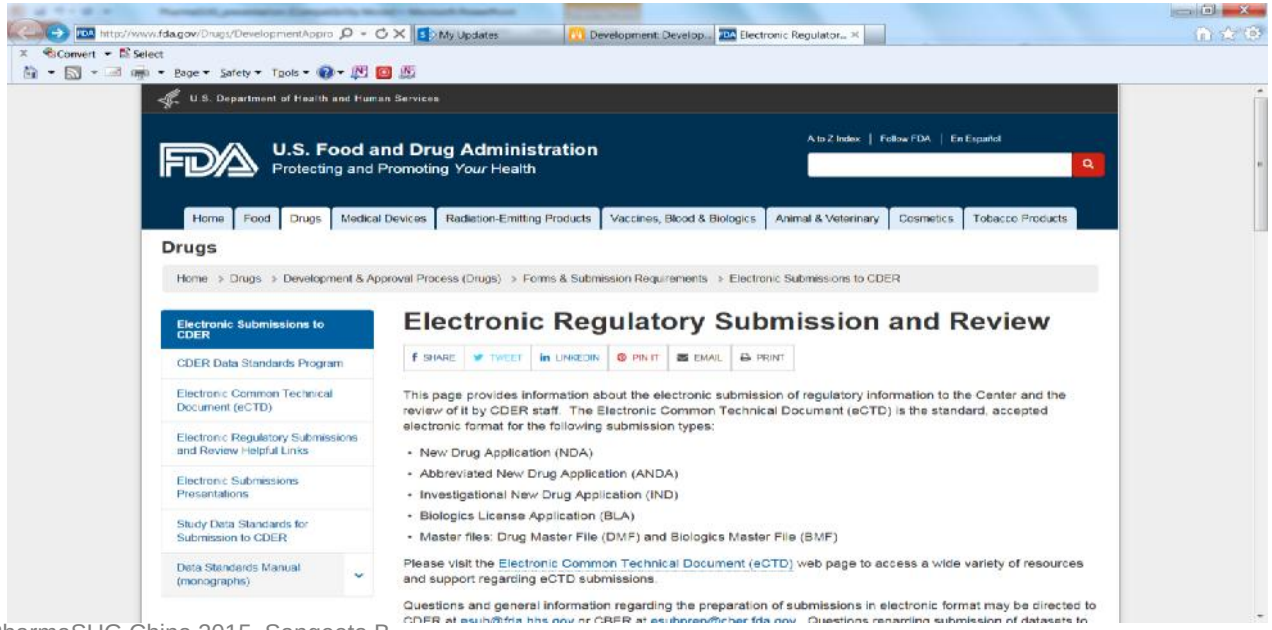
Resources / Pre-Submission



FDA Website
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/default.htm



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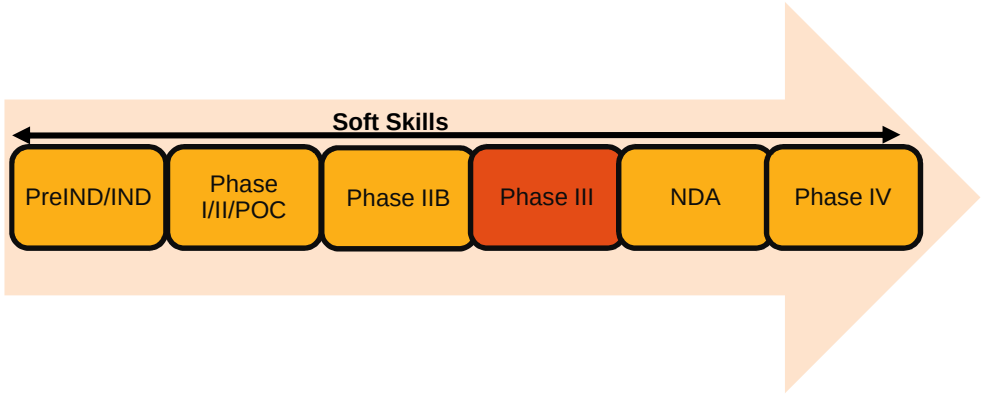
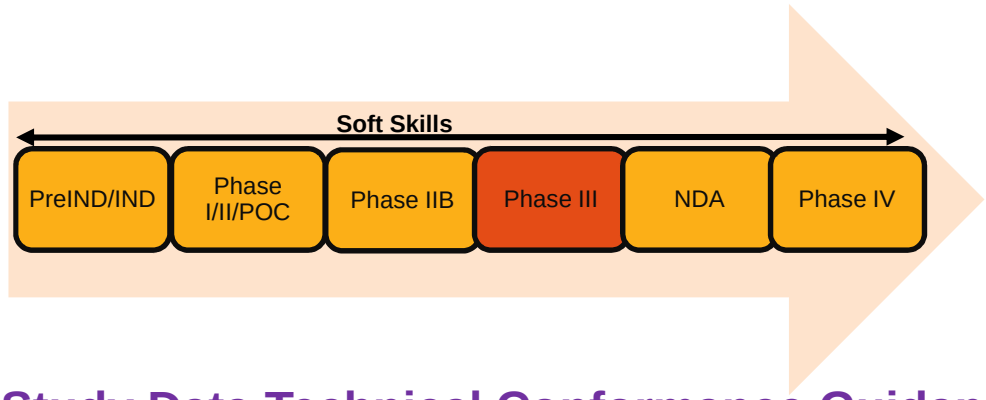
Submission Data Package



- Study Data requirements are covered in the Data Standards Catalog and the Study Data Technical Conformance Guide that are available on the Study Data Standards Resources
- What we submit as electronic dataset definition package
  - SDTM (SAS Transport file)
  - ADAM (SAS Transport file)
  - Study data Reviewer's guide/Analysis Data Reviewer's Guide
  - Define.xml
  - Programs of primary and secondary analysis
  - Annotated CRF

Submission Data Package



Study Data Technical Conformance Guidance asks for Study Data Reviewer's Guide (SDRG) to accompany SDTM

- The SDRG describes any special considerations or directions that may facilitate an FDA reviewer's use of the submitted data.
- The SDRG should include, but is not limited to the following:
    1. Study protocol title, number, and version
    2. Study design
    3. Standards, formats, and terminologies and their versions
    4. Description of study datasets
    5. Data standards validation rules, versions, and issues
    6. Description of all sponsor decisions related to data standard implementations
- The SDRG also provides a summary of SDTM conformance findings.

Tips-PhUSE template available visit the PhUSE website

http://www.phuse.eu/CSS-deliverables.aspx

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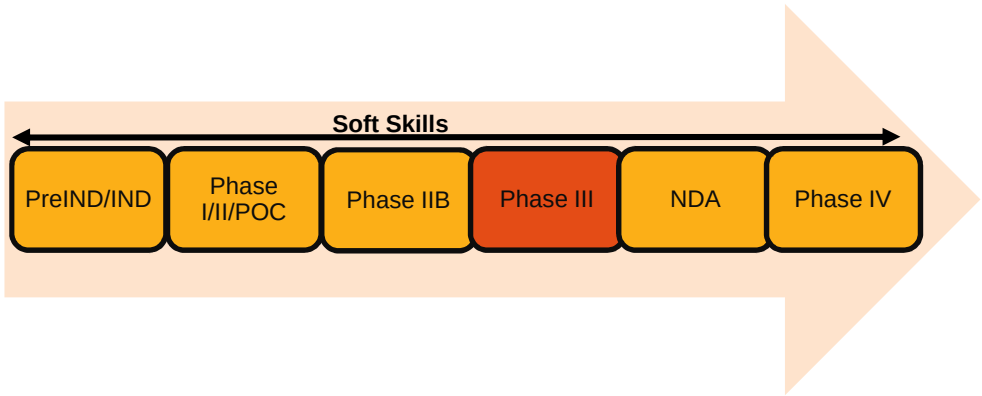
Submission Data Package



Study Data Technical Conformance Guide also asks for Analysis Data Reviewer's guide (ADRG) to accompany ADAM

- The ADRG provides FDA reviewers with context for analysis datasets
- This is in addition to define.xml The ADRG purposefully duplicates limited information found in other submission documentation (e.g., the protocol, statistical analysis plan, clinical study report, define.xml) in order to provide FDA reviewers with a single point of orientation to the analysis datasets
- The ADRG also provides a summary of ADaM conformance findings.

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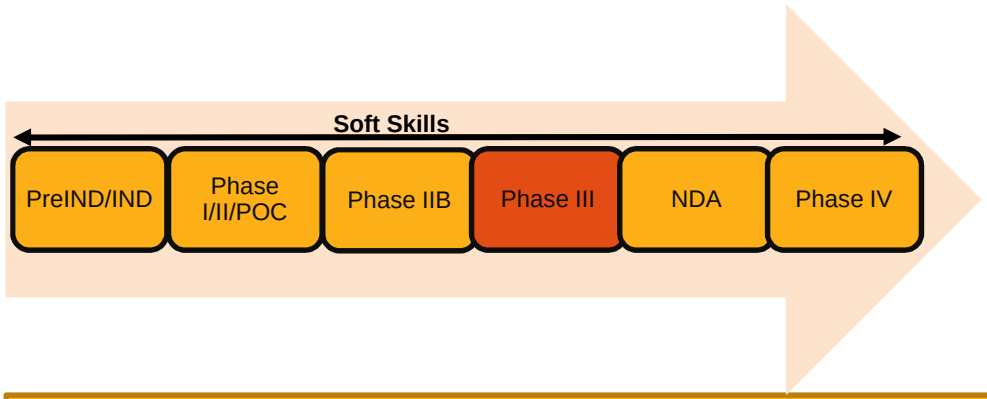
Submission Data Package



Example of explanation of an ADAM efficacy dataset in ADRG

ADPASI – PASI Score Analysis

ADPASI contains one record per subject per parameter per analysis date per analysis visit.

The PASI assessment were conducted for subjects in whom at least 3% of the body surface area (BSA) was affected by psoriatic skin involvement at baseline. The PASI assesses the extent of psoriasis on four body surface areas (head, trunk and upper and lower limbs) and the degree of plaque erythema, scaling and thickness. The head, trunk, upper limbs and lower limbs are assessed separately for erythema, thickening (plaque elevation, induration), and scaling (desquamation). The average degree of severity of each sign in each of the four body regions is assigned a score of 0-4. The area covered by lesions on each body region is estimated as a percentage of the total area of that particular body region.

Table 5-14 Important parameters included in ADPASI

PARAMCD	PARAM	Description	Usage
PSRS75	PASI 75 response	Binary response as to whether the PASI 75 response criteria is met or not	Secondary endpoint
PSRS90	PASI 90 response	Binary response as to whether the PASI 90 response criteria is met or not	Secondary endpoint

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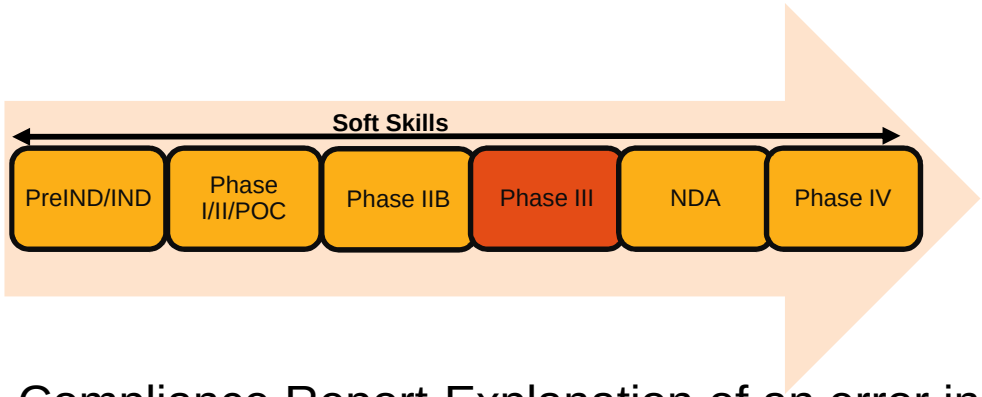
Compliance Report in ADRG



- Compliance Report-Explanation of an error in OpenCDISC

You explain

Dataset	Diagnostic Message	Severity	Explanation
ADDLQI	**Inconsistent value for AVALC**	**Error**	**False positive message. AVAL stores numeric representation of response categories, such as 0, 1, 2, 3, while AVALC stores character representation of response categories, such as "NOT AT ALL", "A LITTLE", "A LOT", "VERY MUCH". This explains inconsistency between AVAL and AVALC..**

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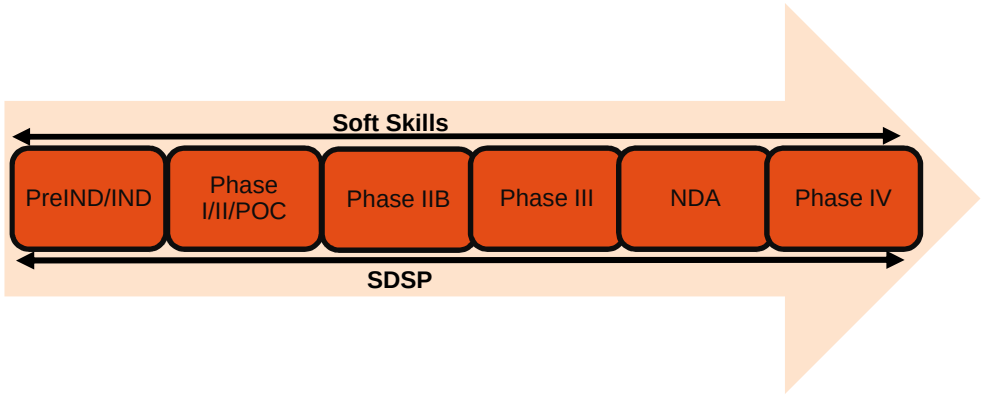
Study Data Standardization Plan



Study data Technical Conformance Guide talks about Study Data Standardization Plan, which should begin at IND discussions and is updated throughout the process

The *Standardization Plan* should include, but is not limited to the following:

1. List of the planned studies
2. Type of studies (e.g., phase I, II or III)
3. Study designs (e.g., parallel, cross-over, open-label extension)
4. Planned data standards, formats, and terminologies and their versions

Tips- Draft template Available through PhUSE CSS

http://www.phusewiki.org/wiki/index.php?title=Study_Data_Standardization_Plan_(SDSP)

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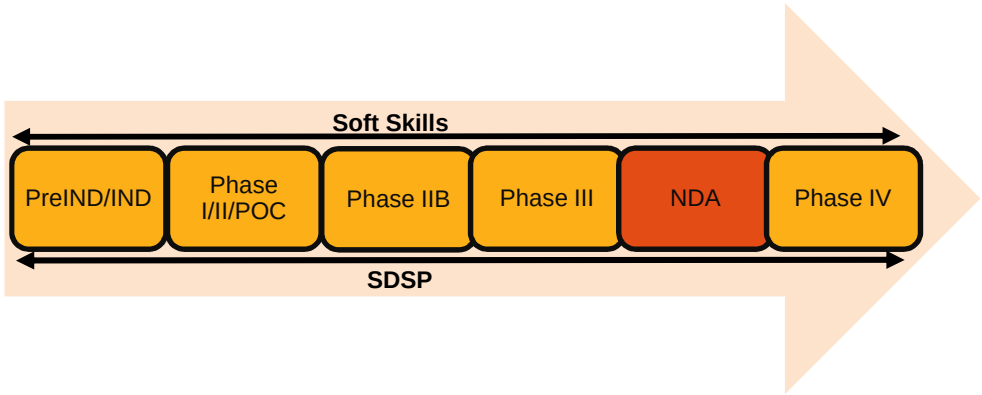
Registration and Approval of NDA



- ❑Advisory Committee Meetings
- ❑90/120 day Safety Updates
- ❑Health Authority Questions
- ❑Approval!!!!!!!

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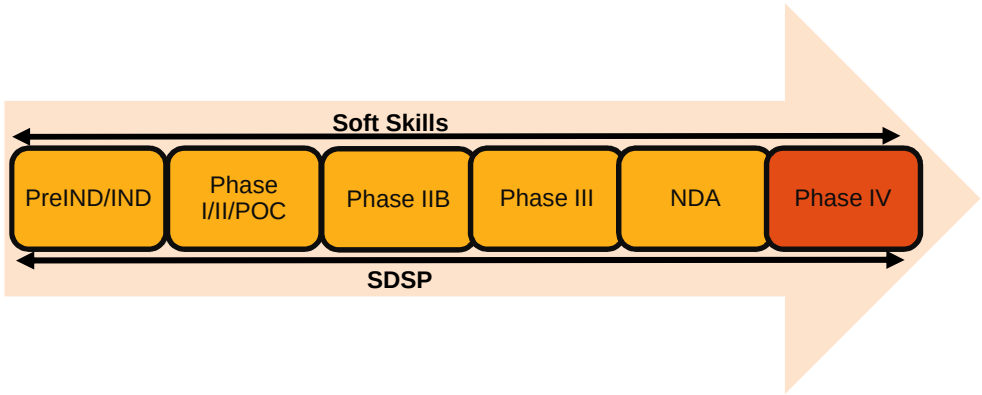
Post Submission



- Phase IV study reporting
- IND Updates
- Product Defense
- Compound Level Pooled Data Available
- Publications

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Soft Skills

- ✓ Plan ahead- gain stakeholder alignment with deliverable timelines
- ✓ Communicate with project team members and with regulatory agencies
- ✓ Manage your stakeholders
- ✓ Adapt to Changes

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Plan Ahead

- Your project consists of 2 pivotal phase 3 studies, and 8 phase 1/II studies
  - What information do you need?

  - Timing of the locks
  - SDTM/ADAM format
  - Pooling Plan?
  - Meddra version?
  - Granular timelines on each study/Pooled data
  - If working with a vendor on creating define
    - detailed timelines setting up contracts,
    - when to send study data,
    - How many iterations

Communicate

- Your project consists of 2 pivotal phase 3 studies, and 8 phase 1/II studies
  - What information do you need?
  - Who do you communicate with?

  - Project Manager or Submission Lead to understand the study reporting and dblock timelines
  - If you are a phase 3 programmer you reach out to the ED programmer to understand the structure of the phase 2 datasets
  - You work with your statistician to define a pooling strategy, prepare for briefing book
  - As you are creating your SDTM/ADAM datasets you communicate with data management and other stake holders
  - As you are authoring your Data Reviewer's guide pay attention to your written skills. Don't be too technical, please explain in a simple language, the issues and other relevant material.

Manage your stakeholders

- Your project consists of 2 pivotal phase 3 studies, and 8 phase 1/II studies.
  - What information do you need?
  - Who do you communicate with?
  - How do you manage your stakeholders

- You want the team to review the reviewer's guides , but they are busy doing other work, explain to them the consequences of not having the review.
- The clinical colleagues very often do not see these deliverables, yet its an important part of submission-manage their expectations
- If you are using a vendor to build define they might need data early, work with your internal team to get them what they want
- If you want others to review the final product, make sure you give them prior notice and ample time to review

Adapt to Changes

- You have been asked to strike 3 months of your timeline.
- How do you manage your stakeholders and still get the time you need to do quality work. How do you adapt? Be innovative?

  - Negotiate
  - If you have a plan you can show exactly how much time each activity is taking
  - Can the dblock dates be shifted?
  - Can the list of TLF's be reduced?
  - Can you be more efficient in how you are doing your work?
    - Perhaps All the common conformance errors across the study can be just described once and referred to, or copied in the other SDRG's.
    - Perhaps your ADAM dataset design strategy can be more lean
  - At the end, you might be able to reduce your timeline by 1.5 months.

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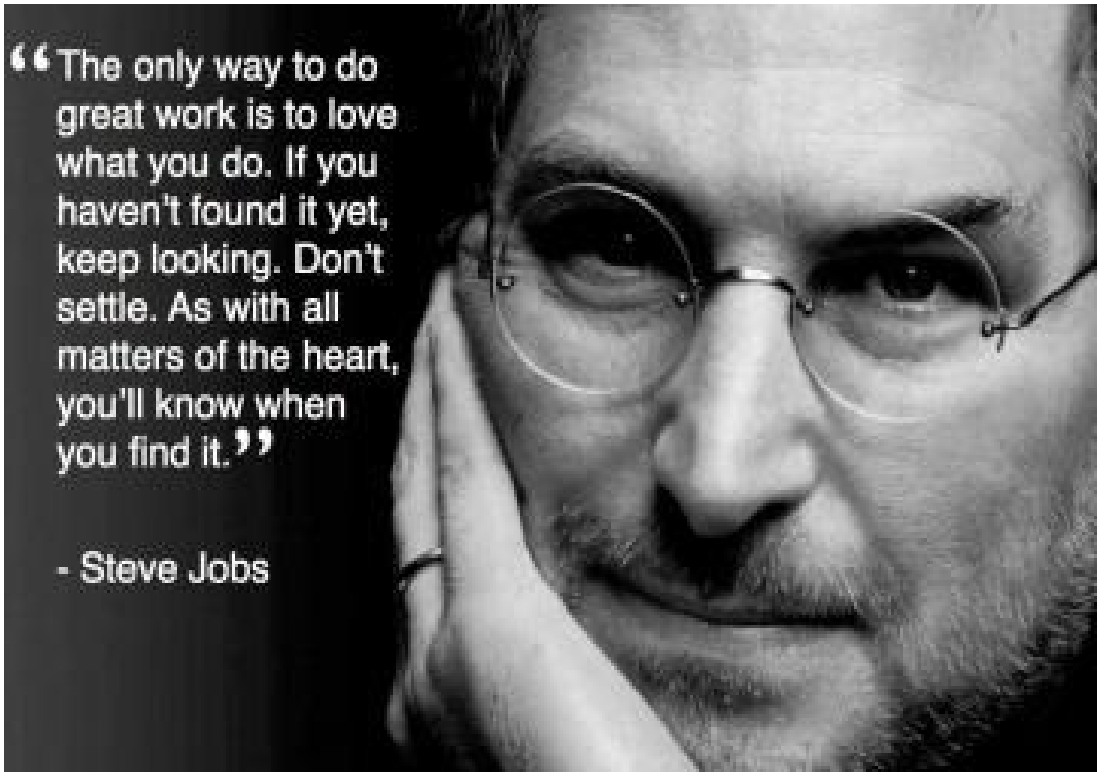
Acknowledgements

- FDA US Food and Drug Administration Homepage http://www.fda.gov/
- phuse Home page : http://www.phuse.eu/
- James Gallagher Global Franchise Head SR - Neuroscience & Retina, Novartis Pharmaceuticals
- Olivier Leconte, Global Head, SR, Novartis Pharmaceuticals
- My fellow professionals who inspire me everyday

Final Thoughts



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