Challenges implementing SDTM and ADAM in oncology platform trials

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Meet the Speaker

Carla Santillan

Title: Principal statistical programmer

Organization: Fortrea

Carla started as a junior programmer at a pharma company called Astellas some years ago, at present she is a principal statistical programmer at Fortrea. Since a bit more than a year ago she became lead programmer of a platform oncology study. With more than 15 years of experience she worked as SDTM specialist, team lead of ADAM conversions for FDA submissions, lead programmer in studies from different therapeutic areas, and participated in preparation of ISS, ISE submission packages.

She likes to share experiences and learn from others; she presented before in other CDISC EU interchange events and hopes this presentation will somehow motivates you to keep improving.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of CDISC.*

- *The authors have no real or apparent conflicts of interest to report.*

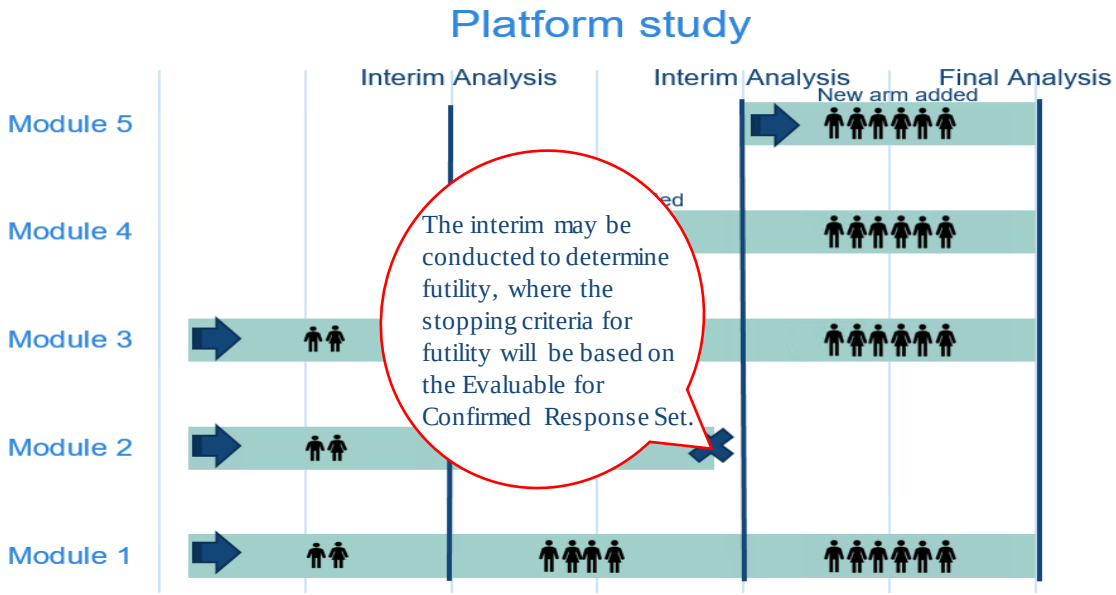
Agenda

1. Platform studies particularities
2. Real study protocol – database history
3. Impact on SDTM - ADAM

Platform studies particularities

Platform study

We define a platform trial as a randomized, adaptive trial, potentially without a planned end date, making it possible to assess multiple interventions (IP), where the treatment arms (modules) may be added or discontinued according to pre-established rules.



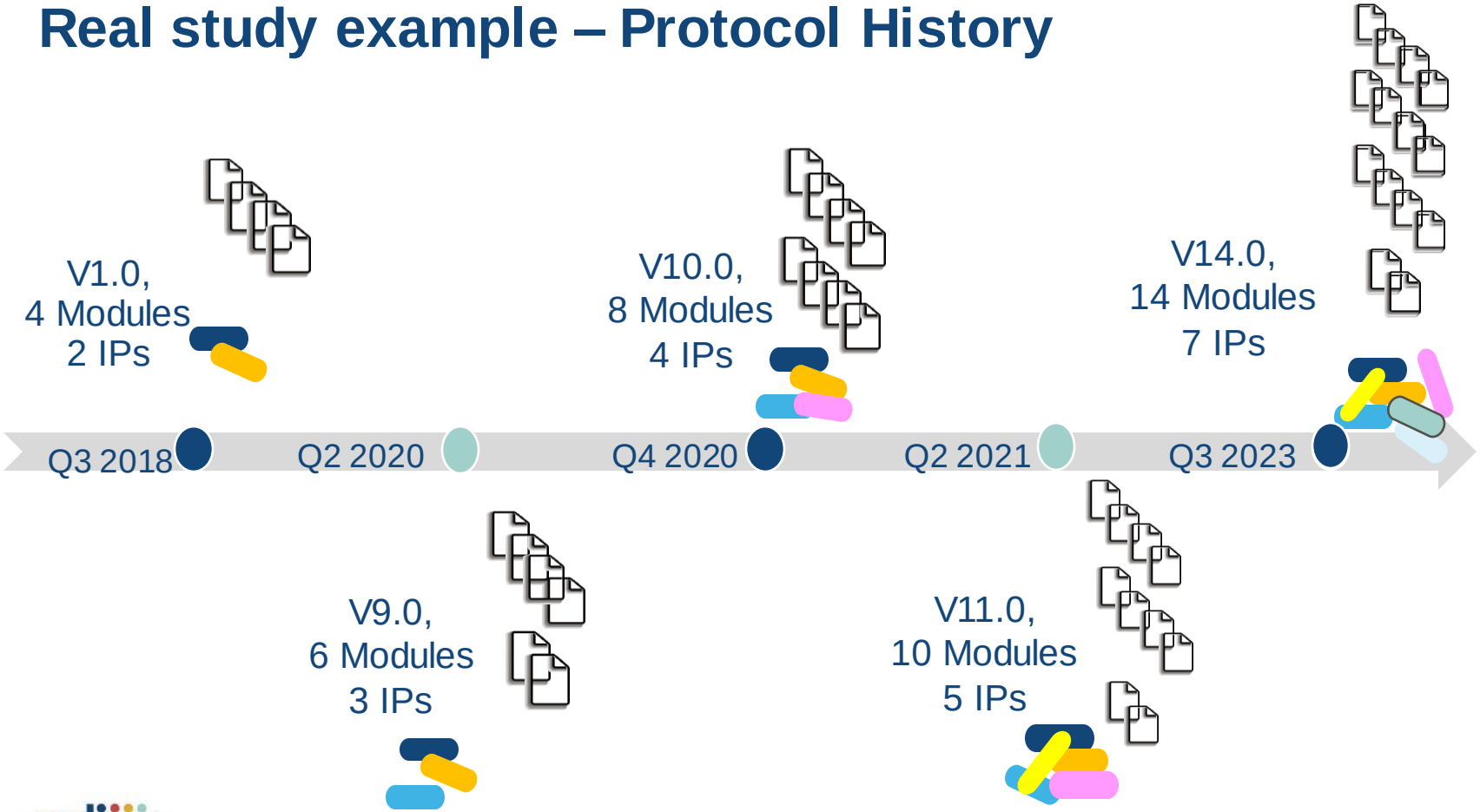
Jay J.H. Park [September 2020], *An overview of platform trials with a checklist for clinical readers [online]*, available from: https://www.sciencedirect.com/science/article/pii/S2451865420300521#:~:text=A%20master%20protocol%20is%20a%20unifying%20study%20design%20that%20includes,multiple%20drugs%20to%20treat%20it

Platform study - characteristics

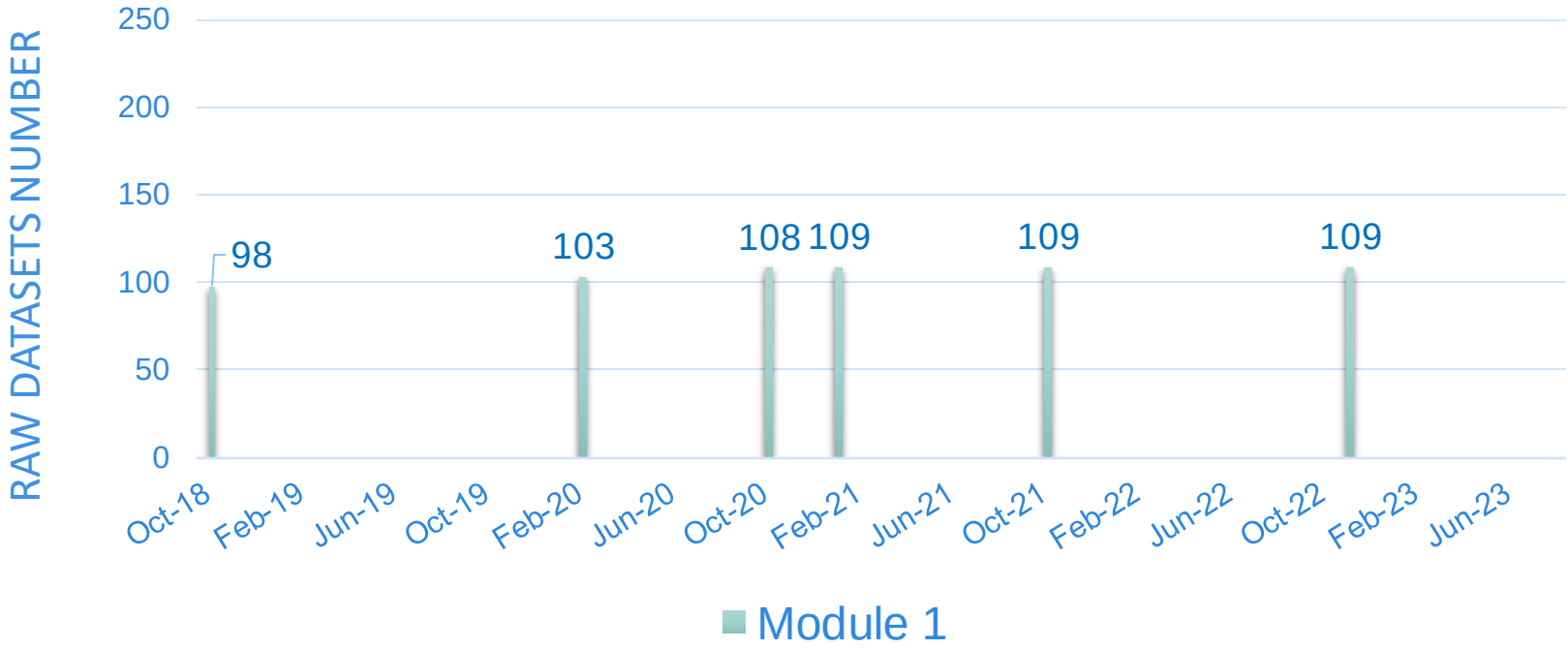
- Trial durations are longer
- Higher number of protocol substantial amendments
  - Higher number of Case Report Forms (CRF) amendments
  - Complex trial designs for a trial that is continuously evolving and having incremental data
- Higher data requirements
  - Large number of amendments for Statistical Analysis Plan (SAP), Table of Contents (TOC) and Table, Figure, Listing (TFL) Mock Shells
    - Highly Complex of Safety and Efficacy endpoints derivation
    - Larger number of TFLs

Real study protocol – database history

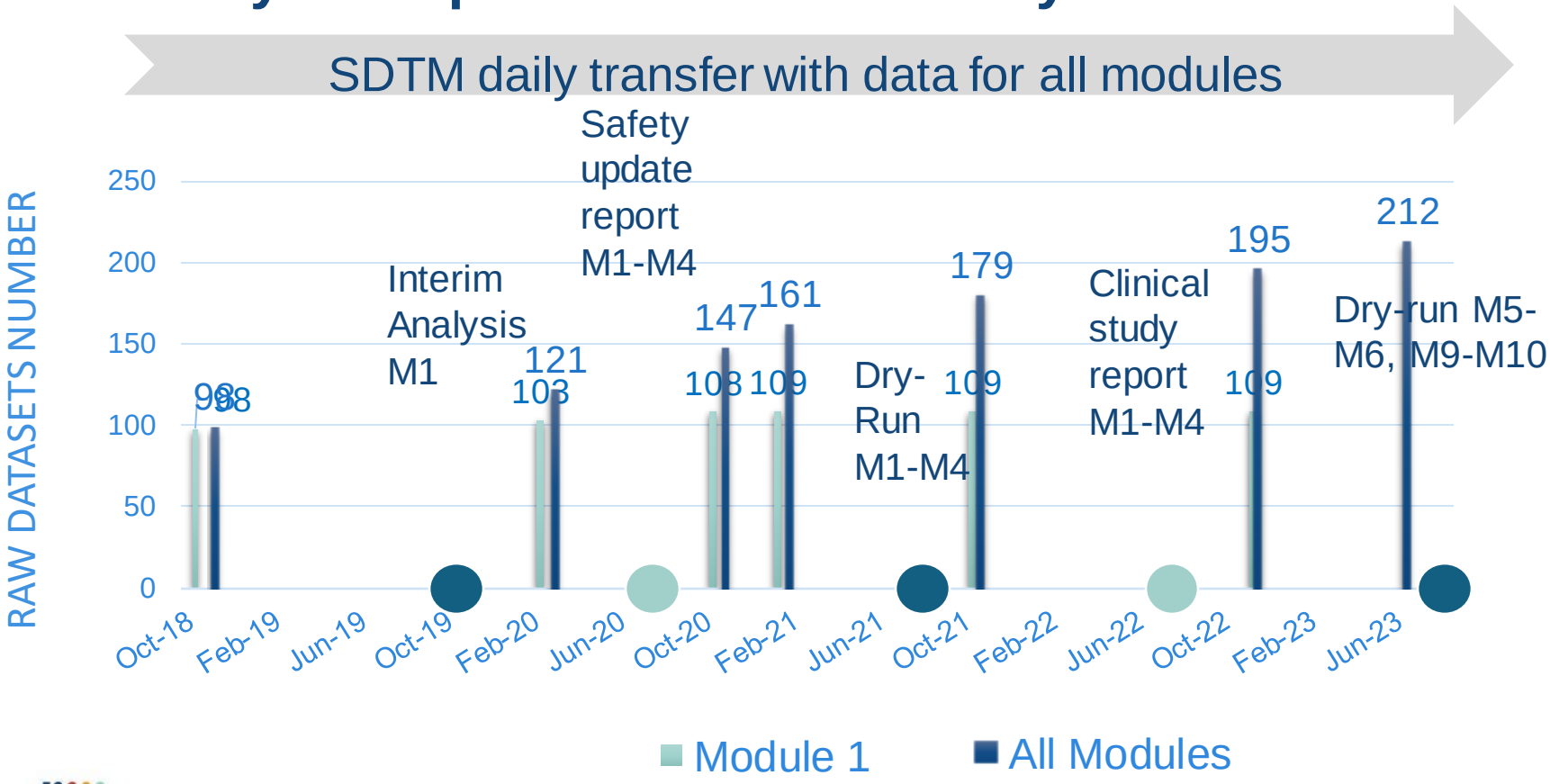
Real study example – Protocol History



Real study example – Database History



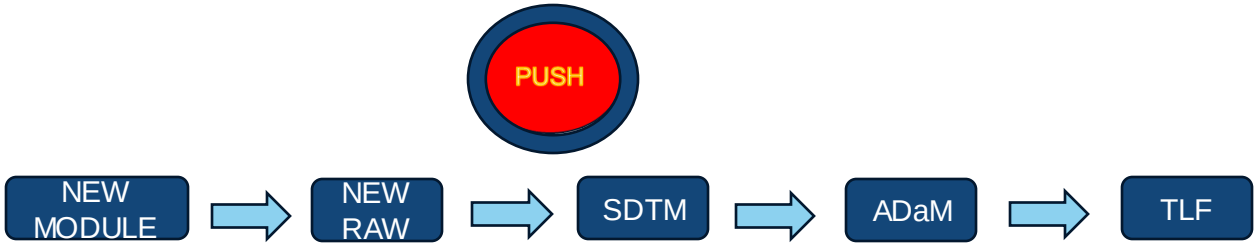
Real study example – Database History



Impact on SDTM - ADaM

Impact on SDTM - ADaM

- First time SDTM and ADaM are created is time consuming, the final goal is reusability, applicable to all modules, that would require minimum changes
- Defensive programming with user warnings (SDTM compliant, logic checks, relationships between domains AE/CM, additional edit checks, etc.) to identify issues sooner in the process
- Many releases will come, short timelines between releases will be proposed, because everything (SDTM, ADaM, TLFs) is programmed



Impact on SDTM - ADaM

- New changes can affect the datasets back and forward

- The amount and nature of changes will affect your timelines, identify them as soon as possible at each release
- There is no one-size-fits-all solution, h range of strategies has to be put in place.
- Flexibility and also some «c to combine the ongoing (and incremental) of analysis at a particular cut-off date and i ight be also retrospective)

Impact on SDTM

- One protocol fits all modules, all SDTM rules are from protocol
- What should be revised at each module, or each release?
  - Raw data module/release specific changes: Adverse events of special interest(AESI), Dose limiting toxicity(DLT), Pharmacokinetic data(PK), Meddra/WhoDrug dictionaries, Protocol deviations, potential prohibited medications…
  - SDTM includes all modules derivations, for variables like: RFENDTC, ARMCD, ARM, some assessments might be module specific and therefore some XXTESTCD
  - TS domains with content for all modules, final content will be based on your submission approach [modular, group of modules, all modules]

Impact on ADaM

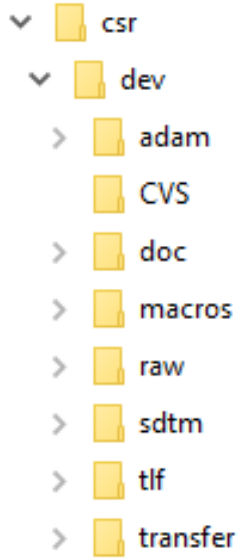
- **One Statistical Analysis Plan(SAP) for all modules**, one ADaM, requires complex derivations logics to handle all sub-studies scenarios
- Structure is defined in a flexible and robust setting capable of covering all possible data scenarios from the study's onset
- ADaM programs minimal module specific checks are required
  - ADSL including ARM/CD specific for Module 1 to Module N, IP**N** specific variables (e.g. IP**1**SDT, Date of First Exposure to IP**1** [to IP**N**]), TRTxxA, TRSDT
  - All BDS domains are affected by visits windows for safety/efficacy that are module specific or/and assessment specific
  - ADAE, AEACN**N** Worst Action Taken with Study Treatment [1to **N**]
  - ADEX oral/infusion drug planned doses, different dose duration calculations
  - Oncology most relevant domains
    - ADTR Tumor Results, Analysis Data
    - ADRESP Visit Response, Analysis Data
    - ADEFF Efficacy Endpoints, Analysis Data

Thank You!

Appendix

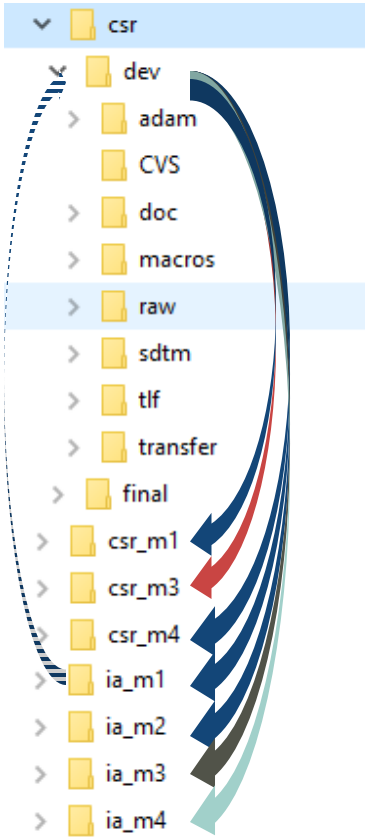
Centralized programming, Fortrea’s approach

Centralized Programming



- The most common strategy in place is to centralize, in each program, the logic for all modules present in the platform study, as they are added in the protocol.
- For SDTMs, this meets the requirement to send to the sponsor daily transfer of the current version of SDTM data created from the overnight database extraction.
- The ADaM and TLFs singular program implements derivations and layout for all modules as per the latest version of SAP and TFL Mock Shells
- Centralized programs are in Central Development folder (csr/dev).
- Each release has its own folder

Sub-folders for ongoing study deliveries



- Module Specific sub-folders are set-up for ongoing study deliveries (dry-run, interim analysis, customized review (e.g., safety), clinical study report).
- Programs and datasets in those folders represent a picture of the version in use at the time of the delivery. Programs are copied from the central development folder and not updated there, if not in rare circumstances.
- In case programs need to be updated in the Module Specific sub-folders, the corresponding csr/dev programs should be updated accordingly as soon as possible, making sure that the change applies to the only relevant module(s).

Appendix

Module specific data selection

Module Specific Data Selection

- For each Module Specific delivery, data are selected to contain information up to the Analysis Date (or Data Cut-Off date) and the desired selection of subjects based on the study modules they belong to.
- Our preferred option is to perform the data selection at the raw data level, in one central program, prior to creating SDTM datasets, so that SDTM datasets, ADaM datasets and transport files will contain the same version of data.