



PHUSE Connect EU 2023

DH11 - Challenges in Oncology Modular studies: Fortrea approach

Francesca Dall'Acqua - Dubravka Georgijevic

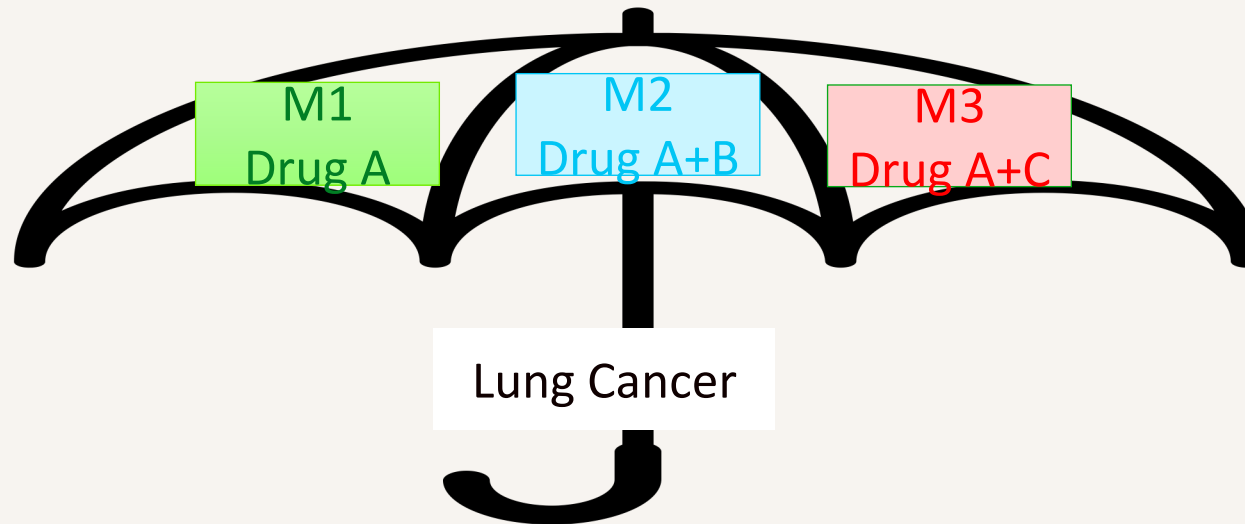


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Definition

An **Umbrella study** is a type of **master protocol** that is defined as “a unifying study design that includes multiple subgroups and sub-studies, with patients having same or different diseases and that employ one or multiple drugs to treat it.’

In particular the Umbrella study is a “protocol with more than one targeted therapy studied for a single disease”



BOGIN V., [June 2020], *Master protocols: New directions in drug discovery [online]*, available from

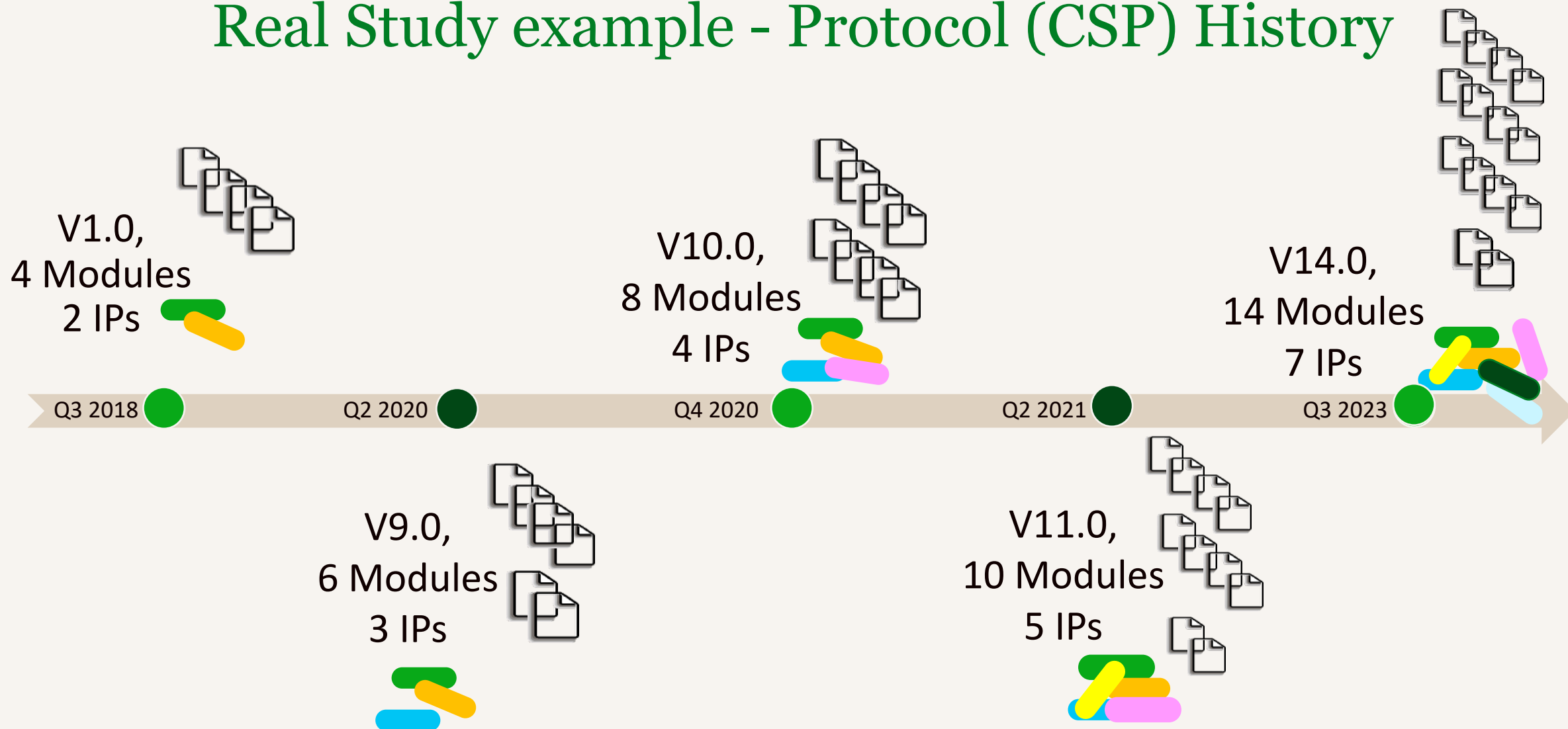
<https://www.sciencedirect.com/science/article/pii/S2451865420300521#:~:text=A%20master%20protocol%20is%20a%20unifying%20study%20design%20that%20includes,multiple%20drugs%20to%20treat%20it.>

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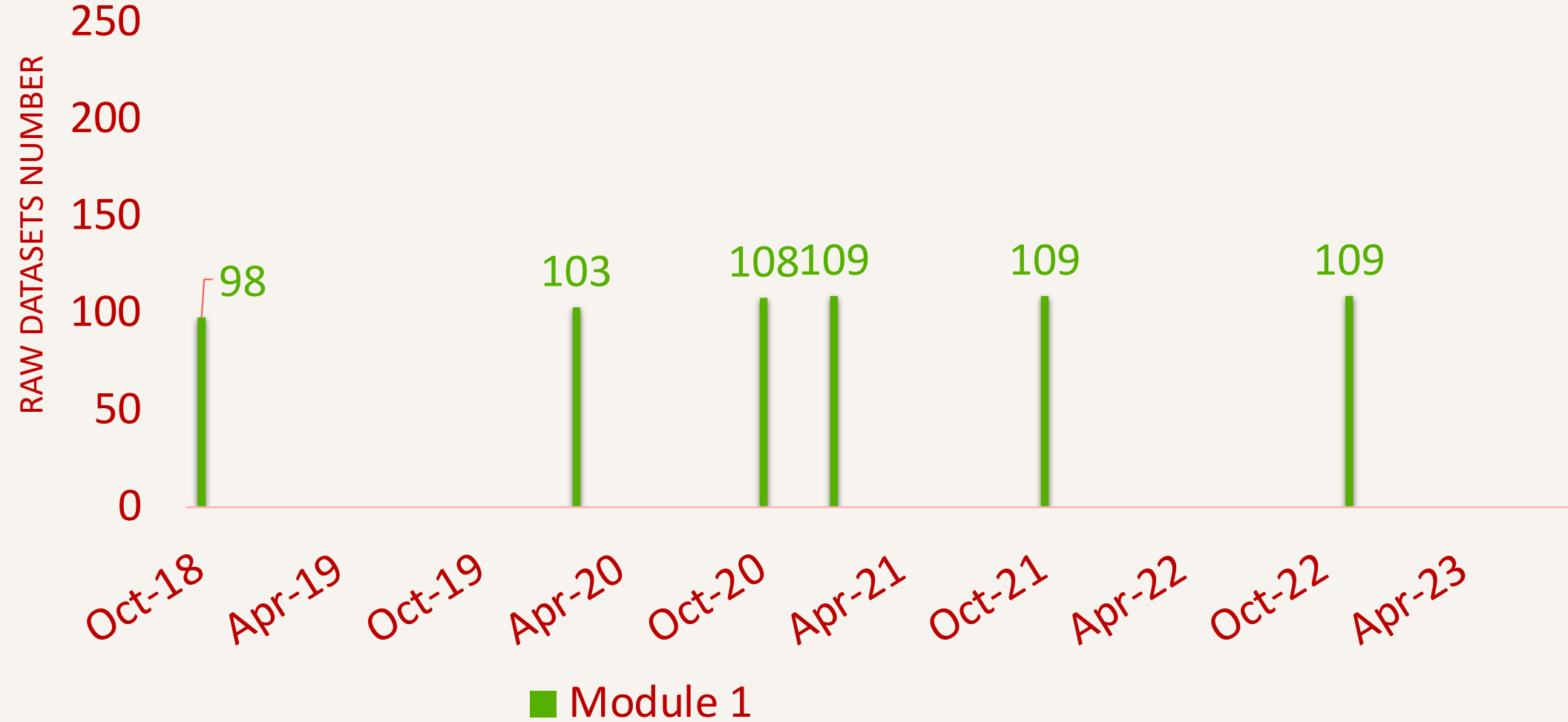
Umbrella Study Characteristics

- Longer trial timelines
- Higher number of protocol substantial amendments
 - Higher number of Case Report Forms (CRF) amendments
 - Complex trial designs made more arduous from the nature continually evolving and incremental of the study
- Increased 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 to produce

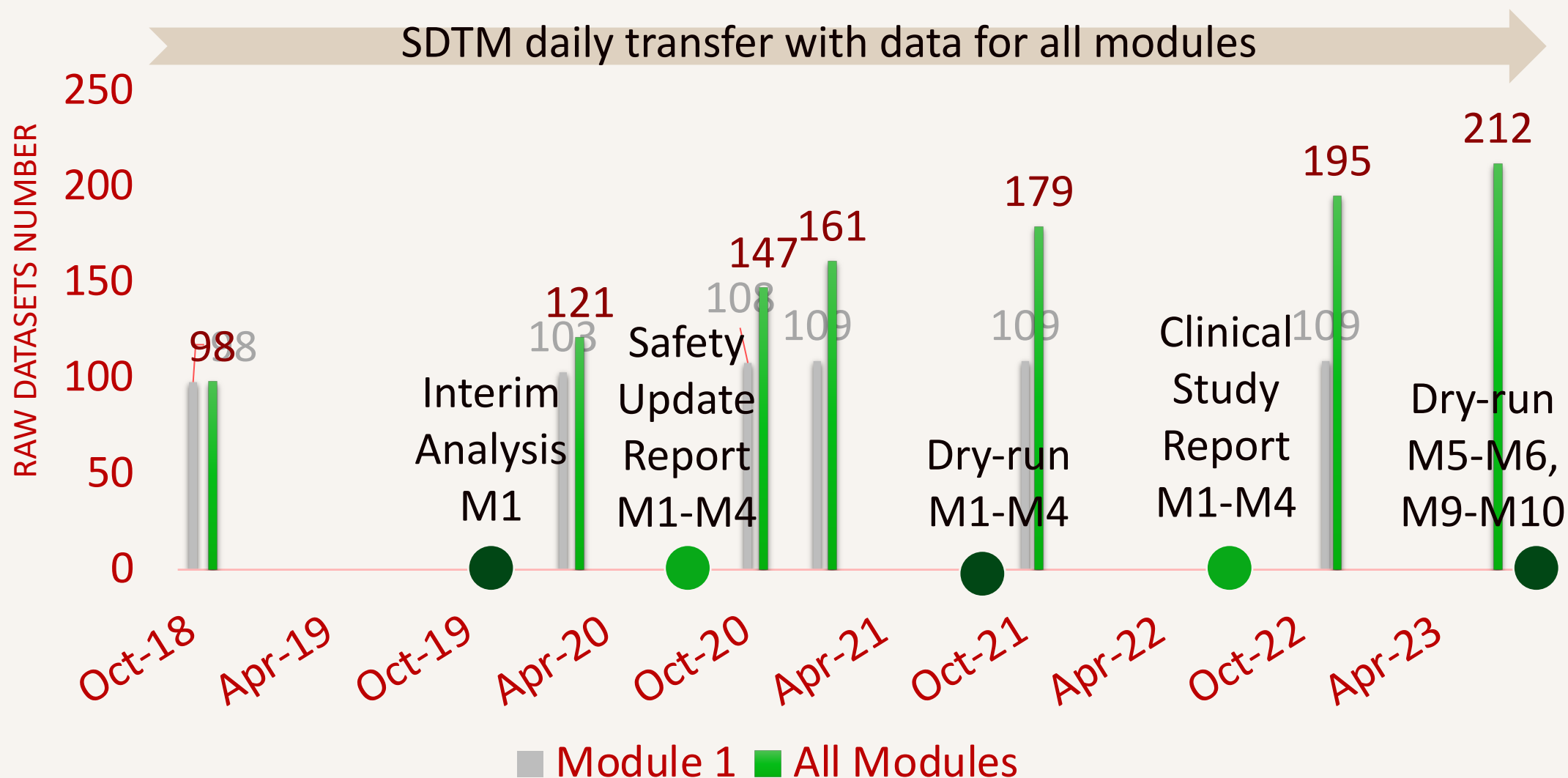
Real Study example - Protocol (CSP) History

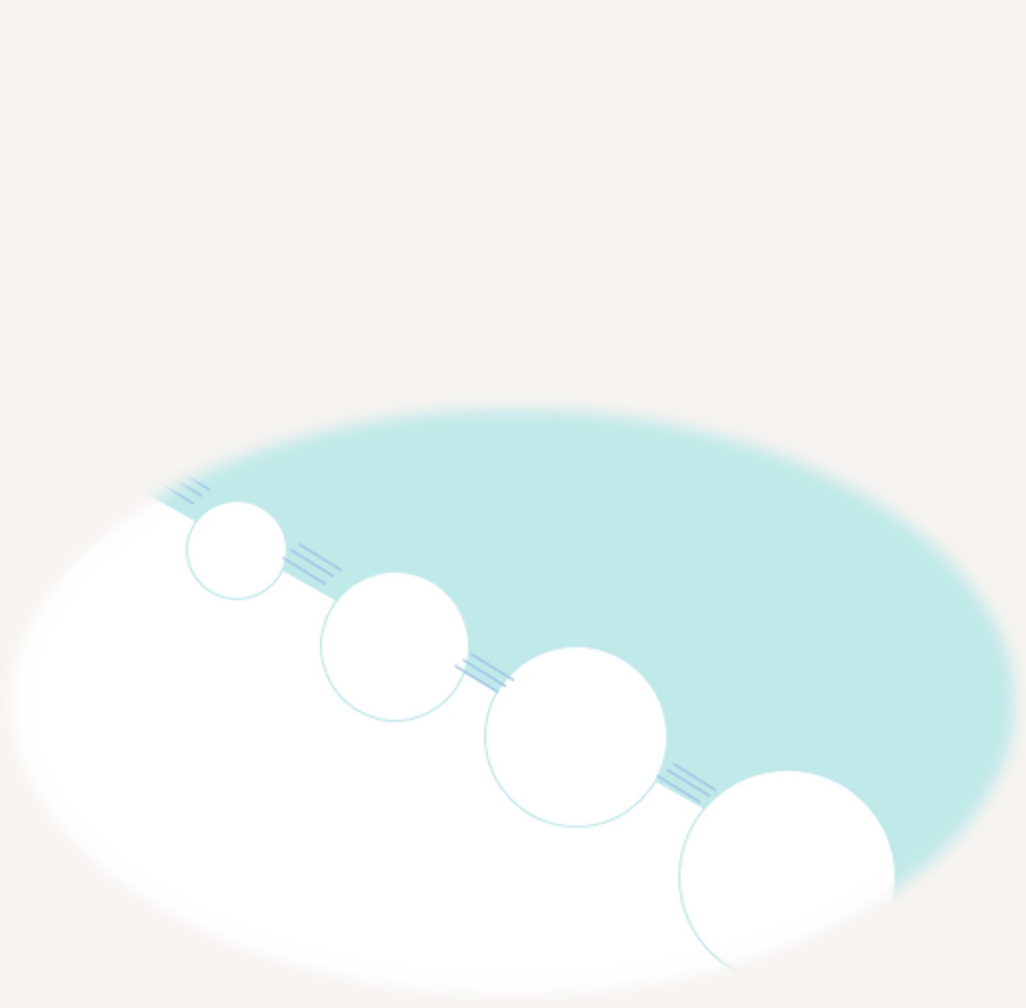


Real Study example - Database History



Real Study example - Database History



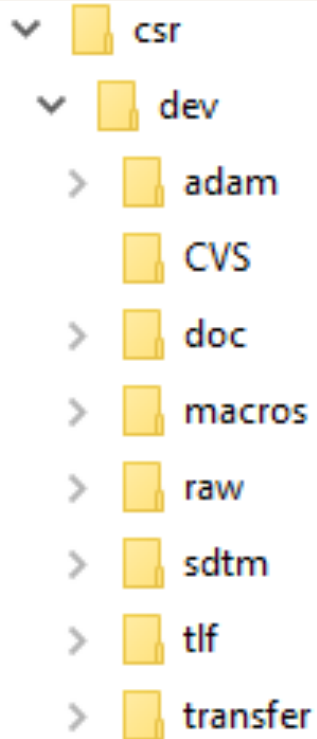


How to avoid the snowball effect

There is no one-size-fits-all solution, but instead a range of strategies has to be put in place.

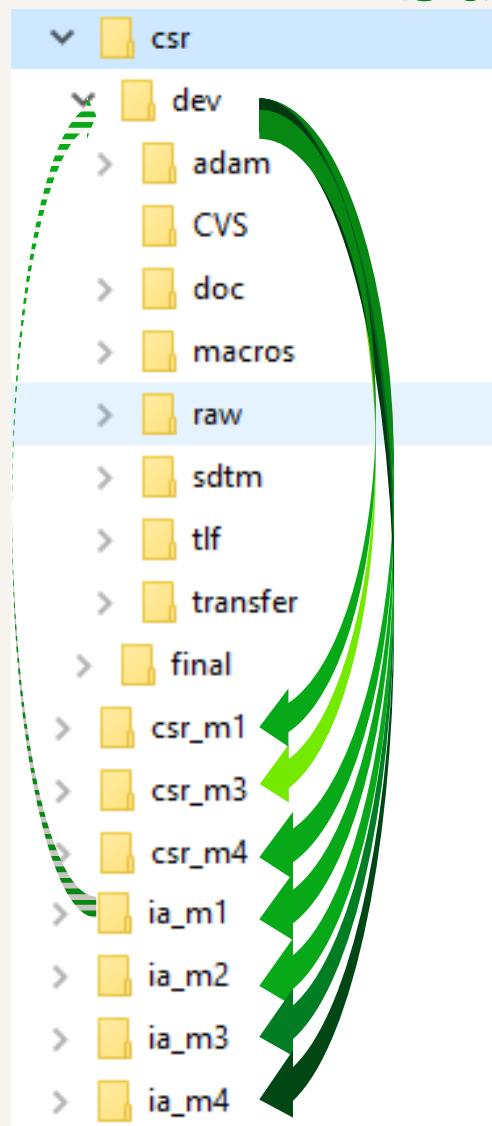
Flexibility and also some «creativity» is also very important to combine the ongoing (and incremental) nature of the study with the need of analysis at a particular cut-off date and for (a) particular module(s) (that might be also retrospective)

Centralized Programming



- The most common strategy in place is to centralize, in each program, the logic for all modules present in the umbrella 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 located in Central Development folder (csr/dev).

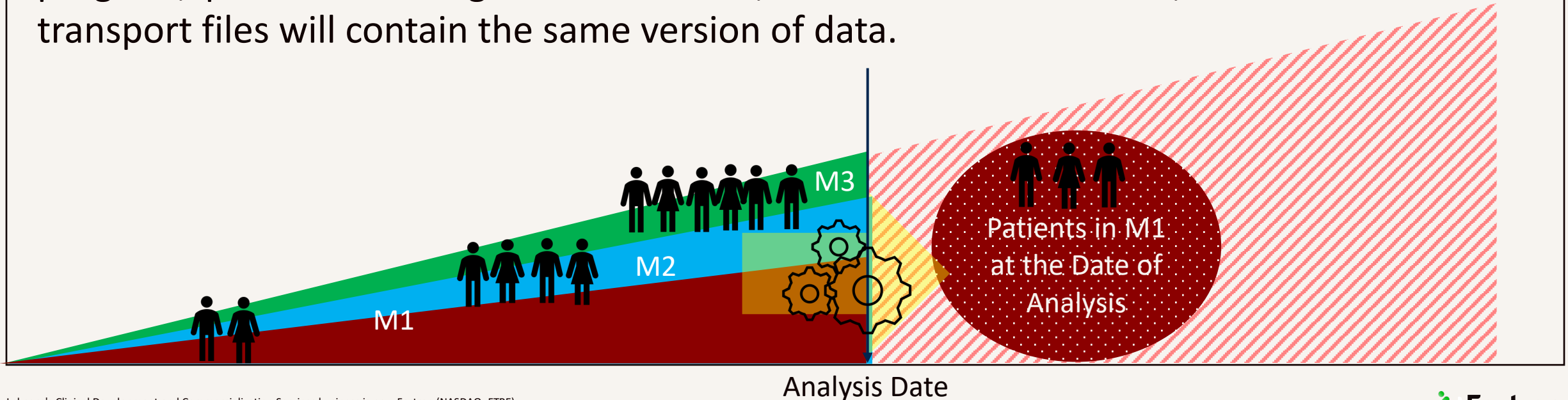
Sub-folders for ongoing study deliveries



- 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).

Module Specific Data Selection

- For each Module Specific delivery, data are selected in order 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.



Tables, Listings and Figures, module specificities

Module 1

	Number (%) of subjects					
	GR1.A		GR1.B		GR1.C	
	(N = xx)		(N = xx)		(N = xx)	
Subjects assigned to treatment	xx	(xx)	xx	(xx)	xx	(xx)

Module 2

	Number (%) of subjects					
	Stratification Group 1			Strat. Group 2		
	GR2.A		GR2.B		Total	
	(N = xx)		(N = xx)		(N = xx)	
Subjects randomised	xx	(xx)	xx	(xx)	xx	(xx)

Table Figures and Listings Flexibilities

Centralized programming is implemented through an extensive use of macros to grant flexibility in customizing

- column header
- footnotes
- slightly different content.

```
%macro by_module(out= , module = );  
  %tlf_reptrt(dsin=xxx, pop=&popfl, module=&module);  
  %tlf_denom(pop=&popfl, module=&module);  
  ...  
  proc report data = xxx_pop;  
    column a b c %tlf_repcol(txt="Number (%) of subjects");  
    %tlf_repdef(width=16, col on page=4);  
  run;  
%mend by_module;
```

derives applicable
treatment groups per
module

derives number of
subjects in each
treatment group

lists the treatment
columns to report

reports define
statements for treatment
groups

Selection of Table Figures and Listings Content

- For what concerns the content of TFLs, one of the challenges is to select the study modules/treatment groups applicable for the delivery in question and applicable to the analysis set used in each output.
- These are the approaches in use:
 - Data Driven
 - Metadata driven programming

Selection of Table Figures and Listings Content

- DATA DRIVEN APPROACH

- Because we apply subject selection at raw data level, SDTM and ADaM datasets contain only the applicable subjects/study modules. The ADaM dataset ADSL, which contains all subjects relevant for the delivery, is used in each TFL program to get the list of modules applicable for the analysis set in question, and then the further TFL code is executed for those modules only.

```
proc sql noprint;
  create table allmodules as
  select distinct group01c, group01
  from adam.adsl
  where SAFFL = 'Y'
  order by group01c;
quit;
data _null_;
  set allmodules;
  file "&work_lib/create_report.sas";
  put '%by_module(out=' group01c ', module=' group01c ');';
run;
%inc "&work_lib/create_report.sas";
```

Selection of Table Figures and Listings Content

- METADATA DRIVEN APPROACHES

1. Modules are defined in the central excel file called ***deliverables*** file and that information is read into SAS to create SAS macro variables.

macro_var_name	macro_var_value
out_parts	M1 M2 M3 M4
out_parts2	M1+M2\$M3+M4\$

Appendix xx.x.x.x

Title

Module 1

Subject identifier	Preferred term (MedDRA version xx.x)	Start date (Study day at start)	End date (Study day at end)	Duration (<<unit>>)	Ongoing at time of enrollment
E0001001	Xxxxxxxx	2021-04 (-500*)	2022-03 (-136*)	NC	N
E0001002	Xxxxxxxx	2022-07-10 (-35)	2022-09 (48*)	NC	Y
	Xxxxxxxx	2022-07-15 (-30)	2022-07-20 (-25)	6	Y

Appendix xx.x.x.x

Title

Module 2

Subject identifier	Preferred term (MedDRA version xx.x)	Start date (Study day at start)	End date (Study day at end)	Duration (<<unit>>)	Ongoing at time of enrollment
E0001001	Xxxxxxxx	2021-04 (-500*)	2022-03 (-136*)	NC	N
	Xxxxxxxx	2022-03-17 (-150)		NC	Y
	Xxxxxxxx	2022-07-10 (-35)	2022-09-02 (20)	55	Y

Appendix xx.x.x.x

Title

Module 3

Subject identifier	Preferred term (MedDRA version xx.x)	Start date (Study day at start)	End date (Study day at end)	Duration (<<unit>>)	Ongoing at time of enrollment
E0001002	Xxxxxxxx	2022-07-10 (-35)	2022-09 (48*)	NC	Y
	Xxxxxxxx	2022-07-15 (-30)	2022-07-20 (-25)	6	Y

Appendix xx.x.x.x

Title

Module 4

Subject identifier	Preferred term (MedDRA version xx.x)	Start date (Study day at start)	End date (Study day at end)	Duration (<<unit>>)	Ongoing at time of enrollment
E0001001	Xxxxxxxx	2021-04 (-500*)	2022-03 (-136*)	NC	N

Content

and that information

ular

Selection of Table

- METADATA DRIVEN APPROACHES

- Modules are defined in the central table and are read into SAS to create SAS macro

macro_var_name	macro_var_value
out_parts	M1 M2 M3 M4
out_parts2	M1+M2\$M3+M4\$

Table xx.x.x

Title

Module 1+2

	Module 1			Module 2		
	GROUP	GROUP	Total	GROUP	Total	
System organ class	1.A	1.B		2.A		
Preferred term	N=xxx	N=xxx	N=xxx	N=xxx	N=xxx	
(MedDRA version <<xx.x>>)	n (%)	n (%)	n (%)	n (%)	n (%)	
Any [[medical/surgical]] history	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	
<<System organ class A>>	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	
<<Preferred term 1>>	x (x.x)	x (x.x)	xx (xx.x)	x (x.x)	x (x.x)	
<<Preferred term 2>>	xx (xx.x)	xx (xx.x)	0	xx (xx.x)	0	
...						

Table xx.x.x

Title

Module 3+4

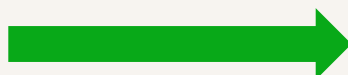
	Module 3			Module 4		
	GROUP	GROUP	Total	GROUP	Total	
System organ class	3.A	3.B		4.A		
Preferred term	N=xxx	N=xxx	N=xxx	N=xxx	N=xxx	
(MedDRA version <<xx.x>>)	n (%)	n (%)	n (%)	n (%)	n (%)	
Any [[medical/surgical]] history	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	xx (xx.x)	

Selection of Table Figures and Listings Content

- METADATA DRIVEN APPROACHES

2. Treatments/modules based on the list of treatment groups present in the TRT codelist in the ADaM specs file (adjusted to each delivery) and also read into a SAS macro variable.

ADaM Specs in Central Development Area			
ID	Name	Term	Decoded
TRT	Treatment	M1	Module 1
TRT	Treatment	M2	Module 2
TRT	Treatment	M3	Module 3



ADaM Specs in Delivery Folder for M1			
ID	Name	Term	Decoded
TRT	Treatment	M1	Module 1

Conclusions

• CENTRALIZED PROGRAMMING PROS AND CONS

PROS	CONS
Meets the requirement of SDTM daily transfer containing all the data collected in the database	Programs are very large in order to implement complex logic (i.e. more study designs that require different Analysis Visit Windows, Baseline definitions, different header blocks or layout for Table)
Centralized code allows us to implement in one place the latest version of the program and ensures it is easier to maintain different disseminated versions of the same program.	If any change in the middle of the process (SDTM, ADaM or TLFs), you have to check backward and forward to evaluate if any impact on other modules and other programs.
Allows the development of a single program for simultaneous and parallel deliveries for different modules.	Stability in the team is very important. Otherwise it is needed to plan longer onboarding period due to high complexity of the programs
In term of resources one dedicated team is enough versus a team per module	

Thank You!

Questions?

Francesca Dall'Acqua - Dubravka Georgijevic

Fortrea

Phuse EU 2023

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the authors at:

Francesca Dall'Acqua

Fortrea Development Ltd

Via Giorgio Washington, 70,

20146 Milano MI, Italia

francesca.dallacqua@fortrea.com

Dubravka Georgijevic

Fortrea Netherlands BV

Schipholweg, 111 2316 XC

Leiden, The Netherlands

dubravka.georgijevic@fortrea.com