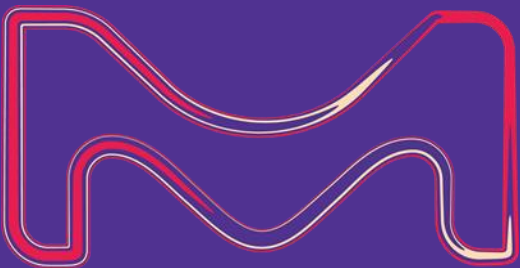


SM09: Advancements in the Evolution of our SMC Story: Process and Technology

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PHUSE EU Connect 2024, 11th of November 2024



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Disclaimer

The views expressed in this talk are those of the speaker and not necessarily those of Merck KGaA

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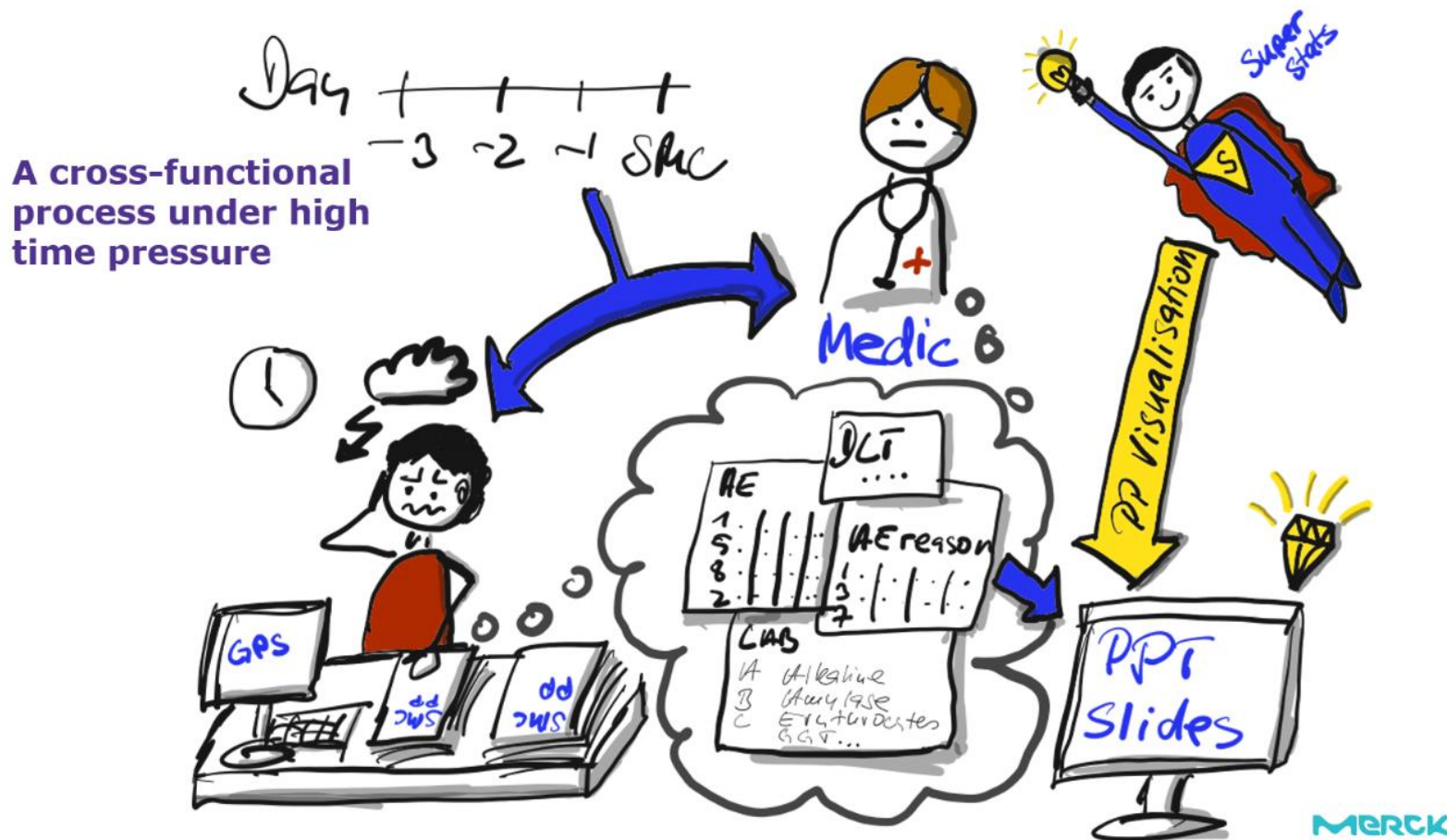
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1. Introduction

Safety Monitoring Committee (SMC) assess the safety, efficacy of the Investigational Medicinal Product (IMP) alone and in combination and perform benefit risk assessment to safeguard the interests of study participants. They monitor the overall conduct of the clinical study and compliance with the study protocol to protect the validity of the study.



1. Introduction



- SMC slides were not homogeneous between projects
- Heterogeneity of involved CROs and involved sponsor staff
- Time Pressure
- Error-Prone and time-consuming copy-and-paste process

1. Introduction

Our Objectives were:

- Streamline workflows
- Improve deliverable usability to accelerate project timelines
- Empower professionals to prioritize critical tasks
- Ensure the safety and well-being of our patients

2. Approach

- Alignment on **standardized SMC materials** requiring minimal adaptations for each study.
- Use **source data** (CDASH) instead of SDTM or ADaM
- **Eliminate manual result transfer** e.g. copy-past results to power-point
- Develop the **aSMC R-package**, which automates the creation of SMC slides

3. SMC material example – SMC slides



3. SMC material example – SMC slides

Agenda

No.	Topic	Representative
1	Welcome and introduction	SMC coordinator and GPS Product Responsible (Chairperson)
2	Study status and protocol deviations	Medical Advisor
3	Clinical update and subject safety (individual level)	Medical Lead
4	Safety update (cumulated level)	GPS Product Responsible
5	DLT Discussion and confirmation by SMC	SMC core members and investigators with patients discussed in cohort
6	Pharmacokinetic data (if available)	PK expert
7	Statistical considerations	<u>Biostatistician</u>
8	SMC alignment and recommendations	SMC code members
9	Next steps: e.g., next SMC meeting planning	GPS Product Responsible

3. SMC material example – SMC slides

Study enrollment status (cumulative)

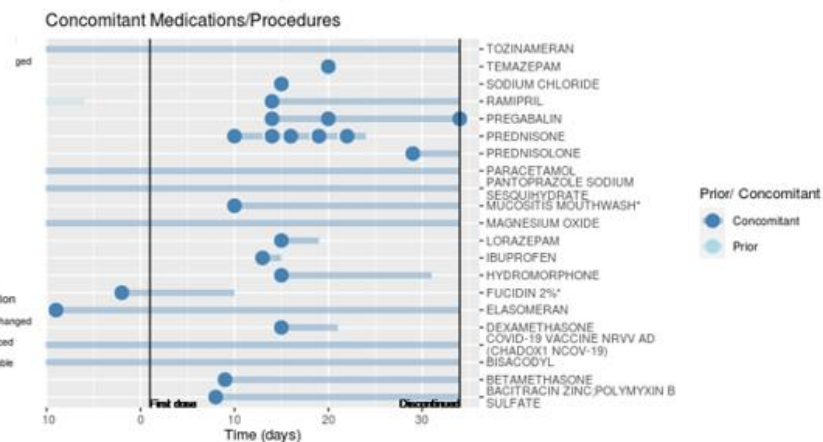
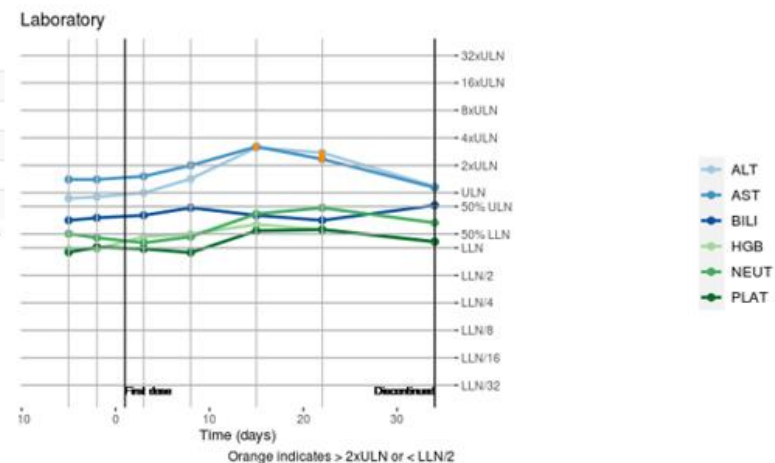
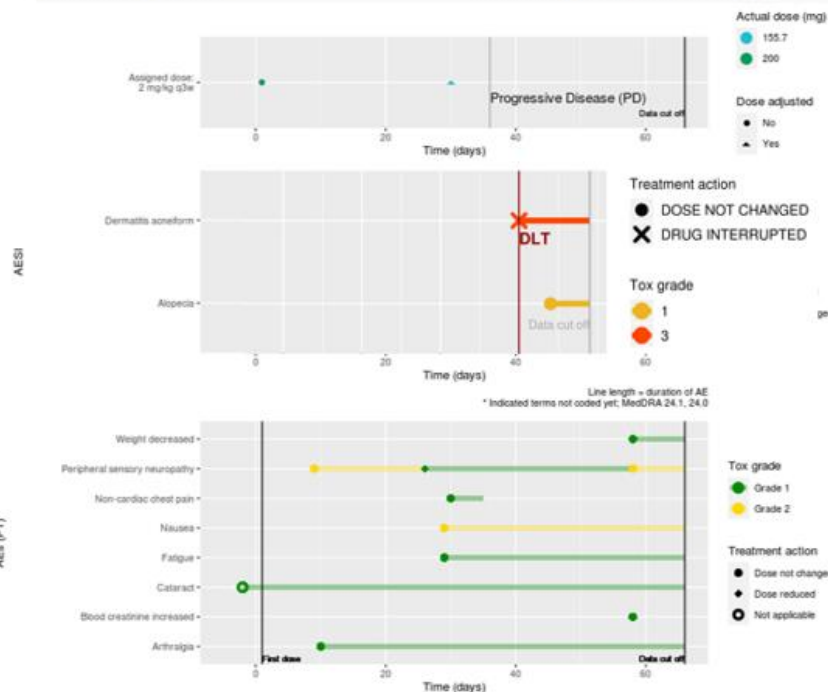
Cohort	Dose level	Subject number	Site of primary tumor	Age/ gender	C1D1	Completed DLT Period	Current cycle	Reason for withdrawal	End of treatment date	End of study date	Comments
Cohort 1	0.4 mg/kg	1010001	CHOLANGIOCARCINOMA	69 F	23-Jan-2021	Y	Off treatment	PD		21-Feb-2021	
Cohort 1	0.4 mg/kg	1020002	LEFT SUBMANDIBULAR LYMPH NODE	76 F	04-Mar-2021	Y	Off treatment	AE	25-Mar-2021	10-May-2021	
Cohort 1	0.4 mg/kg	3010005	BREAST CANCER	65 F	07-Mar-2021	Y	Off treatment	PD	19-Apr-2021	26-Apr-2021	Previously screened as 3010004
Cohort 2	0.8 mg/kg	2020006	MALIGNANT NEOPLASM OF BODY OF PANCREAS	61 M	10-May-2021	Y	Off treatment	PD	19-Jun-2021	07-Jul-2021	Previously screened as 1020001
Cohort 2	0.8 mg/kg	2060006	NON-SMALL CELL LUNG CANCER	72 M	17Apr-2021	Y	Off treatment	PD		19-May-2021	
Cohort 3	1.6 mg/kg	4040005	MALIGNANT NEOPLASM OF PANCREAS	59 M	26-Jun-2021	Y	Off treatment	WbS	03-Aug-2021	02-Sep-2021	
Cohort 3	1.6 mg/kg	1010007	MALIGNANT NEOPLASM OF UNSPECIFIED OVARY	68 F	04-Jul-2021	N	Off treatment		18-Jul-2021	23-Aug-2021	
Cohort 3	1.6 mg/kg	4010001	MALIGNANT NEOPLASM OF THE PANCREAS	58 M	17-Jun-2021	Y	Off treatment	PD	21-Jul-2021	08-Aug-2021	
Cohort 4	1.6 mg/kg	3050006	COLON	71 F	11-Aug-2021	Y	Off treatment	PD	13-Sep-2021	08-Nov-2021	
Cohort 4	1.6 mg/kg	1040002	CECAL ADENOCARCINOMA	60 F	19-Sep-2021	Y	Off treatment		01-Nov-2021	15-Nov-2021	

WbS: Withdrawal by subject; PD: Progressive disease; AE: Adverse event

3. SMC material example – SMC slides

Patient Profile 1204319

Subject, Dose level, Cohort and Site	1204319, 2 mg/kg, Cohort 5, 201
Age, Sex and Race	68, M, Not Hispanic or Latino
Tumor type and Diagnosis Date	RECTAL CANCER, NA
EOT date and reason	2021-12-16, EOT reason: Progressive disease
Prior Anti-Cancer Therapies	CAPECITABINE, FOLFIRI, FOLFOX, Radiotherapy



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3. SMC material example – SMC slides

SMC Recommendation Form - Recommendation/ Decision

Recommendation/ Decision

Dose escalation part

Dose escalation to _____

Expansion of enrollment at dose level _____ for _____ subjects

De-escalation to dose level _____

Maximum tolerated dose at dose level _____

Suspension of enrollment

Switch to different dosing regimen: _____

Adapt cohort size, i.e. change the size for cohorts to _____ subjects

Study may continue with modifications (see comments)

Study should be stopped

Other: _____

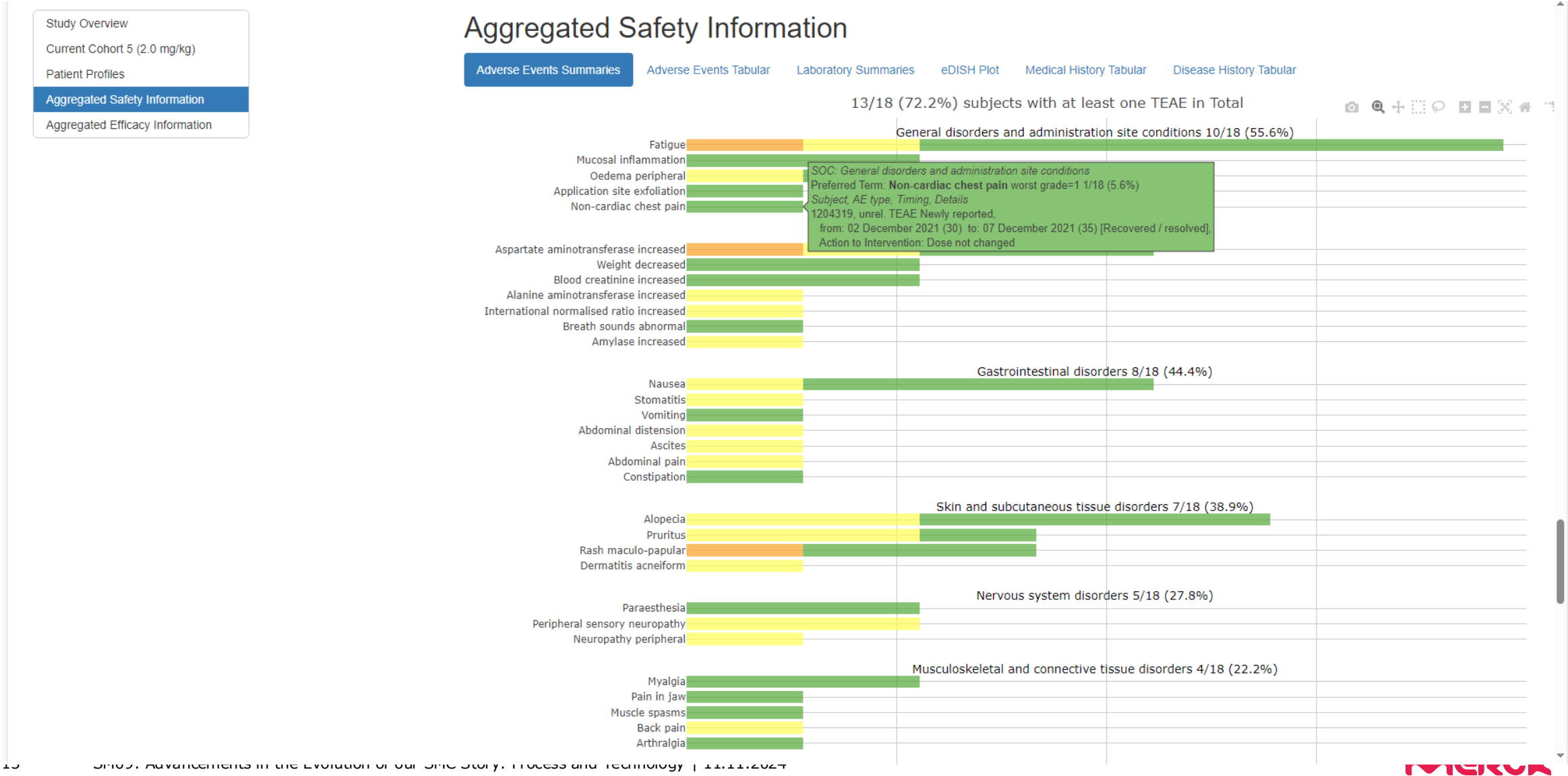
Comments:



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3. SMC material example – HTML TOOL



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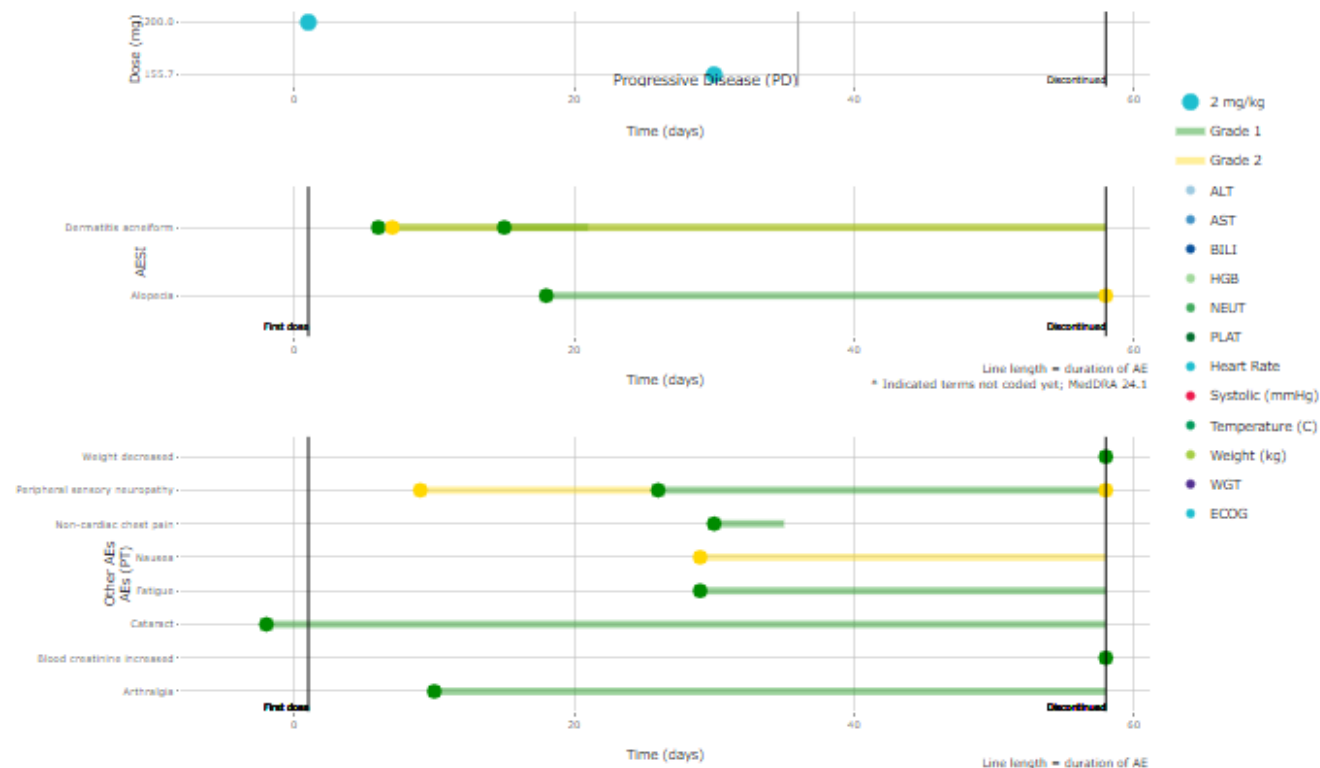
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3. SMC material example – HTML TOOL

Patient Profiles

1204319	1465242	1915789
Subject, Dose level, Cohort and Site		1204319, 2 mg/kg, Cohort 5, 201
Age, Sex and Race		68, M, Not Hispanic or Latino
Tumor type and Diagnostic Date		RECTAL CANCER, NA
EOT date and reason		2021-12-16, EOT reason: Progressive disease
Prior Anti-Cancer Therapies		CAPECITABINE, FOLFIRI, FOLFOX, Radiotherapy



4. Tool Development

- A “tool framework” **prototype** was implemented in R, using `Rmarkdown`, it consists of an initialization script and a set of modules :
 - `DataModel`: Manages the data layer of the tool.
 - `HtmlGenerator`: Programmatically generate HTML files.
 - `PptGenerator`: Programmatically generate PowerPoint slides.
 - `LegacyAsmc`: Make functions from the initial SMC tool available from within the framework.

4. Tool Development

The tool evolved and the project-driven “evolution pressure” lead more features, more adoption, but also revealed some challenges, as the SMC tool was outstretched by project needs.

The codebase became **complex and adaption** were necessary in order to mitigate this and ensure a future-proof tool, a major refactor of the SMC tool codebase was considered.

We took inspiration from **design patterns of frameworks** for other programming languages, we considered the **separation of the codebase** into a data access layer (the 'model') and into business logic (the 'controller').

4. Tool Development

The framework requires three kinds of R files to be specified for the tool:

- **A "model" R files** utilize the frameworks DataModel to make data available throughout the tool: Each model file instantiates the DataModel object, points it to their respective Rds file.
 - AdverseEvents
 - ConcomitantMedication
 - DiseaseHistory
 - Dose
 - LaboratoryData
 - MedicalHistory
 - Subjects
 - VitalSigns

4. Tool Development

- **A "controller" R file** consists of a list that contains functions, i.e. controller methods. These methods act as the "business logic" of the tool: They access data model (or other controllers), perform derivations, calculations, etc., and return an output, that may be used by other controllers or by the 'main' scripts to compile a report.
- For example:
 - `SubjectsController$all_subjects()`,
 - `SubjectsController$subjects_on_treatment()`,
 - `AdverseEventsController$summary_of_adverse_events()`,
 - `StudyOverviewController$Disposition()`

4. Tool Development

- **The "main" R file** is the script, that - on the highest level - generates an output, an html or ppt file. It initializes the framework, accesses the controllers, and compiles the outputs.

4. Tool Development

As part of our R tech stack, notable packages used in the tool are:

- R6 – encapsulation of modules
- Rmd, knitr – document generation
- ggplot2, plotly – figure output
- tibble, kable, flextable, DT – tabular output

5. Where are we?

Refactor of the SMC tool led to the idea to **create a framework**, which is a major step in achieving high levels of automation.

As the further development of both the SMC tool is ongoing, a backlog of features waits for its implementation, further enhancing functionality and programmers experience.

We look forward to extending the codebase of the SMC tool to adjacent scenarios, such as DMC reporting, and integrating the tool within a bigger landscape of static (e.g. PDF/RTF) and interactive (Shiny) reporting.

6. Conclusion

The development of our SMC tool represents a significant step forward in supporting safety monitoring in clinical trials.

As an interactive webpage, it provides comprehensive patient information, including profiles and data summaries, along with features for filtering, screenshots, and zoom functions that facilitate efficient reviews.

This streamlined approach not only boosts efficiency but also empowers our teams to make informed decisions faster and accurate to ensure the safety and well-being of our patients.



Q&A

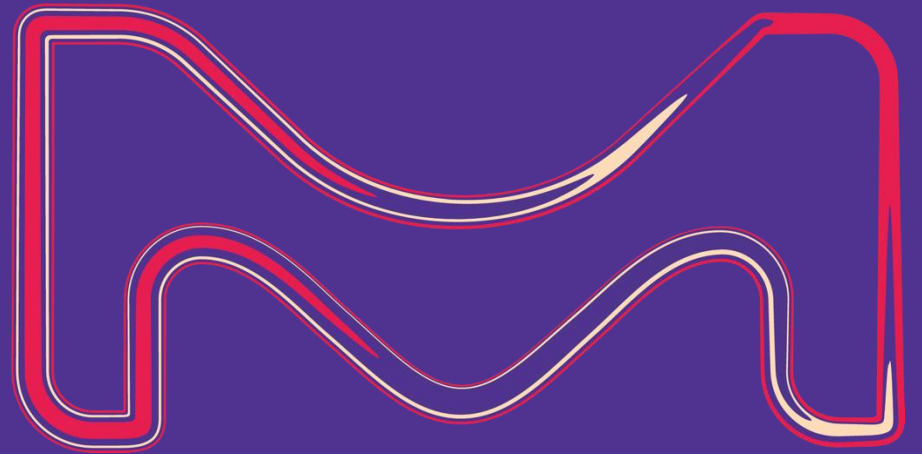
Thank you

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Back up slides

