

Standardized and Automated Template for Dose Escalation Decisions

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Motivation

- Dose escalation (DE) decisions are routine yet pivotal in Ph1 trials
- However, content and format can vary vastly by study team
- Numbers from TLGs get manually pasted and this needs to be repeated for every DE meeting
- DE slides can benefit from standardization of content and automation of slide generation to
 - Improve efficiency and turnaround time
 - Remove typographic errors, reduce repetitive work
 - Comparability of results within and across trials
 - Be FAIR

Objective: Establish a standardized & automated Dose Escalation slide deck template

Considerations



Data Sources

SDTM vs ADaMs
SDTMs allow early adoption



Format

- Patient level data [listings]
- Dose & Patient level summaries [tables]



Implementation

- Quick turnaround time
- Generalizable across studies
- Scalable code for multiple cohorts
- Flexible enough to incorporate new outputs

Scope

Patient level Summaries

- Demographics
- Baseline characteristics
- Prior cancer therapy
- Study treatment
- Adverse events
- Vital signs
- Medical history
- Conmed
- ECG

Dose level Summaries

- Disposition Summaries
- AE overview
- AE, Related & G3-5
- Deaths

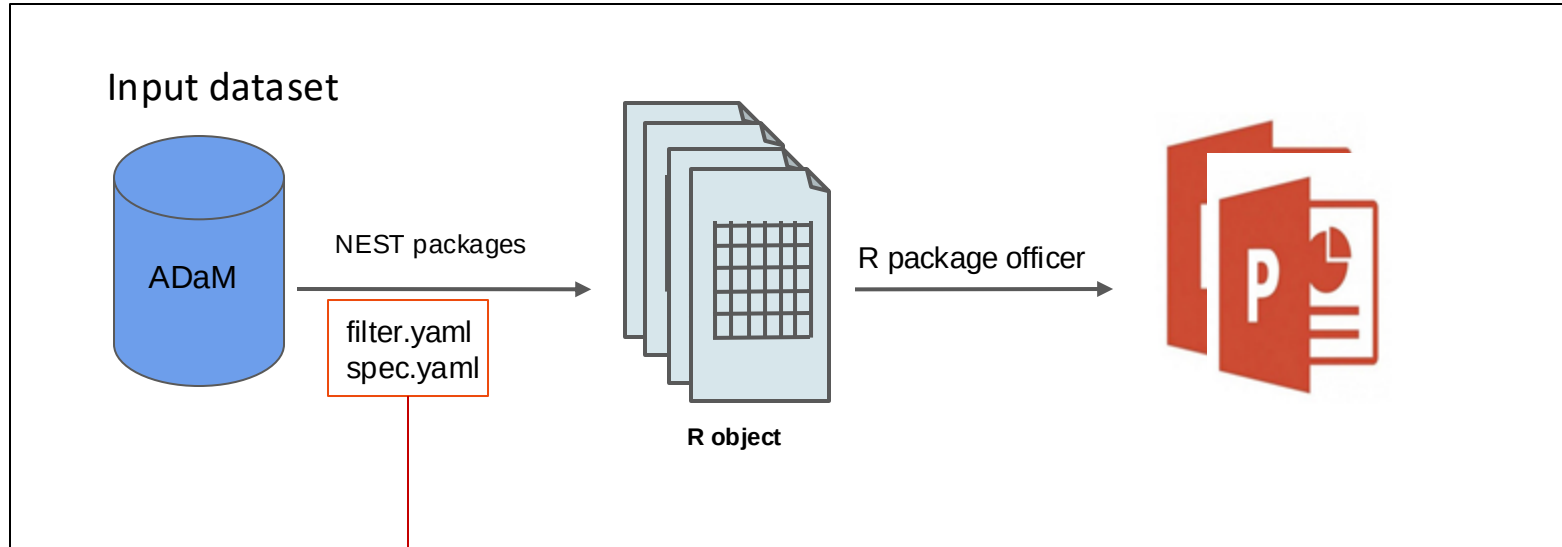
The Tool: autoslideR/autoslider.core

Development

- Upon evaluating existing internal and external tools available, we decided to use autoslideR, an internal R package
 - There is an external version of the package, called autoslider.core which is [available on CRAN](#)
- autoslideR automates the creation of slide decks from clinical outputs (TLGs)

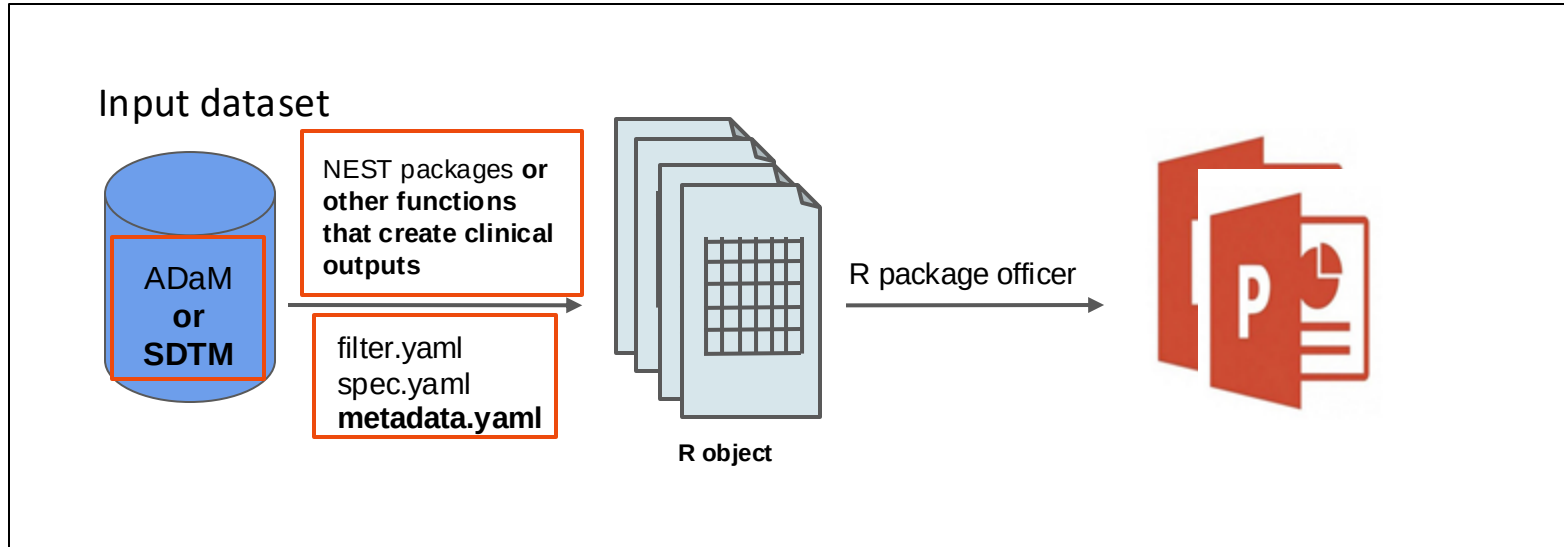


How does autosliderR work?



Slide automation driven by human readable yaml files to minimize efforts of programming in R

How does autosliderR work?



Metadata examples - filters.yaml

```
PP01:  
  title: Patient 01  
  condition: grepl("01", USUBJID)  
  target: dm
```

Patient filter, applied to DM
SDTM domain

```
REL:  
  title: Related AEs  
  condition: AEREL == "Y"  
  target: ae
```

Related AEs filter, applied to AE
SDTM domain

Metadata examples - spec.yaml

```
- program: dm_cohort_list_slide  
  suffix: DM  
  args:  
    dltwin: 21
```

Cohort overview slide

```
- program: df_dm_disease_slide  
  suffix: PP01  
- program: df_mh_slide_gred  
  suffix: MHPP01
```

Patient level slides for patient 01

```
- program: t_ae_sum_g35_sdtm_slide  
  suffix: REL_DM_EX_AE
```

Safety summary slide, filtered on treatment-related AEs

Metadata examples - metadata.yaml

```
data_path: data/sdtmv/  
ro: R01234567  
study_id: PR12345  
cut_date: 17-JUN-2024  
extr_date: 17-JUN-2024  
mtg_date: 21-JUN-2024  
cohort_value: Cohort 1  
spotfire_link: <link>  
gitlab_repo: <link>
```

Used to:

- populate slides with correct molecule name, protocol number, cohort value
- populate a final 'Data Sources' metadata slide

Code - set-up

1

```
# Read in yaml files
filters::load_filters("metadain/tlg/dose_filters.yml")
spec_file <- file.path("metadain/tlg/dose_spec.yml")
metadata <- yaml::read_yaml(file.path("metadain/tlg/dose_metadata.yml"))
```

2

```
# Get path to data from metadata yaml
data_path <- metadata$data_path

# Read in SDTM
dm <- arrow::read_parquet(paste0(data_path, "dm.parquet"))
ae <- arrow::read_parquet(paste0(data_path, "ae.parquet"))
# ... and all other SDTM domains

# Define the list of input data required for slides
de_data <- list(
  "dm" = dm,
  "ae" = ae
  # ... and all other SDTM domains
)
```

3

```
# Load custom functions
lapply(list.files("./R/"), function(x) source(paste0("./R/", x)))
```

Code - create slide deck

4

```
# Run the outputs
# Starting with the spec yaml file
outputs <- spec_file %>%
  read_spec() %>%
  # create the TLGs with the list of SDTM domains as input
  generate_outputs(datasets = de_data) %>%
  # decorate the TLGs with titles, footnotes
  decorate_outputs() %>%
  # add the TLGs to slides in pptx
  generate_slides(
    outfile = "path/to/outfile",
    template = file.path(system.file(package = "autoslider.core"), "/theme/basic.pptx"),
    table_format = autoslider_dose_format
  )
```

5

```
# Append texts to the slides using custom function
append_text_slides(
  outfile,
  study_id = metadata$study_id,
  cut_date = metadata$cut_date,
  # ... and all other values in metadata yaml
)
```

Examples

PR12345

Cohort 1 Dose Escalation Meeting

Clinical Science: [Name]

Safety Science: [Name]

Clinical Pharmacology: [Name]

Clinical Operations: [Name]

Biostatistics: [Name]

Agenda

- Objectives
- Patient Level Summaries
- Aggregate Patient Summaries
- Pharmacokinetics Overview (if applicable)
- Pharmacodynamic Overview (if applicable)
- Overall Summary + Dose Escalation Decision

Study Design

- Insert Study Design Schema here (Highlight Stage of the current DLT - Safety Assessment/ Dose Escalation)

Dose Escalation Meeting Objectives

Review of X patients in Arm X Cohort X (Dosing Level) for purposes of dose escalation decisions on Study Number [study number].

Cohort #	Patient ID	IMP Dose/schedule	Cancer type	C1D1	End of DLT/Safety window	DLT/Safety event Y/N/Not Eval	Treatment status
Cohort 1	01	DL1 60 mg	COLORECTAL CANCER	27NOV2023	08JAN2024		Discon, PROGRESSIVE DISEASE, CYCLE 2 DAY 1
Cohort 1	02	DL1 60 mg	RENAL CELL CANCER	09JAN2024			Discon, PROGRESSIVE DISEASE, CYCLE 1 DAY 1
Cohort 1	03	DL1 60 mg	COLORECTAL CANCER	27MAR2024	08MAY2024		Ongoing
Cohort 1	04	DL1 60 mg	PANCREATIC CANCER	06MAY2024	18JUN2024		Ongoing

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Patient Level Summaries

Adverse Events for Patient: PR12345-01

AE term	AE Start Date (study day)	AE End Date (study day)	Serious?/ DLT?/ AESI?	Initial Grade	Max Grade	IMP1 Related?	IMP2 Related?	IMP1 Action Taken?	IMP2 Action Taken?	Other Causes	Treatment	Outcome
AE1	02DEC2023 (D6)	05DEC2023 (D9)	N/N/N	1	1	N	NA	DOSE NOT CHANGED	NOT APPLICABLE	OTHER	NONE	RECOVERED/RESOLVED
AE2	07DEC2023 (D11)	08DEC2023 (D12)	N/N/N	1	1	Y	NA	DOSE NOT CHANGED	NOT APPLICABLE	NONE	NONE	RECOVERED/RESOLVED
AE3	03JAN2024 (D38)	07FEB2024 (D73)	N/N/N	2	2	N	Y	DOSE NOT CHANGED	DOSE NOT CHANGED	NONE	CORTICOSTEROIDS	RECOVERED/RESOLVED
AE4	03JAN2024 (D38)	07FEB2024 (D73)	N/N/N	2	2	N	Y	DOSE NOT CHANGED	DOSE NOT CHANGED	NONE	CORTICOSTEROIDS	RECOVERED/RESOLVED

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Safety Overview

	Cohort1 – Dose Level 1	All Patients
	(N=4)	(N=4)
Total number of patients with at least one AE	3 (75.0%)	3 (75.0%)
Total number of AEs	12	12
Total number of patients with at least one		
Treatment-related	2 (50.0%)	2 (50.0%)
Grade 3-5 AE	1 (25.0%)	1 (25.0%)
Grade 3-5 Treatment-related AE	0	0
Serious AE	1 (25.0%)	1 (25.0%)

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Data Sources

- Clinical Data Cut-off Date: 17-JUN-2024
- Data extraction date/time: 17-JUN-2024
- Spotfire Weblink: <link>
- Data location on compute platform x: SDTMv files path: <path/to/files>
- Analysis programs located on: <gitlab link to analysis programs>

Learnings from the DE Process & Pilot

Wins

- Overall positive experience with time savings for the team
 - from 3 days to 5 hours for the first DE meeting
 - 1-2 hours for following DE meeting preparations
- Increased collaboration and influence with stakeholders

Improvement areas for the future

- The implementation of the slides is dependent on the timing of SDTM availability
- Some enhancements needed on formats slides generated by `autoslideR`
- Alignment on the amount of customizations for each study's DEM templates
- Alignment on the timing of final slide deck delivery to leave sufficient time for manual updates

Next Steps

- **Project-level**

- One more pilot with either a different DE method / different team
- The WG will finalize the recommendation on DEM process, template & timeline
- Formal roll-out
 - Clinical/Safety team will update process plan
 - Data Science team will update Wiki page
 - Adoption in future DE studies

- **Technical-level**

- Add pilot template functions into `autoslideR/autoslider.core` (validated) package
- Add additional functions based on the proposed DE template
- Recommend best practices for programming team to set this up on our internal platform
- Better documentation on how programming team can make study-specific changes
- Collaborate with `autoslideR` team on potential of further reduction of set-up time, i.e., yaml file

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- `autoslideR` development team (Joe Zhu, Yinqi Zhao, Xiaoli Duan et al.)
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