Paper PP17

Process Design and Tools for Supporting Hematology Blinded Patient Disease Response Review

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ABSTRACT

This paper presents an implementation strategy for process design and building tools for blinded disease response reviews in hematology trials. We translate reviewer requirements into automated, reproducible workflows using SAS®, R and develop algorithm specification and functions for diverse data derivations and protocol-specific response assessment windows for various Hematology malignancies. The solution ensures auditability and traceability by keeping a running log of subjects, reported data and highlighting changes from prior reports delivered. This work demonstrates how leveraging various programming tools within team expertise and thoughtful process design can significantly improve the quality, consistency, and transparency of blinded patient data reviews in Hematology trials, ultimately supporting better clinical decision-making and regulatory compliance.

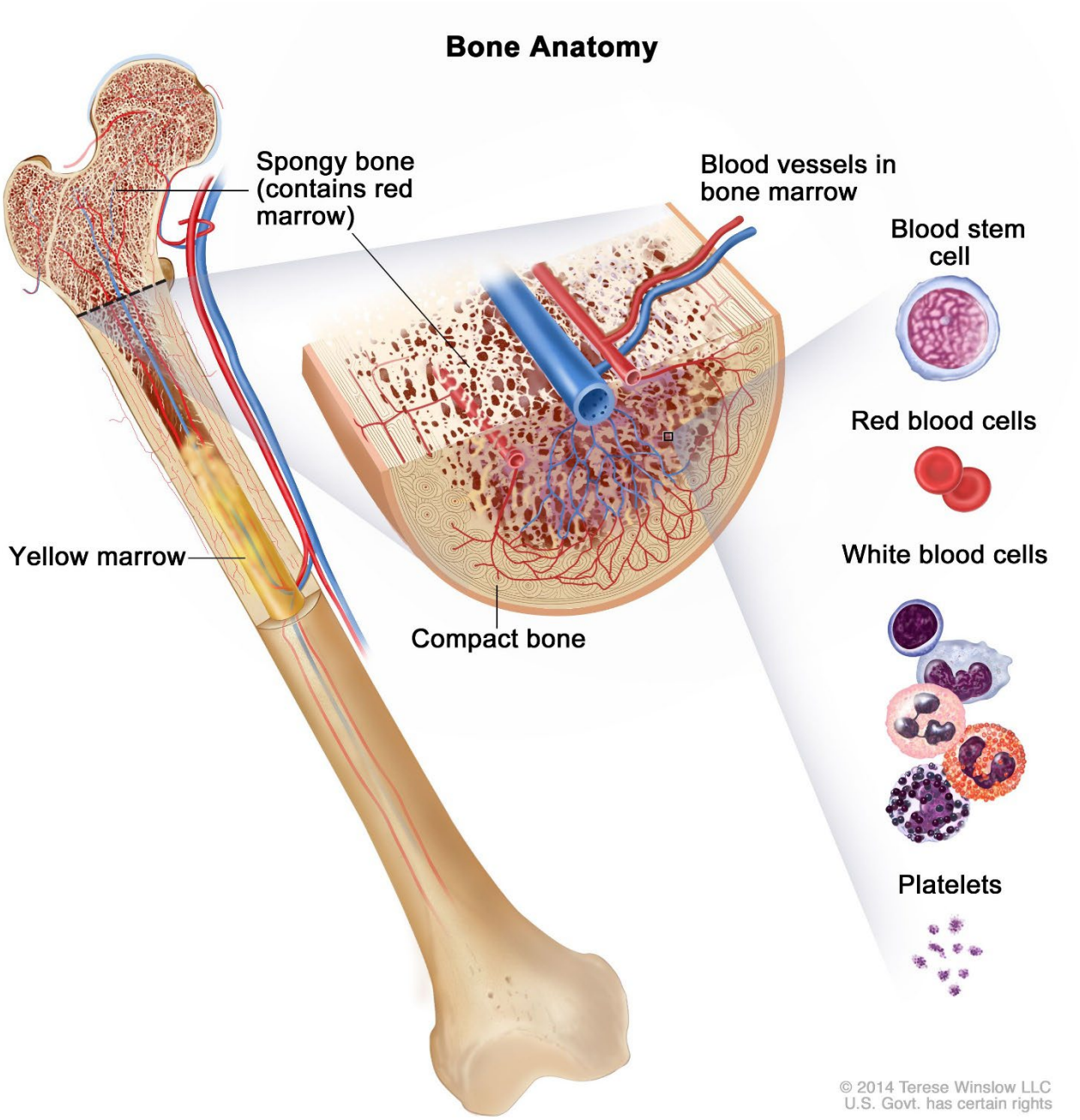
INTRODUCTION

In hematology-oncology trials, treatment response assessment requires reviewers to go over diverse medical data along with radiologic imaging to determine a patient's response to therapy. Disease-specific criteria such as those for Chronic Lymphocytic Leukemia (CLL), Waldenström Macroglobulinemia (WM), and the Lugano classification emphasize different key indicators that must be tracked. Beyond the raw data values, reviewers need interpretable and derived data, these analysis requirements are needed before the ADaM datasets availability. In this paper, we describe our end-to-end approach—from requirements gathering and evaluation of available tools, aligned with our team's programming capabilities, to the development of specifications and processes that operationalize these early response assessment needs.

REQUIREMENTS

The sponsor engages different imaging vendors for Ongoing trials. These imaging vendors can have different requirements for the reports they need from a sponsor to deliver response assessment. Primarily the requirement would be driven by type of response criteria at play. For example, CLL evaluation may focus on complete blood count (CBC) measures like hemoglobin, absolute neutrophil count, absolute lymphocytes count, WBC, derived baseline flag, change from baseline, change from nadir along with bone marrow, lesion examination, procedures, symptoms and adverse events. In contrast, the WM criteria focus on serum IgM, serum immunofixation and cryoglobulinemia over CBC.

Figure 1: Intersection of Bone Marrow, Blood Vessels and Key Hematologic Cells Pertinent to CLL Assessment



Source: https://nci-media.cancer.gov/pdq/media/images/755927.jpg

To collect requirements, it is important the programing team work with statistics, clinical and imaging teams to collect profile requirements from the imaging vendor(s). There will be back-and-forth clarification before the Clinical Data Read Management (CDRM) document can be finalized; this document specifies the response criteria and what needs to be reported for reviewers to evaluate responses. The CDRM will be updated over the course of initial deliverables to better align with the reviewers' requirements.

In our experience these were the broad requirements from programming team planning perspective: -

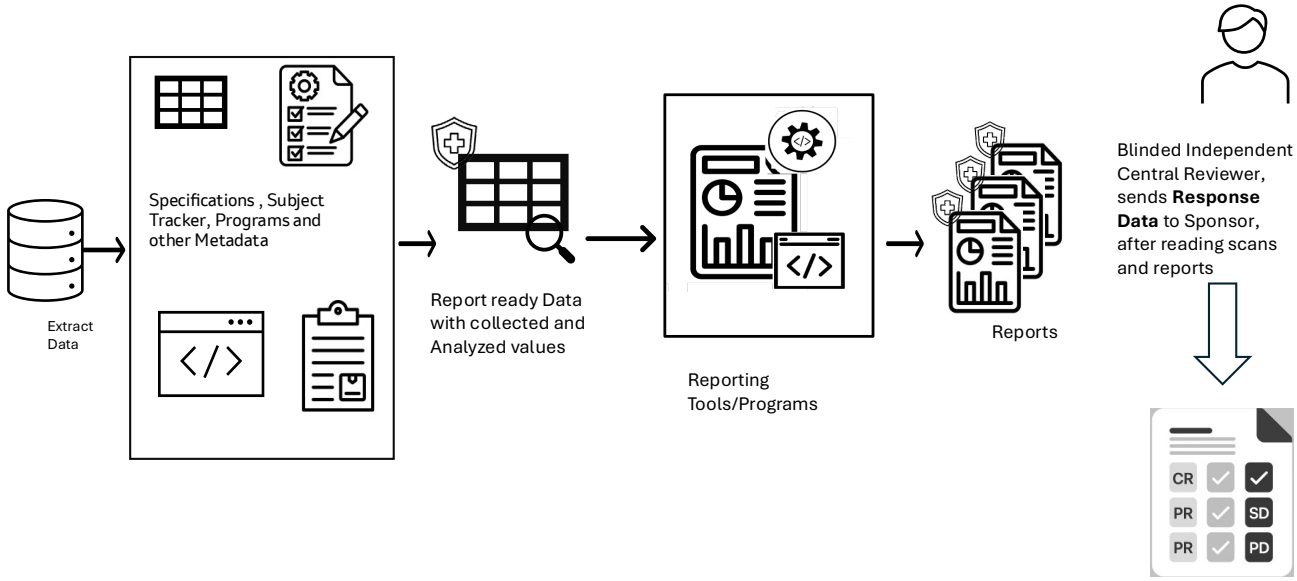
1. Patient profile listings are for a subset of patients and fall under two development types– ones that are specific to a single response criterion (example only WM) and others that are similar for different response criteria (CLL, WM, Lugano) with very minor differences like sub-set of data or some extra columns. The latter can be handled by a common function across different response criteria.
2. Some patient profile listings need to have derived values, for example baseline flags, change from baseline, change from nadir.

3. Radiological assessment windows vary by response criteria. Need to create these windows and assign each reporting record into these window buckets based upon its date.
4. Trace any update to listings already sent to the imaging vendor in subsequent profile listings.
5. Some vendors also prefer a small summary and plots as part of the deliverables.
6. Quick turnaround time between data extraction and delivering validated, internally reviewed profile listings to vendor.

Planning and Decisions on Tools and Processes

Based on requirements, the following overall broad process would be needed: start by extracting data and then feed it into the programs and metadata that produce report-ready data. This data would be input to reporting tools and programs that can output reports to be sent to a reviewer.

Figure 2: Overall process flow

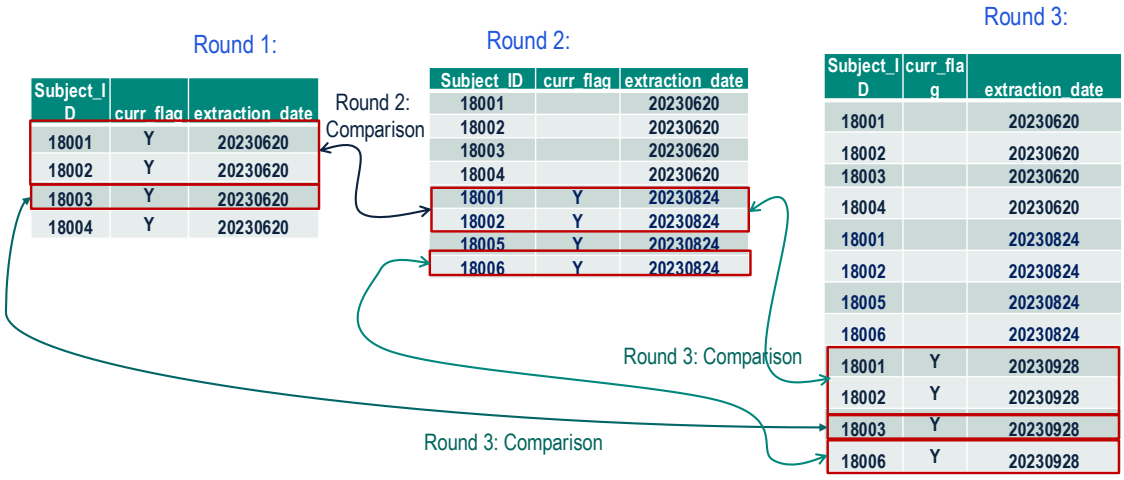


Data Generation- Determination of Tools and Processes

To track changes between deliverables, it is important to have a running log of patients whose profiles are requested. This log, maintained by programmer, lists the subject number and the data extraction dates that were used for their profiles. This list gets updated every round and acts as metadata to direct program to see that data for a subject is compared with correct round of extraction.

Figure 3 explains profile updates tracking, for the requested subjects at each round. For the 4 subjects request in round 3 - three subjects are compared with round 2 and one subject is compared with round 1.

Figure 3: Profile update tracking



Specifications are needed to specify the listing title, unique record identifiers and derivation descriptions for the listing columns. Figure 4 shows the overall metadata, and the column level related metadata is stored in relevant tabs.

Figure 4: Overall metadata and the column level related metadata

Specifications

Data Module	Data Listing Label	Unique Record Identifier	Tab Name
SA	Subject Information	USUBJID	SA
HEM	Hematology Results	USUBJID, SUBJID,LBDTC…	HEM
CM	Transfusion, Growth colony stimulating factors and Vaccines	USUBJID,CMSTDTC,CMDECOD, CMENDTC	CM
BMR	Bone Marrow	USUBJID,BMRDTC, VISIT,BMRMOC	BMR
LSNCL	Lesions by Physical Exam	USUBJID, TRDTC, TRSPID, TRMETHOD, TRCAT, TRLOC	LSNCL
SYM	Constitutional/B-Symptoms	USUBJID,SITENUM,FADTC	OSS
EX	Drug Hold	USUBJID, EXNUMDOS, EXSTDTC, EXENDTC	EX
AE	Adverse Events	USUBJID,AEDECOD,AESTDTC, AEENDTC	AE
MH	Medical History	USUBJID,MHSTDTC,MHTERM	MH
SVISOCLL	Subject Visit Table	USUBJID, SCANDT,SCANY	

Content | SA | HEM | CM | BMR | LSNCL | SYM | EX | BPYAH | AE | SVISOC

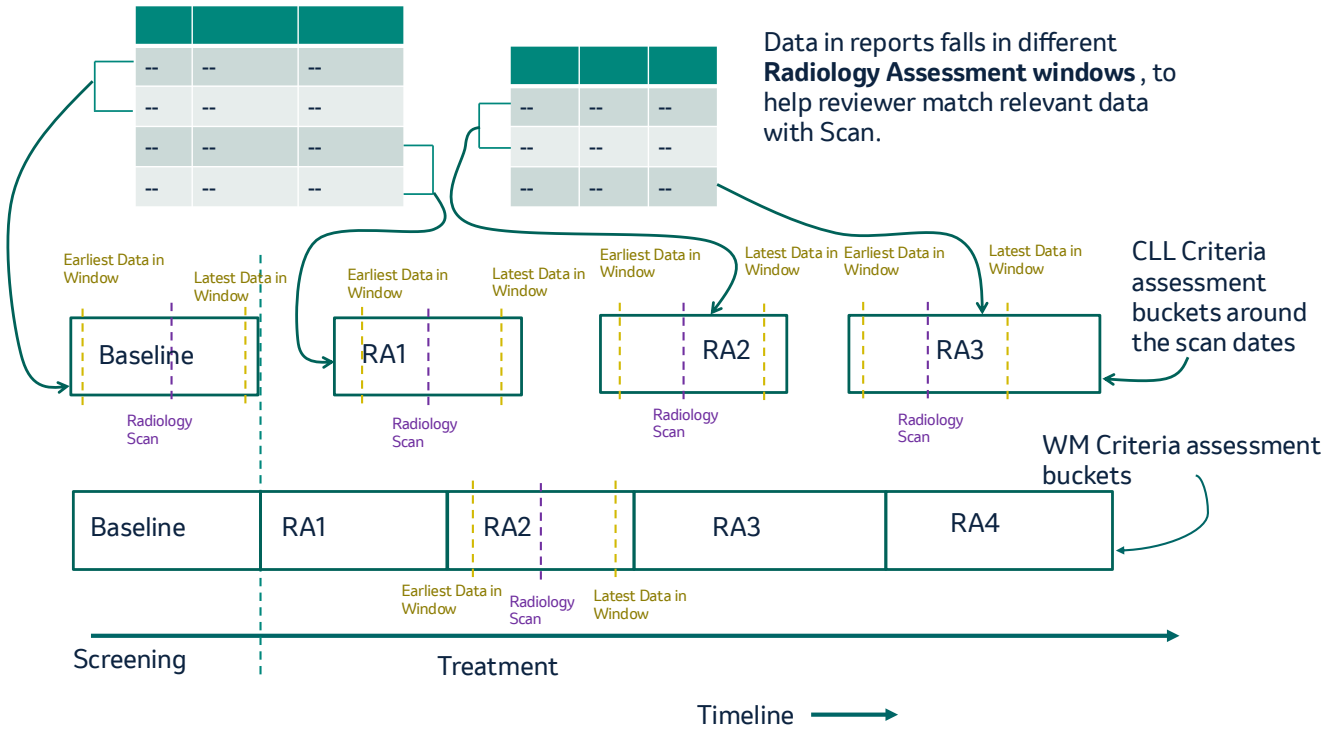
For creation of this data with derived values we need functions that are flexible and are either capable of creating data for multiple listings, based upon different input parameters for listings that are similar or it may be only for a single specific listing

that cannot be generalized.

Figure 5: a program function used to create data for a listing.

Radiological Assessment Windows:
Radiological Assessment Windows vary between response criteria and can also be updated between different study protocols. It is important to get detailed specifications from vendors and clinical. As an example, the CLL window is derived around the scan dates and if gap is small between scans, the later scan is used to establish the windows start and close. In WM, the windows could be predetermined based upon the protocol scan schedule and treatment cycle. Here also there is possibility of more than one scan within the assessment window.

Figure 6: Radiology assessment windows



Change Tracking:
To track changes between different rounds in report ready data, it needs a field to store “NEW” or “UPDATED” values at the record level to track if record is new or got updated as well as a field to track names of columns which got updated, if any.

Figure 7: Record level data fields used to keep track of updates in each round.

MOFL	VARLIST
UPDATED	HAVAL HCHG HPCHG

To highlight updated cells in the listing, a call define within compute block is used to change background to orange

```
compute varlist;/*going through the varlist to highlight the variable fields that
are updated from the previous ver.*/
/*y is initially set to 1*/
   %do %while(&y le %sysfunc(countw(&vars.)) );
/*token is set initially to the variable name of first column to be displayed */
      if index(varlist,"&token.") gt 0 then
         do;
            %let y = %eval(&y + 1);
            call define("_c&y._" ,"style" ,"style={background=orange}");
         end;
      %let token = %scan( &vars ,&y. );
   %end;
endcomp;
```

Tools Considered for Generating the Data:
We considered both R and SAS programming languages for this step and observed all the requirements can be met by both. Due to existing macros in SAS to read specifications, key variables and expertise with SAS, we preferred to use SAS for this step.

Report Generation- Determination of Tools and Processes

These were the generic requirements for the reports from a programming perspective:

1. Ensure listing are easy to read and prevent overflow of columns for wide listing, if possible, over to next page, to help with review.
2. Flag new records and highlight any values that have been updated since the last patient profile listing deliverable.
3. Add an optional patient summary and simple graph within report for visual tracking, as requested by some vendors.
4. One pdf per patient with:
    a. Bookmarks for easy navigation
    b. The current extraction date
    c. The prior extraction date which the subject profile data is compared to, clearly indicated.

We tried both SAS and R. Figure 8 and figure 9 are screen shots from pdf profiles generated using SAS ODS, show tracked changes for a subject, compared with last round. Profiles show Current and Previous extraction dates. Figure 9 shows data compared to the extraction used Figure 8 and by using information stored in MOFL and VARLIST the records are flagged and highlighted as NEW or UPDATED.

Figure 8: SAS ODS PDF

MK9999-099_CLL_100001

Current Extraction Date :30APR2025
Previous Extraction Date :26DEC2024

Hematology Results

Planned Time Point Name	Start Date/Time of lab test	HGB Baseline Flag	HGB Analysis Value	HGB absolute CFB	HGB Percentage CFB	PLAT Baseline Flag	PLAT Analysis Value	PLAT Percentage CFB	ANC Analysis Value	ALC Baseline Flag	ALC Analysis Value	ALC Percentage CFB	ALC Percentage CFN	Modification Flag
	2024-12-14T09:15								1.92					
	2024-12-25T09:58								1.62					
	2025-01-09T10:03								1.16					NEW
	2025-01-17T09:07								0.5					NEW
	2025-01-20T08:09								1.21					NEW
SCHEDULED	2025-01-23		13	4.7	56.6 %		129	51.8 %	1.26		2.68	-65.2 %		NEW
	2025-02-27T14:46								0.12					NEW
	2025-03-02T09:07								0.66					NEW
	2025-03-09T09:16								1.63					NEW
	2025-03-23T16:55								0.48					NEW
	2025-04-05T08:55								0.77					NEW
UNSCHEDULED	2025-04-11		12	3.7	44.6 %		151	77.6 %	0.36		4.02	-47.8 %	50.0 %	NEW
UNSCHEDULED	2025-04-14		12.1	3.8	45.8 %		149	75.3 %	0.68		2.84	-63.1 %	6.0 %	NEW
UNSCHEDULED	2025-04-17						156	83.5 %	0.46		2.87	-62.7 %	7.1 %	NEW
	2025-04-17T10:05								0.46					NEW

Figure 9: SAS ODS PDF

MOFL	VARLIST
UPDATED	HAVAL HCHG HPCHG

MK9999-099_CLL_100001

Current Extraction Date :03DEC2025
Previous Extraction Date :30APR2025

Hematology Results

Planned Time Point Name	Start Date/Time of lab test	HGB Baseline Flag	HGB Analysis Value	HGB absolute CFB	HGB Percentage CFB	PLAT Baseline Flag	PLAT Analysis Value	PLAT Percentage CFB	ANC Analysis Value	ALC Baseline Flag	ALC Analysis Value	ALC Percentage CFB	ALC Percentage CFN	Modification Flag
	2024-12-14T09:15								1.92					
	2024-12-25T09:58								1.62					
	2025-01-09T10:03								1.16					
	2025-01-17T09:07								0.5					
	2025-01-20T08:09								1.21					
SCHEDULED	2025-01-23		13	4.7	56.6 %		129	51.8 %	1.26		2.68	-65.2 %		
	2025-02-27T14:46								0.12					
	2025-03-02T09:07								0.66					
	2025-03-09T09:16								1.63					
	2025-03-23T16:55								0.48					
	2025-04-05T08:55								0.77					
UNSCHEDULED	2025-04-11		12	3.7	44.6 %		151	77.6 %	0.36		4.02	-47.8 %	50.0 %	
UNSCHEDULED	2025-04-14		12.1	3.8	45.8 %		149	75.3 %	0.68		2.84	-63.1 %	6.0 %	
UNSCHEDULED	2025-04-17		12.8	4.5	54.2 %		156	83.5 %	0.46		2.87	-62.7 %	7.1 %	UPDATED
	2025-04-17T10:05								0.46					
	2025-04-19T16:41		11.6	3.3	39.8 %				0.21					
	2025-04-21T09:10		11.3	3	36.1 %				0.12					
	2025-04-23T09:03		10.7	2.4	28.9 %				0.08					
	2025-04-26T09:02		10.8	2.5	30.1 %				0.7					
	2025-04-29T09:11		10.5	2.2	26.5 %				2.73					
SCHEDULED	2025-05-08		11.7	3.4	41.0 %		163	91.8 %	4.24		2.33	-69.7 %		NEW
	2025-05-16T09:12								2.98					NEW

For R we used Quarto markdown. It needs a profile template file(.qmd), with header.tex file and R code to programmatically render the markdown profile template, once for each subject.

- **YAML header** is important to set things like pdf output, its layout and define parameters. Also, it points to header.tex.
- **header.tex** can take input information in form of R character vector, and it can be used to set titles and headers dynamically, control spaces between columns and more.
- **profile .qmd** file is used to generate actual results. KableExtra:: kable_styling () provided options to get a workable format.

Figure 10: YAML header

```yaml
---
title: "Patient Profile"
format:
  pdf:
    geometry: margin=.1in,landscape
    toc: false           # Table of contents page (optional)
    number-sections: false
    pdf-engine: xelatex # or pdflatex; xelatex handles fonts better
    include-in-header: header.tex # set headers and title for pages
    keep-tex: true
params:
  subject_id:

execute:
  echo: false
  warning: false
  message: false
---
```

Figure 11: Header.tex

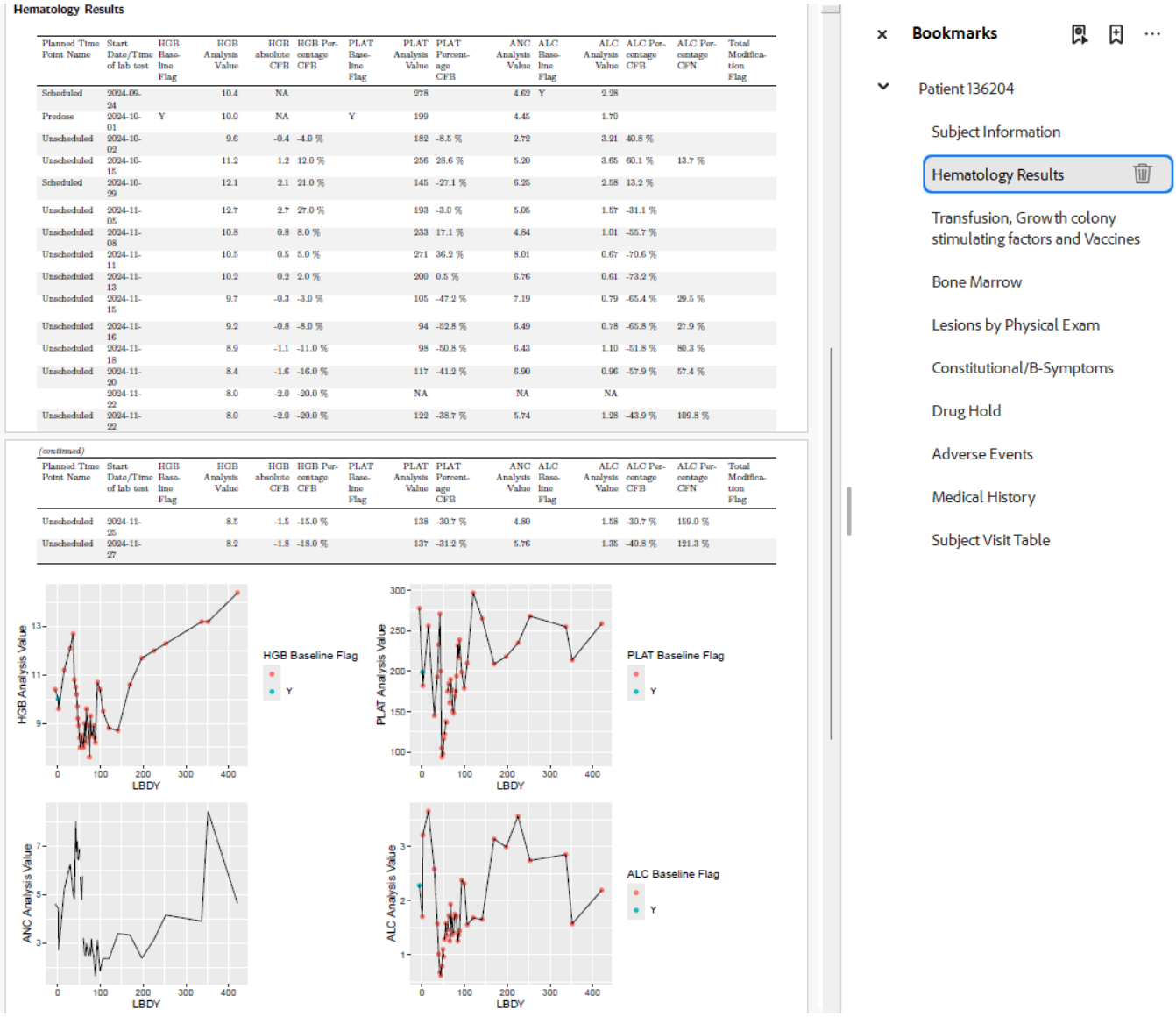
```latex
\setlength{\tabcolsep}{4pt}
% Use fancy headers/footers
\usepackage{fancyhdr}
\pagestyle{fancy}
\fancyhf{} % clear defaults
% Increase header height to avoid overlap
\setlength{\headheight}{24pt}
\setlength{\headsep}{12pt}
% Center-aligned multi-line header
% Use \shortstack to stack lines centered; adjust text as needed
\fancyhead[C]{
  \shortstack{
    \textbf{$studySubjid}
  }
}
% Left-aligned header line (e.g., subject or project)
\fancyhead[L]{
  \shortstack{
    Current Extraction Date :$CurrentDt\\
    Previous Extraction Date :$PreviousDt
  }
}
```

Figure 12: Profile.qmd

```
 heme_label %>%
    kable(format = "latex", longtable = TRUE, booktabs = TRUE) %>%
    kable_styling(latex_options = c("hold_position", "striped","repeat_header"),
font_size = 9)

p1<- ggplot(heme, aes(x = LBDY, y= HAVAL)) +geom_point(aes(colour = HABLFL))+
  geom_line()

p2<- ggplot(heme, aes(x = LBDY, y= PAVAL)) +geom_point(aes(colour = PABLFL))+
  geom_line()
p3<- ggplot(heme, aes(x = LBDY, y= NAVAL)) +  geom_line()
p4<- ggplot(heme, aes(x = LBDY, y= AAVAL)) +geom_point(aes(colour = AABLFL))+
  geom_line()

plot_grid(p1, p2, p3, p4, nrow = 2, ncol = 2, align = "hv", rel_widths = c(1,1),
rel_heights = c(1,1))
```

We think SAS is a good option for simple listings profiles, it requires minimum setup (PROC REPORT+ODS) and provides good control over column width. R is a good option to insert the figures and patient summary texts in reports. Programmers may find it easy to create and insert figures in a grid form with minimal code using R. We felt creating bookmark tree was straight forward in Quarto markdown. One may use R reporting, if vendor likes to see some figures and dynamic patient summary in their report.

Figure 13: Sample screen shot of a subject pdf using R showing insertion of graphs.



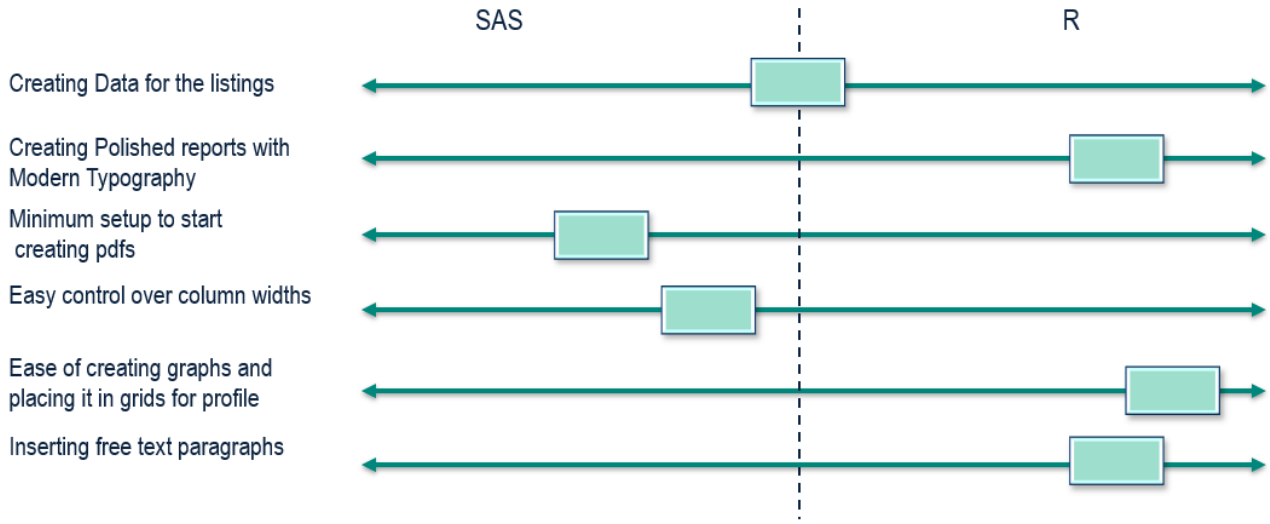
Hematology Results

Planned Time Point Name	Start Date/Time of lab test	HGB Baseline Flag	HGB Analysis Value	HGB absolute CFB	HGB Percentage CFB	PLAT Baseline Flag	PLAT Analysis Value	PLAT Percentage CFB	ANC Analysis Value	ALC Baseline Flag	ALC Analysis Value	ALC Percentage CFB	ALC Percentage CFN	Total Modification Flag
Scheduled	2024-09-24		10.4	NA			278		4.62	Y	2.28			
Predose	2024-10-01	Y	10.0	NA		Y	199		4.45		1.70			
Unscheduled	2024-10-02		9.6	-0.4	-4.0 %		182	-8.5 %	2.72		3.21	40.8 %		
Unscheduled	2024-10-15		11.2	1.2	12.0 %		256	28.6 %	5.20		3.65	60.1 %	13.7 %	
Scheduled	2024-10-29		12.1	2.1	21.0 %		145	-27.1 %	6.25		2.58	13.2 %		
Unscheduled	2024-11-05		12.7	2.7	27.0 %		193	-3.0 %	5.05		1.57	-31.1 %		
Unscheduled	2024-11-08		10.8	0.8	8.0 %		233	17.1 %	4.84		1.01	-55.7 %		
Unscheduled	2024-11-11		10.5	0.5	5.0 %		271	36.2 %	8.01		0.67	-70.6 %		
Unscheduled	2024-11-13		10.2	0.2	2.0 %		200	0.5 %	6.76		0.61	-73.2 %		
Unscheduled	2024-11-15		9.7	-0.3	-3.0 %		105	-47.2 %	7.19		0.79	-65.4 %	29.5 %	
Unscheduled	2024-11-16		9.2	-0.8	-8.0 %		94	-52.8 %	6.49		0.78	-65.8 %	27.9 %	
Unscheduled	2024-11-18		8.9	-1.1	-11.0 %		98	-50.8 %	6.43		1.10	-51.8 %	80.3 %	
Unscheduled	2024-11-20		8.4	-1.6	-16.0 %		117	-41.2 %	6.90		0.96	-57.9 %	57.4 %	
	2024-11-22		8.0	-2.0	-20.0 %		NA		NA		NA			
Unscheduled	2024-11-22		8.0	-2.0	-20.0 %		122	-38.7 %	5.74		1.28	-43.9 %	109.8 %	

(continued)

Planned Time Point Name	Start Date/Time of lab test	HGB Baseline Flag	HGB Analysis Value	HGB absolute CFB	HGB Percentage CFB	PLAT Baseline Flag	PLAT Analysis Value	PLAT Percentage CFB	ANC Analysis Value	ALC Baseline Flag	ALC Analysis Value	ALC Percentage CFB	ALC Percentage CFN	Total Modification Flag
Unscheduled	2024-11-25		8.5	-1.5	-15.0 %		138	-30.7 %	4.80		1.58	-30.7 %	159.0 %	
Unscheduled	2024-11-27		8.2	-1.8	-18.0 %		137	-31.2 %	5.76		1.35	-40.8 %	121.3 %	

Figure 14: This summarizes our relative preference on a sliding scale for executing tasks in SAS vs. R.



CONCLUSION

The planning approach and tool choices we implemented proved effective for our context, enabling clear traceable analysis, consistent and efficient profile generation across the SAS and R workflows we evaluated. The preference scale above summarizing relative strengths of SAS and R for specific tasks may also help teams quickly gauge which environment better fits their needs. That said, there is no single best method for all teams. Optimal decisions should be driven by each team's specific circumstances, including programming expertise, vendor requirements, tooling ecosystem (e.g., organization-specific packages), and available SME support. We offer this experience as a practical starting point, with the expectation that readers will adapt methods and tools to fit their own project needs and constraints.

DISCLAIMER

All interpretations and conclusions are solely those of the author(s) and do not represent the official position of Merck.

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