Shinytized R Markdown:

A Potent OTC Alternative to 1,3,7–Trimethylxanthine Currently Indicated for NDA Document Generation, Among Others

Mark Rothe

22-August-2019

(Updated: 22-August-2019)

What is **1,3,7–trimethylxanthine**???

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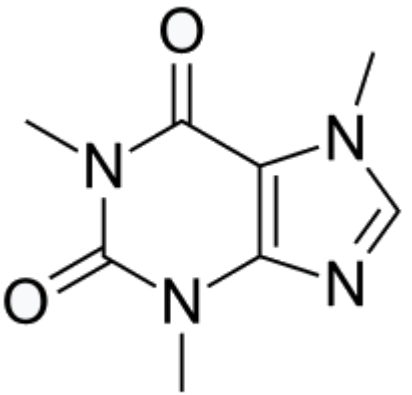
Caffeine*



Caffeine's chemical structure†

[*] Pharmacological Reviews April 1, 2018, 70 (2) 384-411; DOI: https://doi.org/10.1124/pr.117.014407

[†] Arnaud, Maurice. (1993). Metabolism of caffeine and other components of coffee. Caffeine, Coffee and Health. 43-95.

What is **NDA** (**N**ew **D**rug **A**pplication) **document generation**?

What is **NDA** (**N**ew **D**rug **A**pplication) **document generation**?

Documents sent to the FDA for NDA submissions.

"Chemist Lee Geismer looking over an NDA in the 1960s."[*]

[*] https://www.fda.gov/about-fda/histories-product-regulation/summary-nda-approvals-receipts-1938-present

- "Chemist Lee Geismar, who spent 49 years with the FDA, was part of a team that blocked the U.S. marketing of the drug thalidomide."
  —Lisa Fine, *Washington Post*, 23-January-1997*

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- *Goal* ⇒ Minimize these efforts for drug sponsors.

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- *Focus* ⇒ **csdrg.pdf** ≡ **C**linical **S**tudy **D**ata **R**eviewer's **G**uide; "describe(s) any **special considerations** *or* **directions** *or* **conformance issues** that may facilitate an FDA reviewer's use of the submitted data and may help the reviewer understand the relationships between the study report and the data."†

[*] https://www.washingtonpost.com/archive/local/1997/01/23/caretaker-of-the-curatives/bffff9d9-5b20-4c45-9ad4-65abced9ea96/?noredirect=on

[†] Study Data Technical Conformance Guide (March 2018) https://www.fda.gov/media/88173/download

Origin of NDAs:

1938 US Food, Drug, and Cosmetic Act*:

- Required drug sponsors to submit NDAs for the first time.
- Enacted as a result of the **Elixir Sulfanilamide** recall.
- "Elixir" implies alcohol.
- FDA only had recall powers due to **misbranding**: contained poisonous diethylene glycol and not alcohol.
- >100 people died.

[*] https://www.fda.gov/media/110437/download

Purpose of NDAs:

Sponsors provide sufficient information so that the FDA can determine **if**[*]:

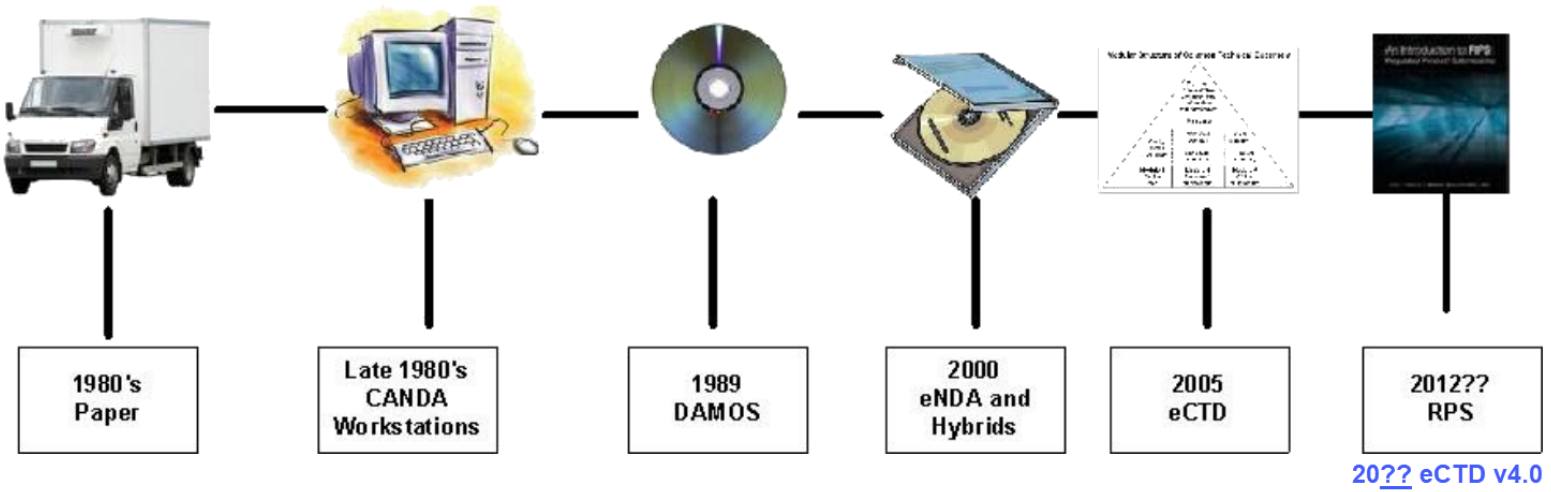
- **℞** is safe & effective.
- Benefits > Risks
- Labeling (package insert) ✓
- **℞**'s manufacturing & quality ✓

[*] https://www.fda.gov/drugs/types-applications/new-drug-application-nda

"Document change control meeting in 5 minutes!" *

Is paper still used for NDAs?

[*] https://www.bebee.com/producer/@mohammed-a-jawad/let-s-go-digital-with-less-paper



The evolution from paper to eCTD.*,†

[*] https://www.academia.edu/22614960/_THE_HISTORY_OF_ELECTRONIC_REGULATORY_SUBMISSIONS_TECHNOLOGIES_A_FOCUS_ON_ECTD_ELECTRONIC_COMMON_TECHNICAL_DOCUMENT_AND_ITS_CHALLENGES_AND_BENEFITS_

[†] http://theectdsummit.com/dissecting-ectd-v4-0/

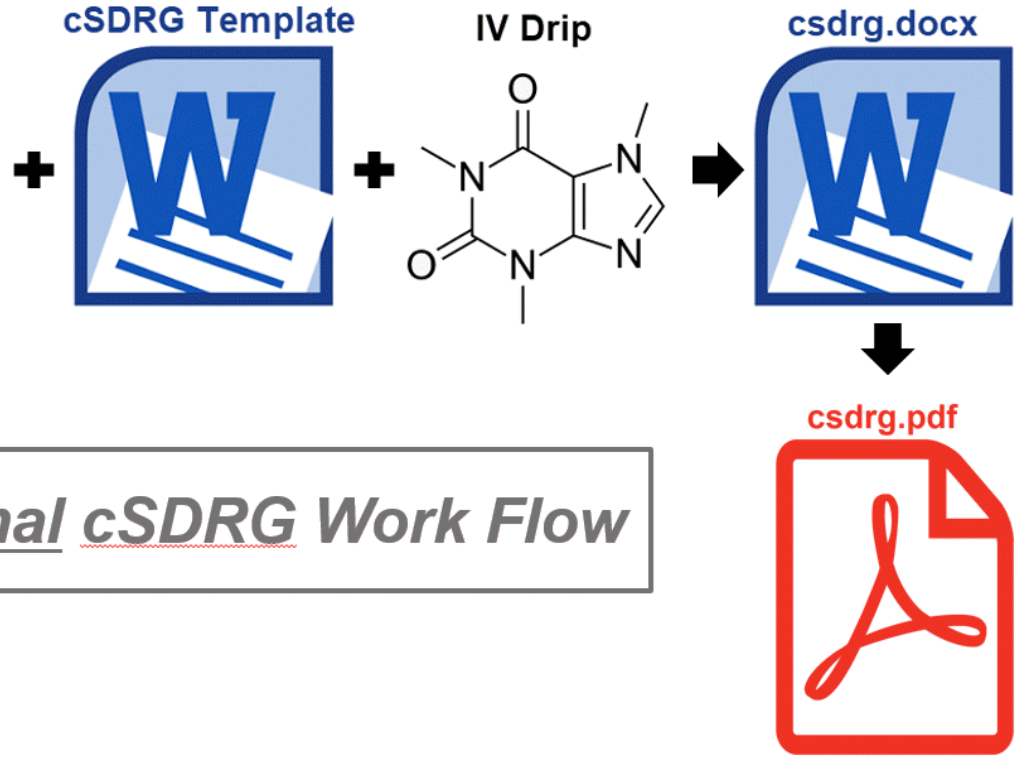
eCTD = **E**lectronic **C**ommon **T**echnical **D**ocument[*,†]

- **5** Modules
- **Module 5: Clinical ⇒ m5**
  - ► **datasets**
    - ► **Study XYZ**
      - ► **tabulations**
        - ► **sdtm**
          - ► **csdrg.pdf**

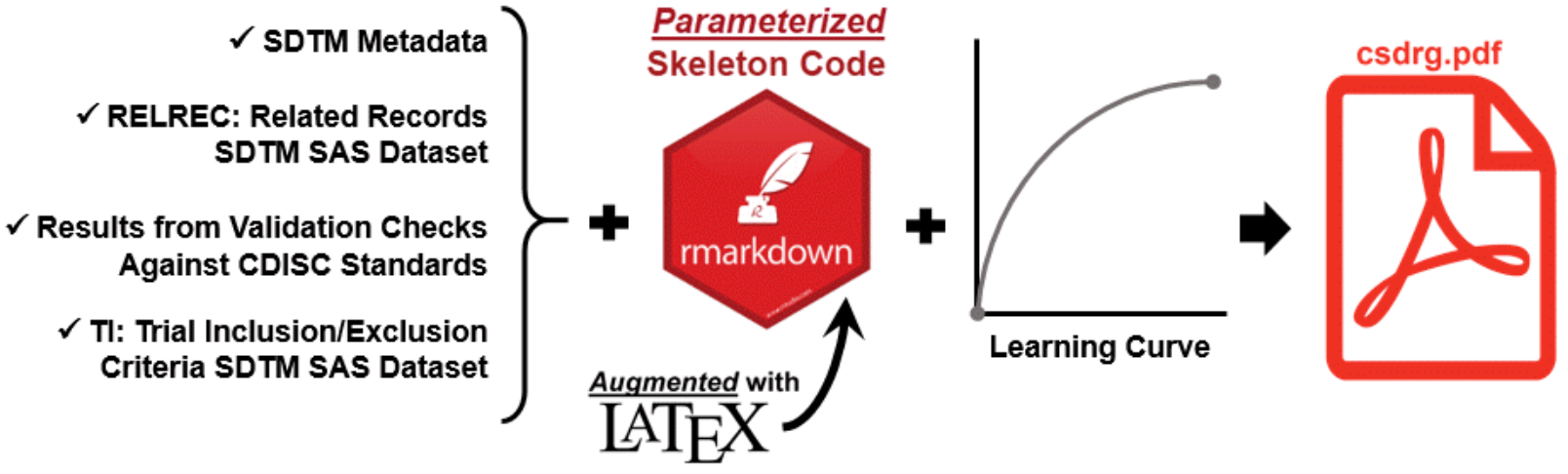
[*] eCTD Technical Conformance Guide (November 2018) https://www.fda.gov/media/93818/download
[†] Study Data Technical Conformance Guide (March 2018) https://www.fda.gov/media/88173/download

- **SDTM** Metadata ≡ **S**tudy **D**ata **T**abulation **M**odel Metadata ⇒ data about how to structure "raw" clinical trial data
- **RELREC** ≡ **REL**ated **REC**ords ⇒ SDTM SAS dataset that contains information linking data across different domains
- **CDISC** ≡ **C**linical **D**ata **I**nterchange **S**tandards **C**onsortium ⇒ neutral, non-profit data standards development organization; manages standards such as SDTM
- **TI** ≡ **T**rial **I**nclusion / Exclusion Criteria ⇒ SDTM SAS dataset containing trial inclusion / exclusion criteria

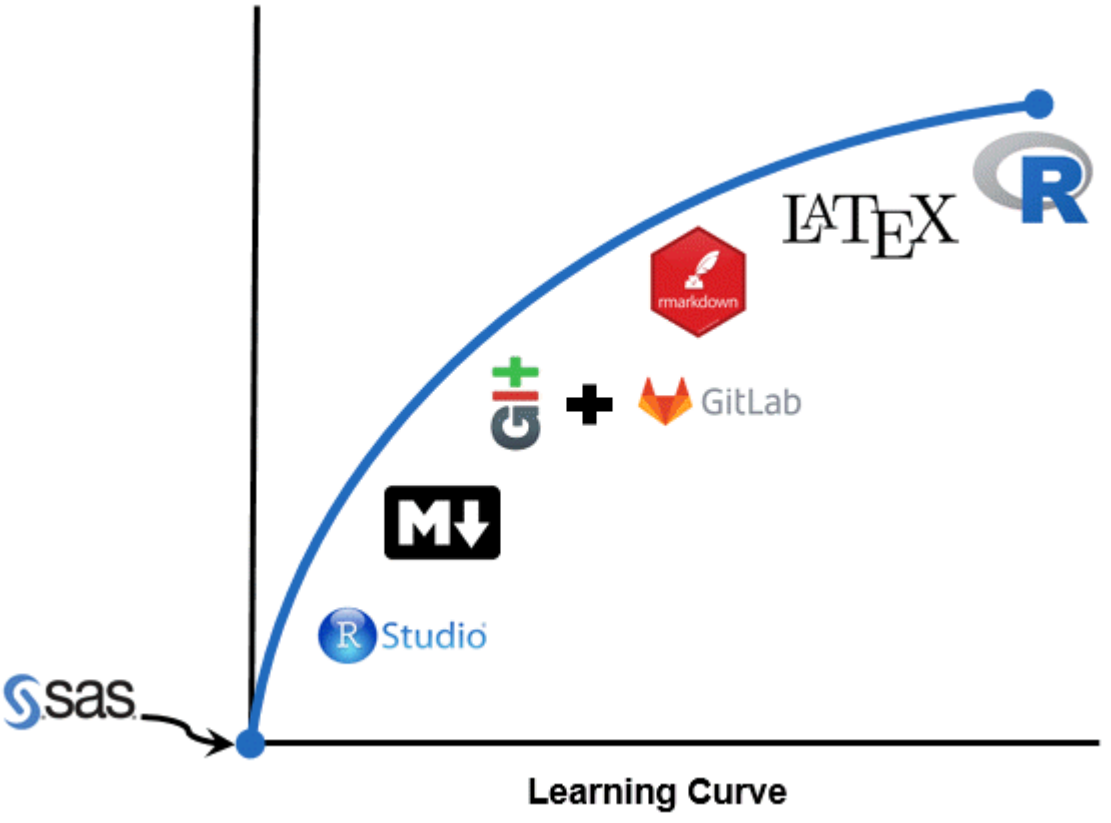
- ✓ SDTM Metadata
- ✓ RELREC: Related Records SDTM SAS Dataset
- ✓ Results from Validation Checks Against CDISC Standards
- ✓ TI: Trial Inclusion/Exclusion Criteria SDTM SAS Dataset



Original cSDRG Work Flow



Initial Idea for cSDRG Work Flow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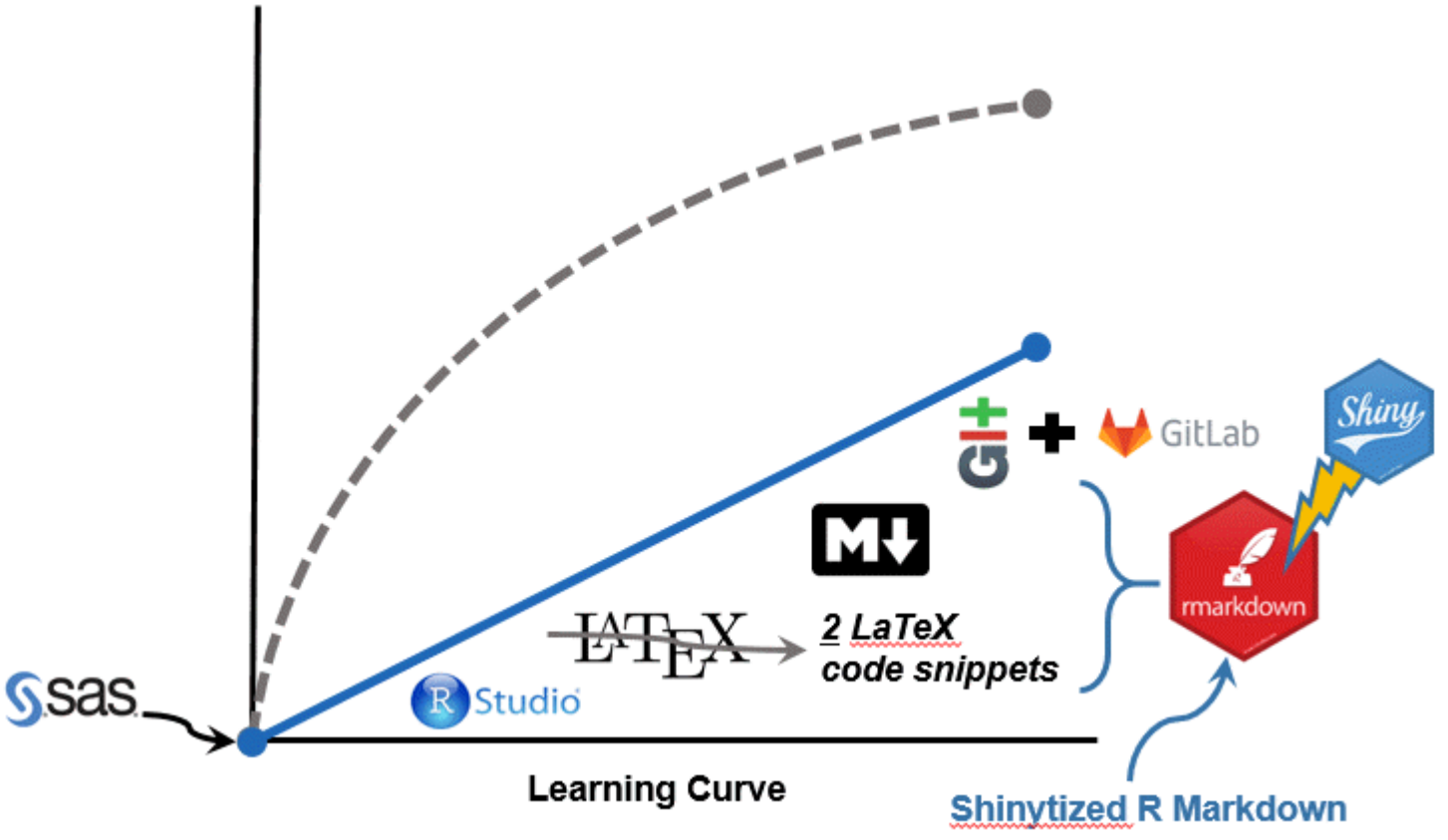
GitLab
RStudio
sas
Learning Curve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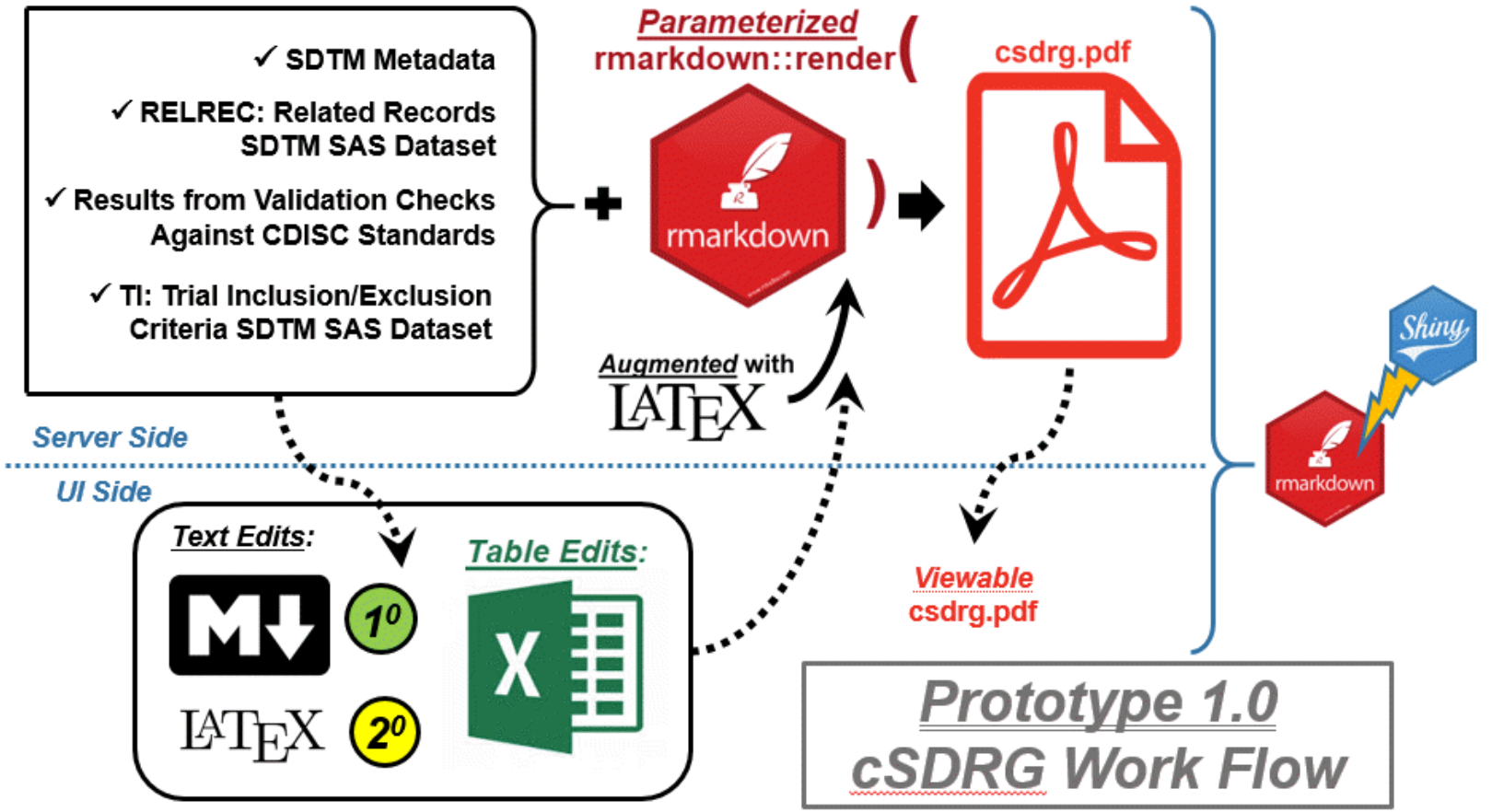
Studio
LaTeX
2 LaTeX
code snippets
GitLab
Shiny
rmarkdown
Learning Curve
Shinytized R Markdown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Server Side
UI Side
Text Edits:
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LaTeX
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Table Edits:
Viewable
csdrg.pdf
Shiny
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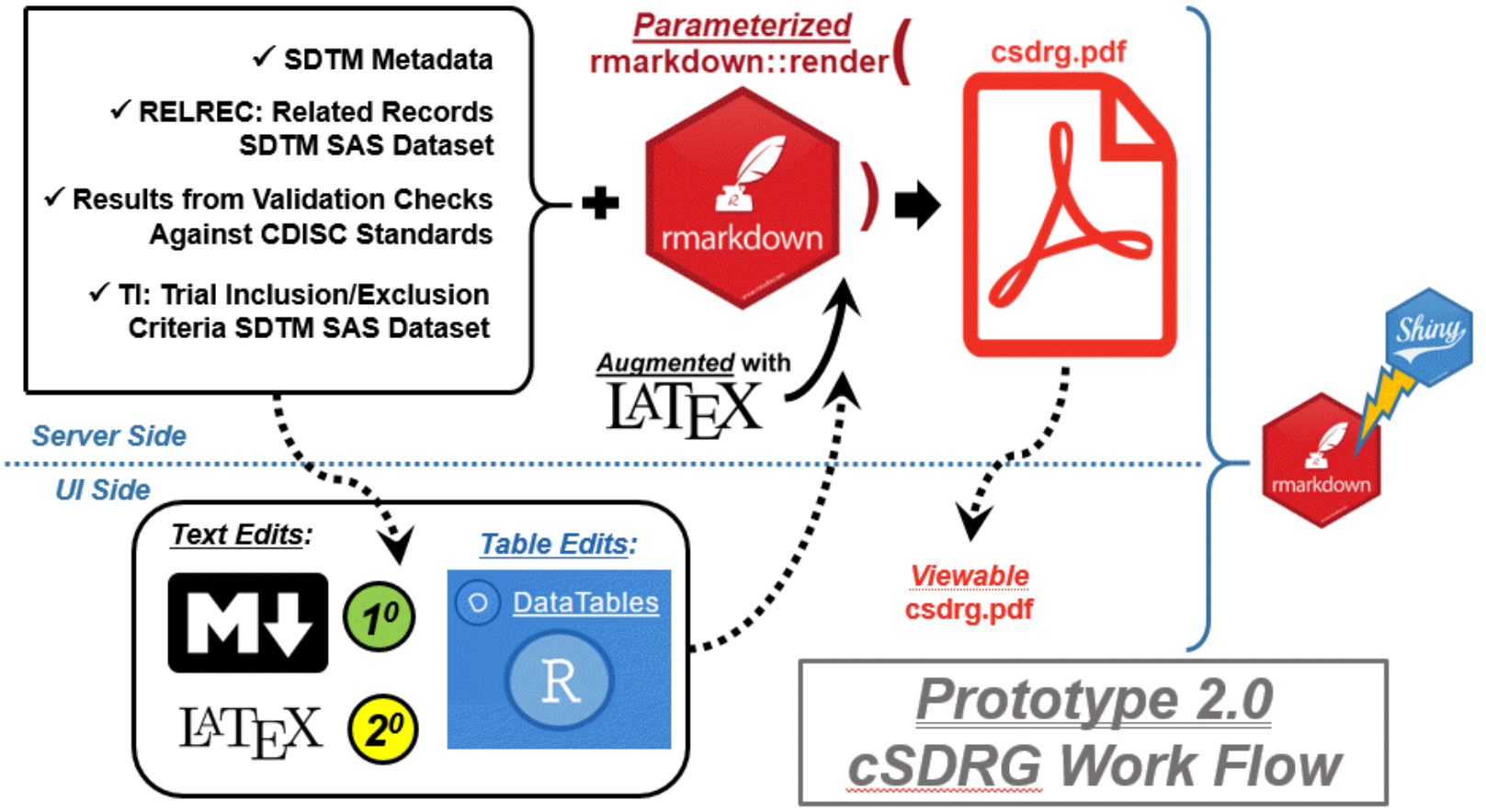
Prototype 1.0
cSDRG Work Flow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Text Edits:
1⁰
LaTeX
2⁰
Table Edits:
DataTables
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Viewable
csdrg.pdf
rmarkdown
Shiny
Prototype 2.0
cSDRG Work Flow

Closer look at the UI Side.

Refresh the text in ALL cSDRG sections! | Section 2 | Section 3 | Section 4 | Section 5 | Section 6 | Save! | Resize

Section 3.1.2 — Death Information:

Recommendation: You can explain the mapping of death information in a specific section.

The death appears:

```
* in DM where DTHFL=Y
* in AE where AEOUT=FATAL
* in DD 'Death Details' and in DS (oncology studies)
```

Markdown Initial Boilerplate

Allow LaTeX to determine page breaks.
OR
Use "\newline".

Section 3.1.3 — Adjudication Data:

Recommendation: You can document the location of adjudication data and the method used to differentiate these data from data collected at the investigational site.

Instruction: Insert graphic or text here.

→ cSDRG App Instruction: Save any relevant graphic as a 'PNG' file in <*RStudi*

```
_Please begin entering the relevant text here._

\begin{figure}[h]

\caption{Adjudication Data}
\centering
\includegraphics{Adjudication_Data.PNG}

\end{figure}

_Please continue entering the relevant text here._
```

Markdown Initial Boilerplate

LaTeX code snippet for figure insertion.

- Key efficacy:

QS, ML, ...

Section 3.1.1 — Location of Key Data:

- Key other:

DM, EX, DS, ...

Real Time Results

Section 3.1.2 — Death Information:

The death appears:

- in DM where DTHFL=Y
- in AE where AEOUT=FATAL
- in DD 'Death Details' and in DS (oncology studies)

Section 3.1.3 — Adjudication Data:

Please begin entering the relevant text here.

```
\begin{figure}[h]

\caption{Adjudication Data}
\centering
\includegraphics{Adjudication_Data.PNG}

\end{figure}
```

Please continue entering the relevant text here.

Section 3.1.4 — Custom/TAUG Domains:

Please enter the relevant text here.

[redacted]

[redacted]

3.1.2 Death Information

The death appears:

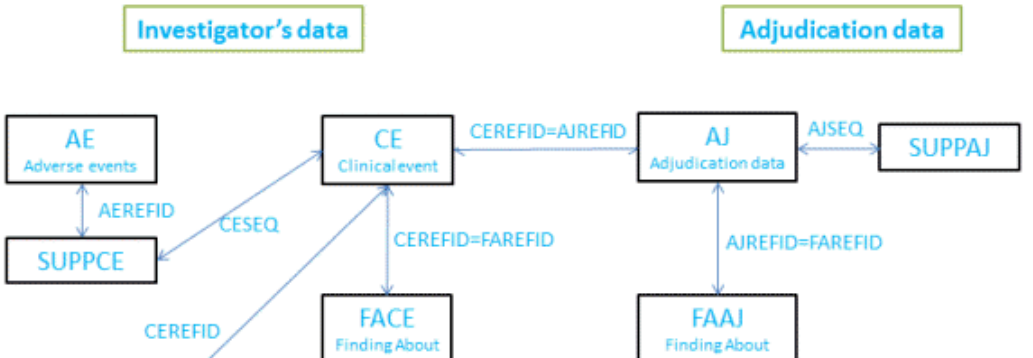
UI Viewable csdrg.pdf

- in DM where DTHFL=Y
- in AE where AEOUT=FATAL
- in DD 'Death Details' and in DS (oncology studies)

3.1.3 Adjudication Data

Please begin entering the relevant text here.

Figure 3.1: Adjudication Data



Instructions | Controls | cSDRG PDF

UI Viewable csdrg.pdf

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Auto-generated TOC hyperlinks are a function of the available Trial Design Datasets.

Instructions | Controls | cSDRG PDF

[redacted]

Please continue entering the relevant text here.

2.3 Trial Design Datasets

- Are Trial Design datasets included in the submission? ***Yes***

Auto-generated internal hyperlinks are a function of the available Trial Design Datasets.

[redacted]

Dataset	Dataset Label
TA	Trial Arms
TE	Trial Elements
TI	Trial Inclusion/Exclusion Criteria
TS	Trial Summary
TV	Trial Visits

2.3.1 TA—Trial Arms

Please enter the relevant TA text here.

Summary:

- *Goal* ⇒ Minimize the resource intensive **EXTRA** efforts expended by drug sponsors on **mundane & repetitive** NDA submission tasks.
- 1 solution ≡ Shinytized R Markdown for generating the Clinical Study Data Reviewer's Guide (csdrg.pdf)
- *Desired* benefit ≡ Ease transition from SAS to R Markdown and R.
- Next steps:
  - Iterate through prototypes onto R package development.
  - Apply to other FDA deliverables (e.g. the **A**nalysis **S**tudy **D**ata **R**eviewer's **G**uide (adrg.pdf)[*]).

[*] High Quality Study Data Standards for Submission (PhUSE 2019) https://www.lexjansen.com/phuse-us/2019/sa/SA03.pdf