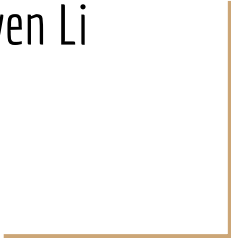


A thin, light brown L-shaped line that starts with a horizontal segment and then turns 90 degrees downward.

# Regulatory Report Automation with R

Shimeng Huang & Suwen Li  
Roche Canada

A thin, light brown L-shaped line that starts with a vertical segment and then turns 90 degrees to the left.

# Background

- Get our medicines to patients faster
  - Optimize the Dossier
    - Automate the Clinical Study Report (CSR)
    - Enable content reuse
- The rise of the R language
  - Experiments with R on report automation



*faster*  
**FILING**



# Background

## 8.3 ANALYSIS OF ADVERSE EVENTS

This section should provide an overview of the types of adverse events and the number and percentage of patients with adverse events, using preferred terms grouped by MedDRA system organ class (SOC). For large studies, with a large number of AEs, the section should include the following, with subsections as appropriate:

- Most Frequent AEs (e.g., cutoff of  $\geq 5\%$  incidence, depending on the data)
- AEs with X% difference between treatment arm and control arm (optional)
- AEs by MedDRA SOC
- AEs by causality (if appropriate)

Differences in laboratory result abnormalities reported as AEs (e.g., hematological AEs) should be mentioned but cross-refer to the laboratory results sections for further information.

An individual patient listing of all AEs and a glossary of investigator terms and preferred terms for AEs reported in the study should be placed in the Primary Data Listings.

Lengthy tables should be placed in the Supporting Data Presentations. Shorter summary tables of the most frequent events (e.g., based on incidence cutoffs) are helpful in the text.

### Most Frequent AEs

Mention most frequent AEs and most frequently affected SOC; if the full summary is long, use a percentage cutoff, (e.g., cutoff of  $\geq 2\%$  or  $5\%$  incidence, depending on the data) for the text and place full table in appendix. Highlight differences between treatment groups or by dose.

Highlight any AEs considered important for the trial drug, including events for antiplatelet drugs or infusion-related reactions for monoclonal antibodies, and to AEs/Selected AEs for more detailed analysis.

Mention AEs that are expected

### Treatment Group Differences

In parallel-group studies, focus on a comparison of AE incidence between treatment groups, including differences, or trends across doses in a dose-ranging study. In general, neither statistical tests of hypotheses nor estimates of treatment effects are performed on AE data for individual trials, since the studies are powered for efficacy and not for detecting differences in safety data between treatment groups. However, it may be helpful to define a cutoff to examine the data for differences, in a descriptive way, and to ensure a systematic approach. Judgment must then be applied in interpreting the potential relevance of any such differences,

## 8.3 ANALYSIS OF ADVERSE EVENTS

### C.2.6.2.4 - Message

In clinical summary documents, start each results section with a high-level statement summarizing the takeaway message based on the clinical interpretation of results. These statements should be written in a way that facilitates reuse to the clinical overview and label. In the CSR, this can be used to write a concluding statement, if applicable.

### C.2.6.2.4 - Findings

Required: Incidence of AEs

The incidence of AEs of any grade in <ArmA> was [higher/lower than/comparable to] <ArmB> (<%PatientAEArmA> in <ArmA> and <%PatientAEArmB> in <ArmB>, respectively).

Optional: If Frequent AE table is available include the following.

In <ArmA>, the most frequently reported (equal-to or greater than <%ThresholdMostFreqAEArmA> of patients in <ArmA>) AEs by [SOC/PT] were <MostFreqAE1SOCArmA>, <MostFreqAE2SOCArmA>... <MostFreqAE nSOCArmA> in descending order of frequency.

In <ArmB>, the most frequently reported (equal-to or greater than <%ThresholdMostFreqAEArmB> of patients in <ArmB>) AEs by [SOC/PT] were <MostFreqAE1PTArmB>, <MostFreqAE2PTArmB>... <MostFreqAE nPTArmB> in descending percentage of an AE in <ArmB> that is observed more in <ArmB> than in <ArmA> in descending order of frequency.

Optional: If significant differences in incidence between treatment arms include

A [notable/clinically significant] difference in incidence between treatment <ArmA> and <ArmB> was observed for <1stFrequentAEStudyArmsDifference> (<%1stFrequentAEStudyArmsDifferenceArmA> vs. <%1stFrequentAEStudyArmsDifferenceArmB>, respectively), <2ndFrequentAEStudyArmsDifference> (<%2ndFrequentAEStudyArmsDifferenceArmA> vs. <%2ndFrequentAEStudyArmsDifferenceArmB>, respectively), and <nFrequentAEStudyArmsDifference> (<nFrequentAEStudyArmsDifferenceArmA> vs. <nFrequentAEStudyArmsDifferenceArmB>, respectively).

## 8.3 ANALYSIS OF ADVERSE EVENTS

The incidence of AEs of any grade in atezo+cobi was higher than pembro (85% in atezo+cobi and 60% in pembro, respectively).

In atezo+cobi, the most frequently reported (equal-to or greater than 10% of patients in atezo+cobi) AEs by PT were nausea, vomiting, and headache in descending order of frequency.

In pembro, the most frequently reported (equal-to or greater than 10% of patients in pembro) AEs by PT were vomiting, nausea, and diarrhea in descending percentage of an AE in pembro that is observed more in atezo+cobi than in pembro in descending order of frequency.

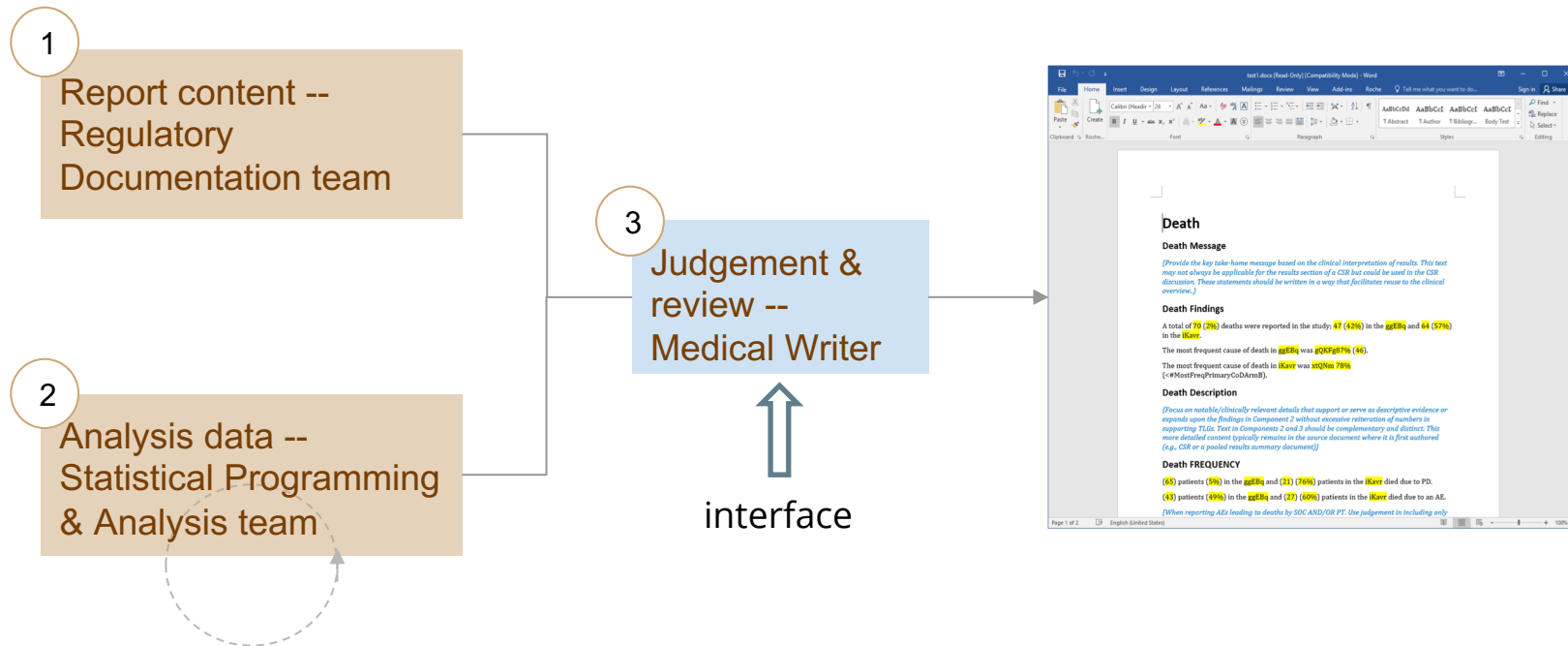
A clinically significant 2% or higher difference in incidence rate between treatment atezo+cobi and pembro was observed for headache (15% vs. 20%, respectively), and fatigue (8% vs. 1%, respectively).

Current State

Prototype V1 - Writer View

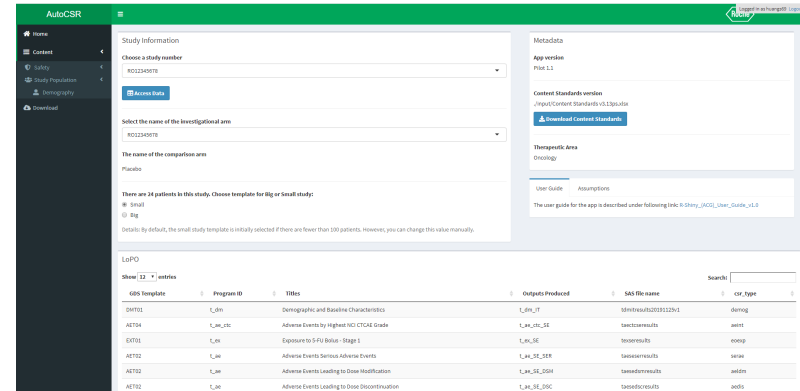
Prototype V1 - Reviewer View

# Workflow



# AutoCSR: Application Design

- AutoCSR is an internally developed tool for CSR automation
- It consists of two R packages:
  - **autoCSR** --- backend processing
    - Connect to content standards
    - Gather analysis data
    - Ensamble reports
  - **autoCSRweb** --- frontend interface
    - Collect user inputs
    - Display and download draft reports



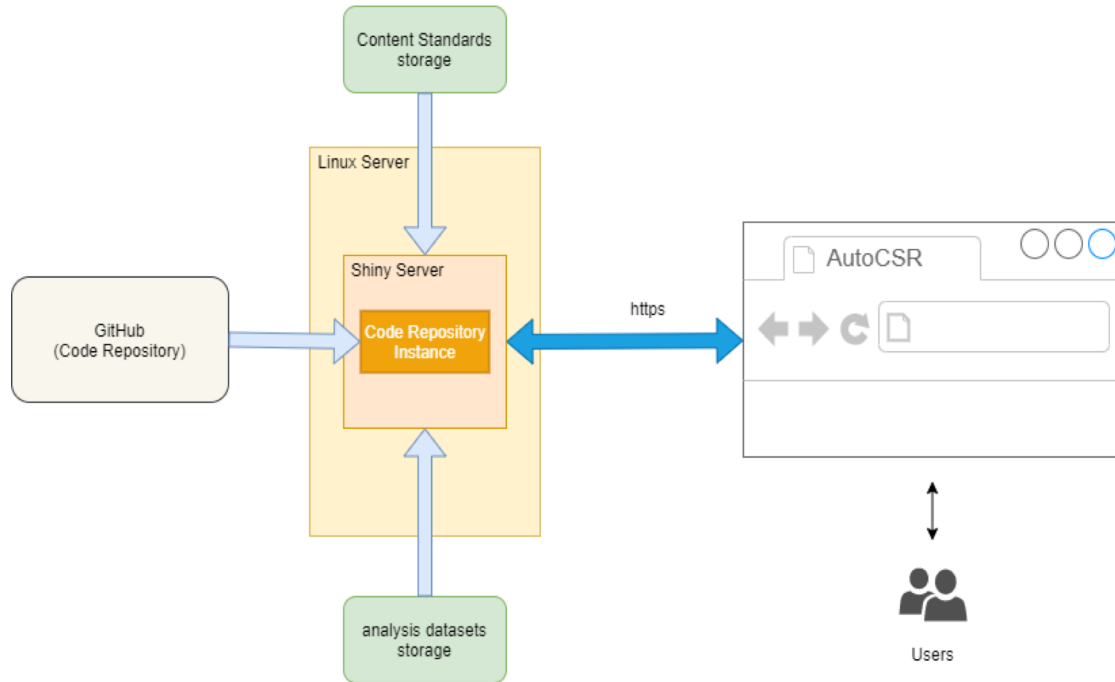
The screenshot shows the AutoCSR web application interface. The top navigation bar includes 'Home', 'Content', 'Study Information', 'Study Requirements', 'Study Results', and 'Download'. The main content area is divided into several sections:

- Study Information:** Includes a 'Choose a study number' dropdown menu with 'R02245070' selected, an 'Access data' button, and a 'Select the name of the investigational arm' dropdown menu with 'R02245070' selected. Below this is a section for 'The name of the comparison arm' with a 'Placeholder' text.
- Metadata:** Includes 'App version' (Prod 1.1), 'Content Standards version' (Impact Content Standards v3.1.1), and a 'Download Content Standards' button.
- Therapeutic Area:** Includes a 'Knowledge' section.
- User Guide:** Includes a link to 'Assumptions' and a note about the user guide for the app.

Below these sections is a table titled 'LSPs' with columns for 'GDS Template', 'Program ID', 'Titles', 'Outputs Produced', 'SAS file name', and 'csr\_type'. The table contains 6 rows of data:

| GDS Template | Program ID | Titles                                         | Outputs Produced | SAS file name             | csr_type |
|--------------|------------|------------------------------------------------|------------------|---------------------------|----------|
| DH001        | C_001      | Demographic and Baseline Characteristics       | L_001_01         | demographics001001001001  | demog    |
| AE004        | C_001_001  | Adverse Events by Highest NCI CTCAE Grade      | L_001_001_04     | adverseevents001001001004 | adverse  |
| EX001        | C_001      | Exposure to S-FU (Stage 1)                     | L_001_001        | exposure001001001001      | expos    |
| AE002        | C_001      | Adverse Events Serious Adverse Events          | L_001_001_02     | adverseevents001001001002 | serious  |
| AE003        | C_001      | Adverse Events Leading to Dose Modification    | L_001_001_03     | adverseevents001001001003 | adverse  |
| AE002        | C_001      | Adverse Events Leading to Dose Discontinuation | L_001_001_02     | adverseevents001001001002 | adverse  |

# AutoCSR: System Structure



# AutoCSR: Demo



AutoCSR

Logged in as huangs69 Logout

Home

Content

Download

Study Information

Choose a study number

BL8040

Access Data

Select the name of the investigational arm

The name of the comparison arm

-

There are \_\_\_\_ patients in this study. Choose template for Big or Small study:

Small

Big

Details: By default, the small study template is initially selected if there are fewer than 100 patients. However, you can change this value manually.

LoPO

Metadata

App version

Pilot 1.1

Content Standards version

./input/Content Standards v3.13ps.xlsx

Download Content Standards

Therapeutic Area

Oncology

User Guide

Assumptions

The user guide for the app is described under following link: R-Shiny\_(ACG)\_User\_Guide\_v1.0

# AutoCSR: Tech Explained (Part I)

## - Report content

```
> print(tree_t4, "objName", "objType", "Usage")
```

| LevelName | objName                          | objType  | Usage   |
|-----------|----------------------------------|----------|---------|
| 1 Root    | Death                            | Cat - IP | RQD     |
| 2 --L5_1  | Death Message                    | Comp     | RQD     |
| 3 --L6_1  | Para - AG                        | Comp     | RQD     |
| 4 --L5_2  | Death Findings                   | Comp     | RQD     |
| 5 --L6_1  | Para - AG                        | Comp     | RQD     |
| 6 --L6_2  | Para                             | CND      | CND     |
| 7 --L6_3  | Para                             | CND      | CND     |
| 8 --L6_4  | Para                             | CND      | CND     |
| 9 --L6_5  | Para                             | CND      | CND     |
| 10 --L7_1 | Para - AG                        | CND      | CND     |
| 11 --L7_2 | Para                             | CND      | CND     |
| 12 --L7_3 | Para                             | CND      | CND     |
| 13 --L7_4 | Para                             | CND      | CND     |
| 14 --L7_5 | Para                             | CND      | CND     |
| 15 --L5_3 | Death Description                | Comp     | RQD     |
| 16 --L6_1 | Para - AG                        | RQD      | RQD     |
| 17 --L6_2 | Death FREQUENCY                  | Sub-Comp | RQD     |
| 18 --L7_1 | Para                             | CND      | CND     |
| 19 --L7_2 | Para                             | CND      | CND     |
| 20 --L7_3 | Para - AG                        | RQD      | RQD     |
| 21 --L7_4 | Para                             | RQD      | RQD     |
| 22 --L6_3 | Death RELATEDNESS                | Sub-Comp | CND     |
| 23 --L7_1 | Para                             | CND/OPT  | CND/OPT |
| 24 --L7_2 | Para                             | CND/OPT  | CND/OPT |
| 25 --L6_4 | Death TIMING OF DEATH EVENTS     | Sub-Comp | CND     |
| 26 --L7_1 | Para                             | CND      | CND     |
| 27 --L8_1 | Para - AG                        | CND      | CND     |
| 28 --L7_2 | Para                             | CND      | CND     |
| 29 --L8_1 | Para - AG                        | CND      | CND     |
| 30 --L6_5 | Death EVENTS DUE TO OTHER CAUSES | Sub-Comp | CND     |
| 31 --L7_1 | Para                             | CND      | CND     |
| 32 --L5_4 | Death Source                     | Comp     | RQD     |
| 33 --L6_1 | Para - AG                        | RQD      | RQD     |
| 34 --L6_2 | Para                             | RQD      | RQD     |

Standardized content in related spreadsheets

Standardized content in data.tree

# AutoCSR: Tech Explained (Part I, cont.)

| Cat/Comp Object Name         | Object Typ | Type        | Tree L4          | L5 Cat/ Comp Object ID (Primary) | L6 Sub Comp Object ID (Primary) | Conditional Logic                                                                                                                                     | Tech Logic for Condition (code)                                           | USAGI   | Content+Variables                                                                                                                                                                                                                                                                                                                       |
|------------------------------|------------|-------------|------------------|----------------------------------|---------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------|---------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Death RELATEDNESS            | Comp       | Description | C_2_6_2_2_Deaths | C.2.6.2.2.3                      | C.2.6.2.2.3.3                   | If there are a small number of AEs leading to death.                                                                                                  | <#DeathAESTudyTreatmentArmA> + <#DeathAESTudyTreatmentArmB> == 0          | CND     |                                                                                                                                                                                                                                                                                                                                         |
|                              | Para       | Description | C_2_6_2_2_Deaths | C.2.6.2.2.3                      | C.2.6.2.2.3.1                   | If no deaths were considered related to the study treatment by the investigator                                                                       | <#DeathAESTudyTreatmentArmA> + <#DeathAESTudyTreatmentArmB> == 0          | CND/OPT | No deaths were considered related to study treatment by the investigator.<br><#DeathAESTudyTreatmentArmA> (<%DeathAESTudyTreatmentArmA>) patients in the <ArmA> died due to AEs assessed as related to study treatment by the investigator<br>(SAELLeadingToDeathStudyTreatmentPtnArmA_#DeathAELLeadingToDeathStudyTreatmentPtnArmA(S)) |
|                              | Para       | Description | C_2_6_2_2_Deaths | C.2.6.2.2.3                      | C.2.6.2.2.3.2                   | If some deaths due to AEs were considered related to the study treatment by the investigator                                                          | <#DeathAESTudyTreatmentArmA> + <#DeathAESTudyTreatmentArmB> > SmallDeath_ | CND/OPT | <#DeathAESTudyTreatmentArmB> (<%DeathAESTudyTreatmentArmB>) patients in the <ArmB> died due to AEs assessed as related to study treatment by the investigator<br>(SAELLeadingToDeathStudyTreatmentPtnArmB_#DeathAELLeadingToDeathStudyTreatmentPtnArmB(S))                                                                              |
|                              | Para       | Description | C_2_6_2_2_Deaths | C.2.6.2.2.3                      | C.2.6.2.2.3.2                   | If deaths occurred after the last study treatment and this was predefined in the protocol, or if there were deaths prior to the first study treatment | <#DeathAfterLastPeriod>>0   <#DeathPriorToFirstTreatment>>0               | CND     | INFESTATIONS / SEPTIC SHOCK 1 (0.2%), RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / ASPIRATION 1 (0.2%), and RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / PULMONARY EMBOLISM 1 (0.2%).                                                                                                                                         |
| Death TIMING OF DEATH EVENTS | Comp       | Description | C_2_6_2_2_Deaths | C.2.6.2.2.3                      | C.2.6.2.2.3.4                   |                                                                                                                                                       |                                                                           | CND     | In the Placebo + nab-Paclitaxel the most frequent AEs leading to death by SOC (equal to or greater than 0%) were: GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS / DEATH 1 (0.2%), CARDIAC DISORDERS / ACUTE MYOCARDIAL INFARCTION 0, and HEPATOBIILIARY DISORDERS / HEPATIC FAILURE 0.                                           |

## Death RELATEDNESS

6 (1.3%) patients in the Atezolizumab + nab-Paclitaxel died due to AEs assessed as related to study treatment by the investigator (GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS / DEATH (1), GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS / MUCOSAL INFLAMMATION (1), HEPATOBIILIARY DISORDERS / AUTOIMMUNE HEPATITIS (1), INFECTIONS AND INFESTATIONS / PNEUMONIA (1), INFECTIONS AND INFESTATIONS / SEPTIC SHOCK (1), RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / ASPIRATION (1), and RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS / PULMONARY EMBOLISM (1)).

3 (0.7%) patients in the Placebo + nab-Paclitaxel died due to AEs assessed as related to study treatment by the investigator (GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS / DEATH (1), CARDIAC DISORDERS / ACUTE MYOCARDIAL INFARCTION (1), and HEPATOBIILIARY DISORDERS / HEPATIC FAILURE (1)).

## Death TIMING OF DEATH EVENTS

[The majority of Fewer] deaths occurred more than 30 days after the last study drug administration (348 (90.6%)).

(Repeat the same statement for other arm)

Note that in the Atezolizumab + nab-Paclitaxel 4 (0.4%) occurred prior to patient receiving treatment and thus is included for the ITT population, but not in the safety evaluable population.

(Repeat the same statement for other arm)

# AutoCSR: Tech Explained (Part II)

## - Analysis dataset

| __ANALYSIS_FORMAT      | ARM<br>Description of Planned Arm | ARM_FORMAT<br>Description of Planned Arm (format) | __LEVEL1_FORMAT                                       | __CONTENT    | __DESTINATION | __VALUE   |
|------------------------|-----------------------------------|---------------------------------------------------|-------------------------------------------------------|--------------|---------------|-----------|
| Total Number of Deaths | ARM A                             | ARM A@(N=292)                                     |                                                       | countpercent | table         | 14 (4.8%) |
| Total Number of Deaths | ARM B                             | ARM B@(N=822)                                     |                                                       | countpercent | table         | 50 (6.1%) |
| Total Number of Deaths | All                               | All@(N=1114)                                      |                                                       | countpercent | table         | 64 (5.7%) |
| Primary Cause of Death | ARM A                             | ARM A@(N=292)                                     | n                                                     | count        | table         | 14        |
| Primary Cause of Death | ARM A                             | ARM A@(N=292)                                     | Adverse Event                                         | countpercent | table         | 6 (42.9%) |
| Primary Cause of Death | ARM A                             | ARM A@(N=292)                                     | Progressive Disease                                   |              |               |           |
| Primary Cause of Death | ARM A                             | ARM A@(N=292)                                     | Other                                                 |              |               |           |
| Primary Cause of Death | ARM A                             | ARM A@(N=292)                                     | COR PULMONARE                                         |              |               |           |
| Primary Cause of Death | ARM A                             | ARM A@(N=292)                                     | MASSIVE STROKE                                        |              |               |           |
| Primary Cause of Death | ARM A                             | ARM A@(N=292)                                     | PATIENT WAS HOSPITALIZED ON 25 APRIL 2018 DUE TO F... |              |               |           |
| Primary Cause of Death | ARM A                             | ARM A@(N=292)                                     | RESPIRATORY FAILURE DUE TO INTERSTITIAL PNEUMONIA...  |              |               |           |
| Primary Cause of Death | ARM A                             | ARM A@(N=292)                                     | UNKNOWN                                               |              |               |           |
| Primary Cause of Death | ARM A                             | ARM A@(N=292)                                     | Unknown                                               |              |               |           |
| Primary Cause of Death | ARM B                             | ARM B@(N=822)                                     | n                                                     |              |               |           |

t\_dtht01\_AB\_Se\_out - Notepad

File Edit Format View Help

Deaths, Safety Patients

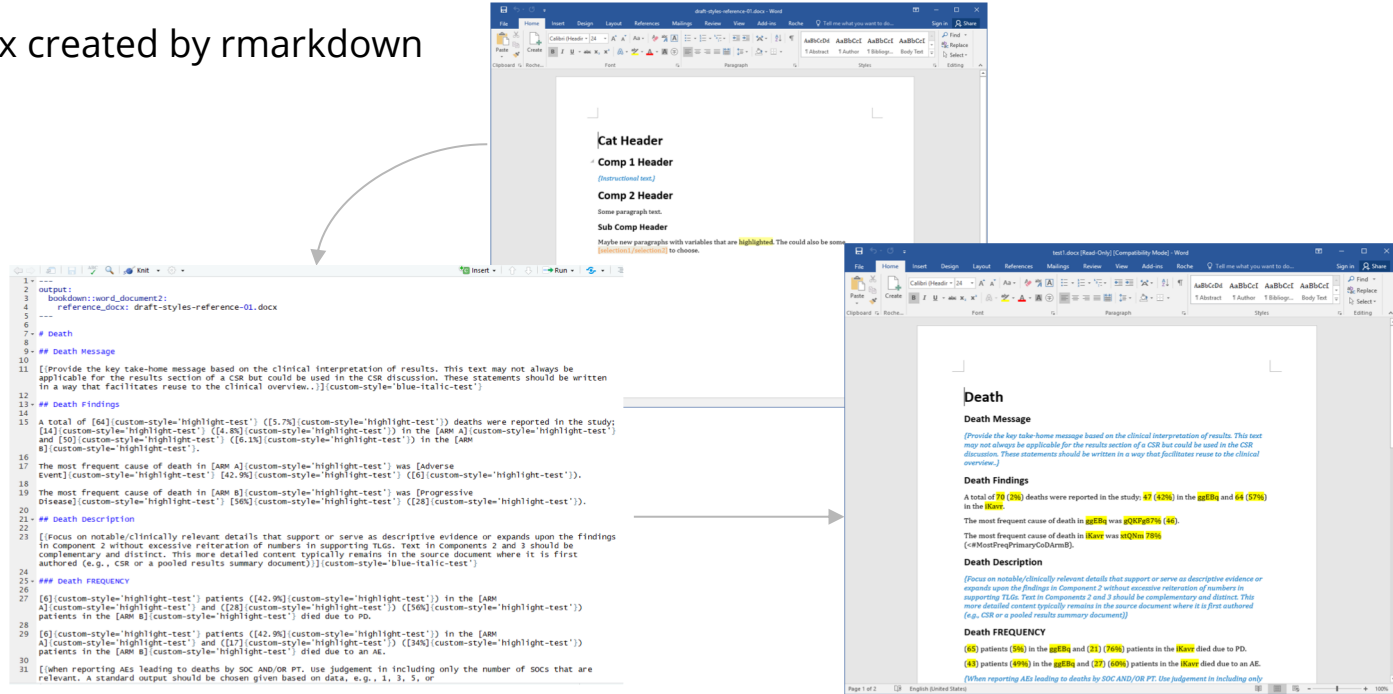
Protocol: xxxxxx

|                                                                                                               | ARM A<br>(N=292) | ARM B<br>(N=822) | All<br>(N=1114) |
|---------------------------------------------------------------------------------------------------------------|------------------|------------------|-----------------|
| Total Number of Deaths                                                                                        | 14 ( 4.8%)       | 50 ( 6.1%)       | 64 ( 5.7%)      |
| Primary Cause of Death                                                                                        |                  |                  |                 |
| n                                                                                                             | 14               | 50               | 64              |
| Adverse Event                                                                                                 | 6 (42.9%)        | 17 (34.0%)       | 23 (35.9%)      |
| Progressive Disease                                                                                           | 6 (42.9%)        | 28 (56.0%)       | 34 (53.1%)      |
| Other                                                                                                         | 2 (14.3%)        | 5 (10.0%)        | 7 (10.9%)       |
| COR PULMONARE                                                                                                 | 0                | 1 ( 2.0%)        | 1 ( 1.6%)       |
| MASSIVE STROKE                                                                                                | 0                | 1 ( 2.0%)        | 1 ( 1.6%)       |
| PATIENT WAS HOSPITALIZED ON 25 APRIL 2018 DUE TO FEBRILE NEUTROPENIA AND DIED ON 28 APRIL DUE TO SEPTIC SHOCK | 0                | 1 ( 2.0%)        | 1 ( 1.6%)       |
| RESPIRATORY FAILURE DUE TO INTERSTITIAL PNEUMONIA ( INDUCED BY DOCETAXEL CHEMOTHERAPY )                       | 1 ( 7.1%)        | 1 ( 2.0%)        | 2 ( 3.1%)       |
| UNKNOWN                                                                                                       | 1 ( 7.1%)        | 0                | 1 ( 1.6%)       |
| Unknown                                                                                                       |                  |                  |                 |
| Days from Last Study Drug Administration                                                                      |                  |                  |                 |
| n                                                                                                             | 14               | 50               | 64              |
| <= 30 days                                                                                                    | 5 (35.7%)        | 21 (42.0%)       | 26 (40.6%)      |
| > 30 days                                                                                                     | 9 (64.3%)        | 29 (58.0%)       | 38 (59.4%)      |
| Primary Cause by Days from Last Study Drug Administration                                                     |                  |                  |                 |
| <= 30 days                                                                                                    |                  |                  |                 |
| n                                                                                                             | 5                | 21               | 26              |
| Adverse Event                                                                                                 | 5 ( 100%)        | 16 (76.2%)       | 21 (80.8%)      |
| Progressive Disease                                                                                           | 0                | 5 (23.8%)        | 5 (19.2%)       |
| > 30 days                                                                                                     |                  |                  |                 |
| n                                                                                                             | 9                | 29               | 38              |
| Adverse Event                                                                                                 | 1 (11.1%)        | 1 ( 3.4%)        | 2 ( 5.3%)       |
| Progressive Disease                                                                                           | 6 (66.7%)        | 23 (79.3%)       | 29 (76.3%)      |
| Other                                                                                                         | 2 (22.2%)        | 5 (17.2%)        | 7 (18.4%)       |

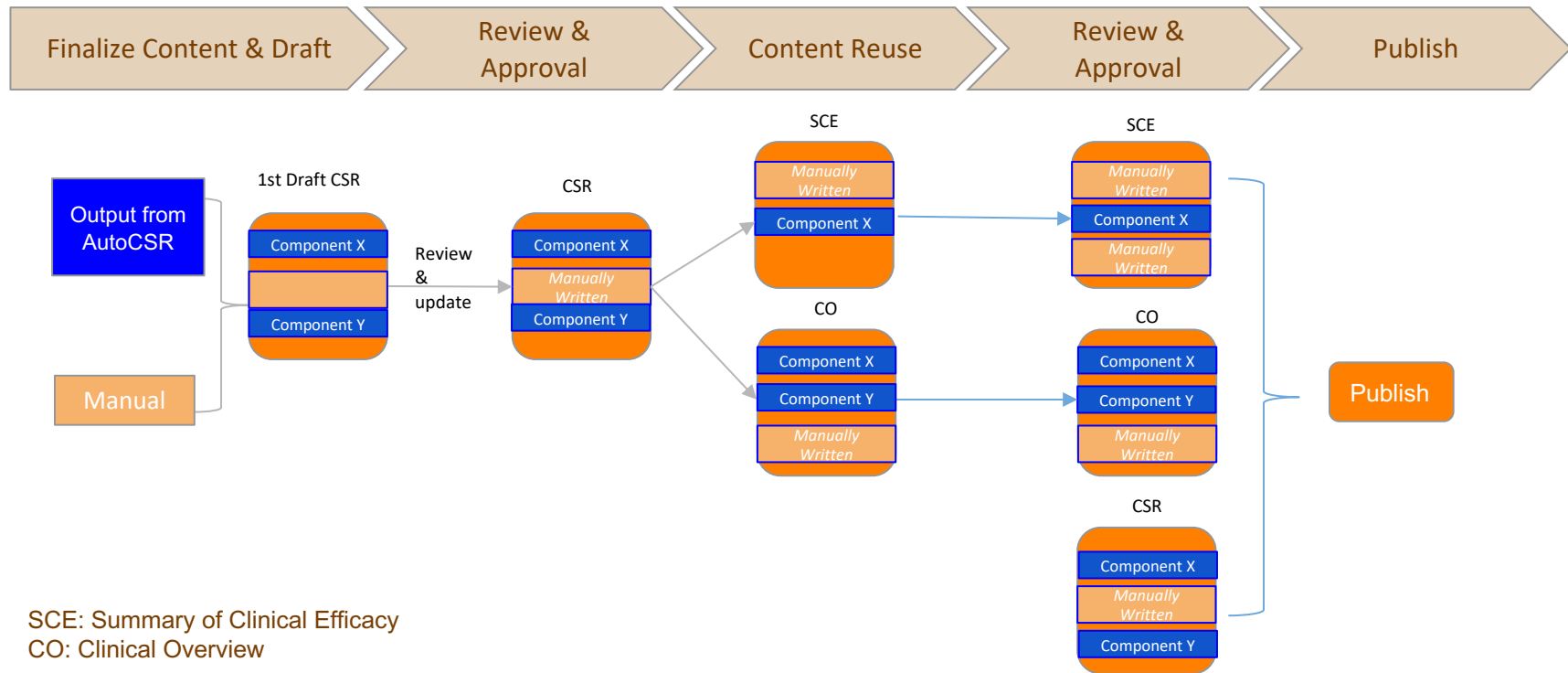
Program: root/clinical\_studies/ro\_testing/cdp\_testing/spa\_testing/data\_analysis/FF/work/work\_all/program/t\_dtht01.sas  
 Output: root/clinical\_studies/ro\_testing/cdp\_testing/spa\_testing/data\_analysis/FF/work/work\_all/output/t\_dtht01\_AB\_Se\_out  
 21FEB2019 16:46 Page 1 of 1

# AutoCSR: Tech Explained (Part III)

- .docx created by rmarkdown



# AutoCSR: Beyond CSR



# Next Steps

- Continuous collaboration with multiple teams
- Flexibility or standardization on content
- Workflow integration
- Gathering ideas for improvements



*Doing now what patients need next*