Auto Subgroup TLG Generation With R Shiny

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Background

What Is A Subgroup

- As per the guideline of EMA/CHMP,

The term 'subgroup' will be used to refer to a subset of the clinical trial population defined by one or more intrinsic and extrinsic factors (see ICH-E5) of the patients under investigation, usually measured at baseline.

- As per guideline of China NMPA,

亚组人群（简称亚群）指 总体人群中具有某些特征的一个子集，亚组是全人群中的一个子集，亚组通常由患者的一个或多个内在和/或外在因素（见 ICH E5）来定义，而且应具有一定的临床意义。

EMA/CHMP/539146/2013: Guideline on the investigation of subgroups in confirmatory clinical trials.
NMPA:药物临床试验亚组分析指导原则 （试行）

Typical List of Subgroup

Region

Age

Sex

Race

Baseline severity measure

Clinical events in previous years

Baseline medication

Baseline blood biomarker

What Are Subgroup Analyses

- **Content**

  - Splitting all the participant data into subgroups, to make comparisons between them

  - Usually done for subsets of participants (e.g. males/females or different geographical locations)

- **Purpose**

  - Investigating heterogeneous results, or to answer specific questions about particular patient groups, types of intervention or types of study

"Most trials report subgroup analysis (median = 4 subgroups)"
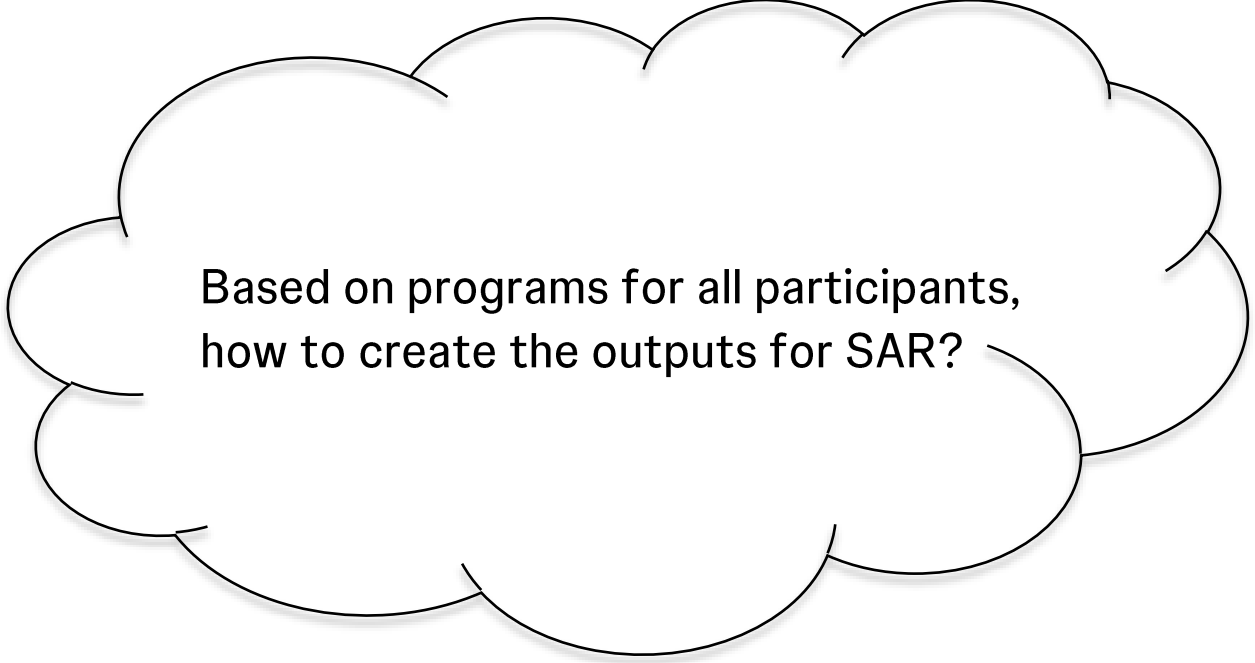
- Assmann SF, Lancet 2000; 355:1064-1069;

Case Study

**A Subgroup Analysis in Support of NMPA Submission**

Backgroud

- A subgroup analysis report (SAR) is required to evaluate the consistency of results among all participants. This report includes safety and efficacy analyses conducted on specific sub-populations within a multi-regional clinical trial (MRCT).

- Global clinical study report (CSR) has been finalized for the MRCT, with the R programs to create outputs for all participants available.

- Sub-populations:
  - ✓ East Asia
  - ✓ China*

* China mainland

Based on programs for all participants,
how to create the outputs for SAR?

Regular Approach
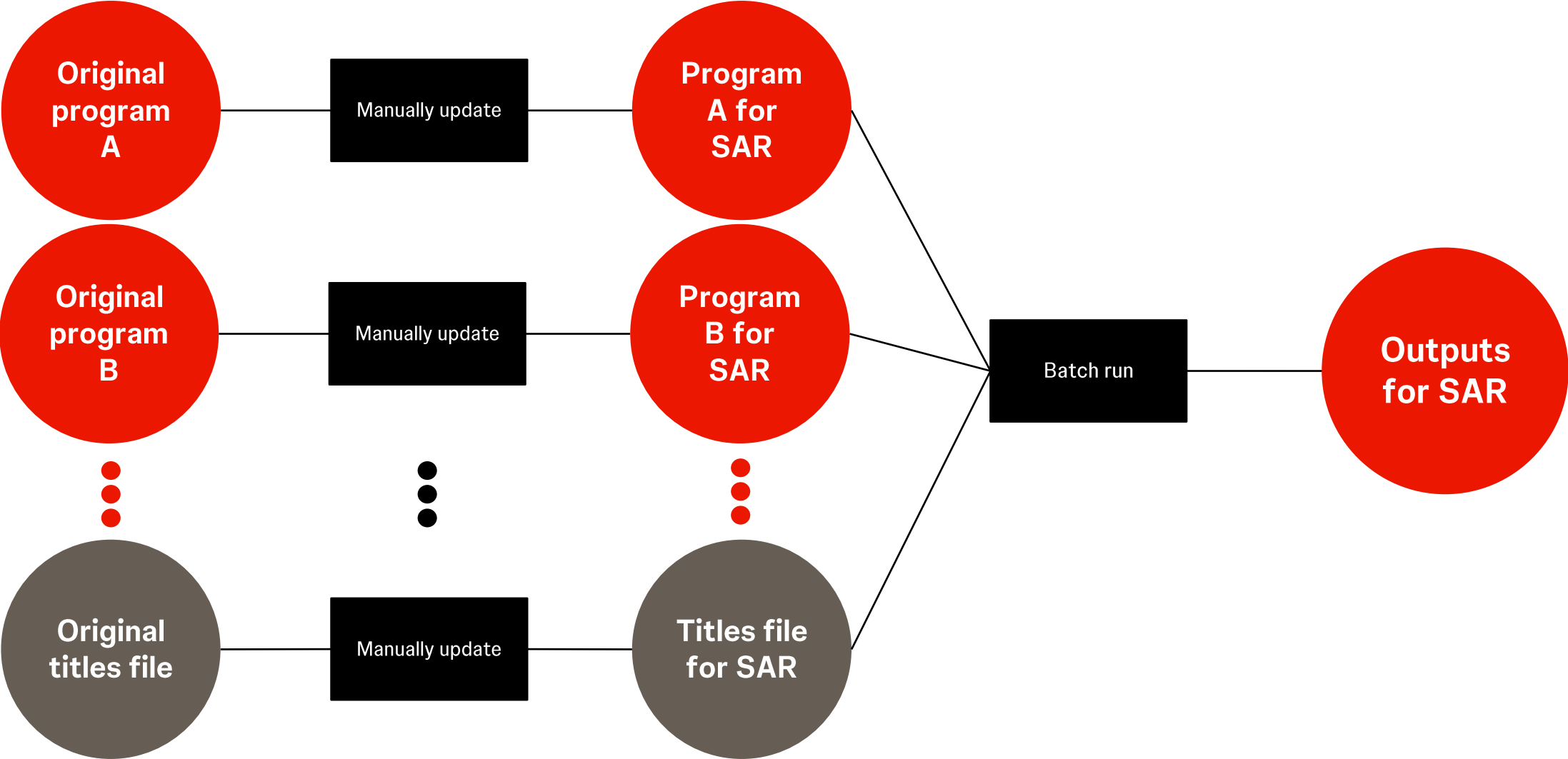
A Closer Look at The 'Manually Update'

Original program tsflab04

- tsflab01dc1.r
- tsflab01di.r
- tsflab01ec1.r
- tsflab01fc1.r
- tsflab01fccp.r
- ☑ tsflab04.r
- tsflab05.r
- tsflabrb05.r
- tsflabrb05cp.r
- tsflabrb06.r

Code update:

- Update program header

- Filtering on the input dataset

- Change output id

```
# Program Name : tsflab04ea.r

adsl <- read_sas(read_path(a_in,"adsl.sas7bdat")) %>%
    filter(REGION == "East Asia")
adlb <- read_sas(read_path(a_in,"adlb.sas7bdat")) %>%
    filter(REGION == "East Asia")

##define the ID of TLGs
tblid<-"TSFALB04ea"
```

Program A for SAR

Next original program tsflab05

A sip of water

- tsflab01dc1.r
- tsflab01di.r
- tsflab01ec1.r
- tsflab01fc1.r
- tsflab01fccp.r
- tsflab04.r
- ☑ tsflab05.r
- tsflabrb05.r
- tsflabrb05cp.r
- tsflabrb06.r

●●● Repeat it for China sub-population **X2**

A Closer Look at The 'Manually Update'

Original titles file

☑ 📄 titles.xlsx

A sip of water

| 89 | TSFAE02 | TITLE | Number of Subjects With Treatment-emergent Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study XXXXXXX) |

| 89 | TSFAE02ea | TITLE | Number of Subjects With Treatment-emergent Adverse Events by System Organ Class and Preferred Term for East Asia Population; Safety Analysis Set (Study XXXXXXX) |

💾

Titles file for SAR

It's never too bad to absorb water and walk around, but is there a way to improve the process?

Customized user inputs

R programs processing in batch

R Shiny!

New Workflow
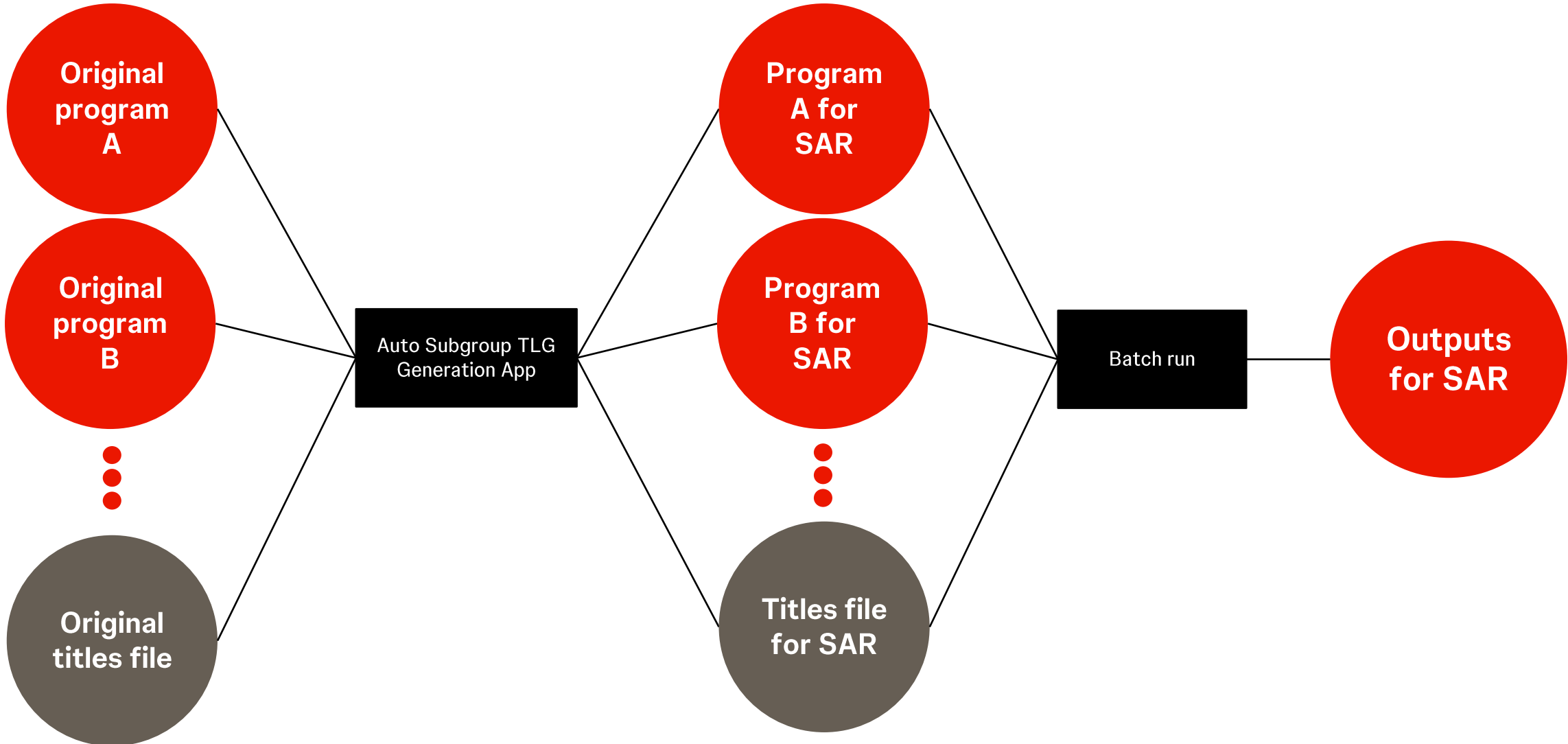
Auto Subgroup TLG Generation App

Auto Subgroup TLG Generation

1. Choose programs you want to update

Select Level of Original Programs

PDEV	▼

☐ Other Path

Programs

Nothing selected	▼

☑ Alphabetic order

2. Update titles.xlsx based on your selections in step.1

Upload titles.xlsx

Browse...	No file selected

Add to title ID

e.g. jpn|njpn

Suggest: Please add only lowercase letters as suffix. Uppercase letters will be converted to lowercase and '-' will be removed when generating the rtf output

Add to title

e.g. for Japan Population|for Non-Japan Pop

Note: A new titles.xlsx will be created in your pdev input folder. Please avoid unconscious update

Create titles.xlsx

3. Update the programs

Add output ID from step 2

	▼

☐ Other output ID

Group variable

COUNTRY	▼

Subgroup population

Nothing selected	▼

Confirm	Undo

Create programs

1. Select Programs for SAR

- shinyWidgets::pickerInput
  - Multiple choices
  - Search box

2. Update titles.xlsx File

2. Update titles.xlsx based on your selections in step.1

Upload titles.xlsx

Browse...	No file selected

Add to title ID

ea|chn

Suggest: Please add only lowercase letters as suffix. Uppercase letters will be converted to lowercase and '-' will be removed when generating the rtf output

Add to title

for East Asia Population|for China Population

Note: A new titles.xlsx will be created in your pdev input folder. Please avoid unconscious update

Create titles.xlsx

- Multiple subgroups at the same time

TSFAE03	TITLE	Number of Subjects With Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term; Safety Analysis Set (Study XXXXXXX)
TSFAE03	FOOTNOTE1	Key: SAE = serious adverse event.
TSFAE03ae	TITLE	Number of Subjects With Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term for East Asia Population; Safety Analysis Set (Study XXXXXXX)
TSFAE03ea	FOOTNOTE1	Key: SAE = serious adverse event.
TSFAE03chn	TITLE	Number of Subjects With Treatment-emergent Serious Adverse Events by System Organ Class and Preferred Term for China Population; Safety Analysis Set (Study XXXXXXX)
TSFAE03chn	FOOTNOTE1	Key: SAE = serious adverse event.

3. Update Programs

- Previous inputs will be carried over

- Programs will be updated with the selected filtering criteria by simply clicking (no need to open up files/type codes/save files)

- Programs can be updated for multiple subgroups at the same time

```
## apply population filter
subpop_subject_list <- read_sas(read_path(a_in, 'adsl.sas7bdat')) %>%
  filter(COUNTRY %in% c('CHN', 'JPN', 'KOR')) %>%
  pull(USUBJID)

filter(USUBJID %in% subpop_subject_list)
```

3. Update the programs

Add output ID from step 2

ea ▼

☐ Other output ID

Group variable

COUNTRY ▼

Subgroup population

CHN, JPN, KOR ▼

Select All	Deselect All

COUNTRY

CHN	✔
JPN	✔
FRA	
RUS	
CAN	
TUR	
USA	
GBR	
KOR	✔
DEU	

3. Update the programs

Add output ID from step 2

ea ▼

☐ Other output ID

Group variable

COUNTRY ▼

Subgroup population

CHN, JPN, KOR ▼

Confirm | Undo

ID	Var	Selection
ea	COUNTRY	CHN, JPN, KOR
chn	COUNTRY	CHN

Create programs

Outputs for SAR

TSIDEM01: Demographics and Baseline Characteristics; Safety Analysis Set (Study XXXXXX)

	Dummy Treatment A	Dummy Treatment B	Dummy Treatment C	Total
Analysis set: Safety Analysis Set	27	8	19	54
Sex				
N	27	8	19	54
Female	15 (55.6%)	3 (37.5%)	8 (42.1%)	26 (48.1%)
Male	12 (44.4%)	5 (62.5%)	11 (57.9%)	28 (51.9%)
Age, years				
N	27	8	19	54
Mean (SD)	35.6 (9.95)	27.3 (9.95)	33.6 (11.15)	33.6 (10.58)
SE	1.92	3.52	2.56	1.44
Median	37.0	24.0	30.0	32.0
Range	(18; 53)	(18; 49)	(18; 55)	(18; 55)
18 - <=30 years	9 (33.3%)	6 (75.0%)	10 (52.6%)	25 (46.3%)
>30 - <=45 years	14 (51.9%)	1 (12.5%)	6 (31.6%)	21 (38.9%)
>45 - <=55 years	4 (14.8%)	1 (12.5%)	3 (15.8%)	8 (14.8%)

TSIDEM01ea: Demographics and Baseline Characteristics for East Asia Population; Safety Analysis Set (Study XXXXXX)

	Dummy Treatment A	Dummy Treatment B	Dummy Treatment C	Total
Analysis set: Safety Analysis Set	10	2	11	23
Sex				
N	10	2	11	23
Female	8 (80.0%)	1 (50.0%)	5 (45.5%)	14 (60.9%)
Male	2 (20.0%)	1 (50.0%)	6 (54.5%)	9 (39.1%)
Age, years				
N	10	2	11	23
Mean (SD)	34.1 (11.00)	24.0 (1.41)	34.7 (12.19)	33.5 (11.24)
SE	3.48	1.00	3.68	2.34
Median	34.0	24.0	32.0	30.0
Range	(18; 50)	(23; 25)	(18; 55)	(18; 55)
18 - <=30 years	5 (50.0%)	2 (100.0%)	5 (45.5%)	12 (52.2%)
>30 - <=45 years	3 (30.0%)	0	4 (36.4%)	7 (30.4%)
>45 - <=55 years	2 (20.0%)	0	2 (18.2%)	4 (17.4%)

TSIDEM01chn: Demographics and Baseline Characteristics for China Population; Safety Analysis Set (Study XXXXXX)

	Dummy Treatment A	Dummy Treatment B	Dummy Treatment C	Total
Analysis set: Safety Analysis Set	7	2	2	11
Sex				
N	7	2	2	11
Female	5 (71.4%)	1 (50.0%)	0	6 (54.5%)
Male	2 (28.6%)	1 (50.0%)	2 (100.0%)	5 (45.5%)
Age, years				
N	7	2	2	11
Mean (SD)	36.4 (11.25)	24.0 (1.41)	21.5 (4.95)	31.5 (11.26)
SE	4.25	1.00	3.50	3.40
Median	38.0	24.0	21.5	25.0
Range	(23; 50)	(23; 25)	(18; 25)	(18; 50)
18 - <=30 years	3 (42.9%)	2 (100.0%)	2 (100.0%)	7 (63.6%)
>30 - <=45 years	2 (28.6%)	0	0	2 (18.2%)
>45 - <=55 years	2 (28.6%)	0	0	2 (18.2%)

Discussion

Benefit

Efficiency gained

With the introduction of automation, manual work is significantly minimized, reducing hours of labor to minutes.

Less error-prone

It reduces human errors that often occur due to the tedious and repetitive nature of tasks.

Accessibility

Once published online, a Shiny App is readily accessible as long as an internet connection is available.

User-friendly interface

It allows for easy navigation and user input. This approach can be applied not only for regional subgroup analysis in China or Japan submissions but also for any other subgroup analysis (such as sex, age groups)

Limitations and Looking Forward

It currently only works for subgroup analysis with the same layout. Side by side table is not applicable yet.

It cannot automatically handle the case where statistical analysis fails due to reduced sample size after data subsetting. Verification is still required.
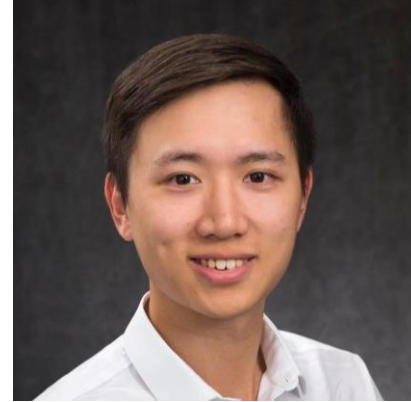
Moving forward, the use of natural language for updating programs offers a more generalized approach, showing great promise.

Team Members

Jiaqi Song
SAS Macro

Yufan Chen
R Shiny App

Acknowledge

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Thank you

If you have more questions, please contact:
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