Analysis Datasets in Vaccine Clinical Trials

Jingyee Kou, Ph.D.
CBER/OBE

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Disclaimer

The findings and conclusions in this presentation have not been disseminated by the Food and Drug Administration and should not be construed to represent any Agency determination or policy.

Outline

- Background
- Legacy data conversion (SDTM)
- Validation & Define file
- Analysis data creation (ADaM)
- Reproducibility
- Issues in analysis datasets
- Sex analysis as pilot
- Future research

Background *(1)*

- CBER accepts data submissions in CDISC format since 2010.

- As of date
  - 4 in blood products submitted
  - 1 in vaccine submitted
  - 1 vaccine BLA coming

Background *(2)*

- CBER/OBE Vaccine Database Initiative

- Goal:

  Promote standardization of vaccine dataset format so that CBER staff can more rapidly and effectively perform analyses of efficacy and safety across studies and across products.

Preventative Vaccine Clinical Trials *(1)*

- Vaccines are for healthy individuals
- Licensed vaccine may ultimately be used in millions of humans
- Clinical trials to obtain a *reasonable degree* of assurance that a vaccine is not associated with any serious adverse events before licensure
- Detect rare but serious adverse reactions challenging, limited by study size and low incidence rates

Preventative Vaccine Clinical Trials *(2)*

- Efficacy trial could be large due to low incidence rate of disease
- Antibody immune responses (immunogenicity) may be used as a surrogate
- Usually 1 dose, infant vaccines could be as high as 4 doses at specified ages

CDISC Formats

- CDISC: Clinical Data Interchange Standards Consortium
- SDTM: Study Data Tabulation Model (aka: raw data, listing data, etc.)
- ADaM: Analysis Data Model (aka: analysis datasets)

Legacy Datasets

- Licensed vaccine
- Select 4 US studies
- Male and female
- Include approximately 8,000 subjects
- About 5,000 received test vaccine
- Active control

Converted SDTM data

- DM: demographics
- DS: disposition
- IE: inclusion/exclusion criteria
- EX: exposure
- LB: laboratory results
- AE: adverse events
- CM: concomitant medications
- CO: comments
- SC: subject characteristics

Conversion Issues

- CDISC format based on drug trials not necessarily suitable for vaccine trials

Example:

- End Date:

  - Vaccination date may be used as treatment start date, what is the end date for 1 dose? For multiple doses?

  - Decision: not to use

Adverse Events & AE Domain

- Type of AEs captured in clinical trials:
  - Common local reactions (e.g., swelling)
  - Systemic adverse reactions (e.g., fever)
  - Rare and serious adverse events (e.g., seizures, hospitalizations, death, etc.
- Include all AEs into the AE domain

Immunogenicity

- Immunogenicity is used as a surrogate measurement for vaccine efficacy
- Considered as a “correlate” of protection
- Used when efficacy trial is not feasible due to a currently licensed vaccine
- LB domain is for laboratory results, not appropriate for immunogenicity
- New domain is in the making

Validation & Define file

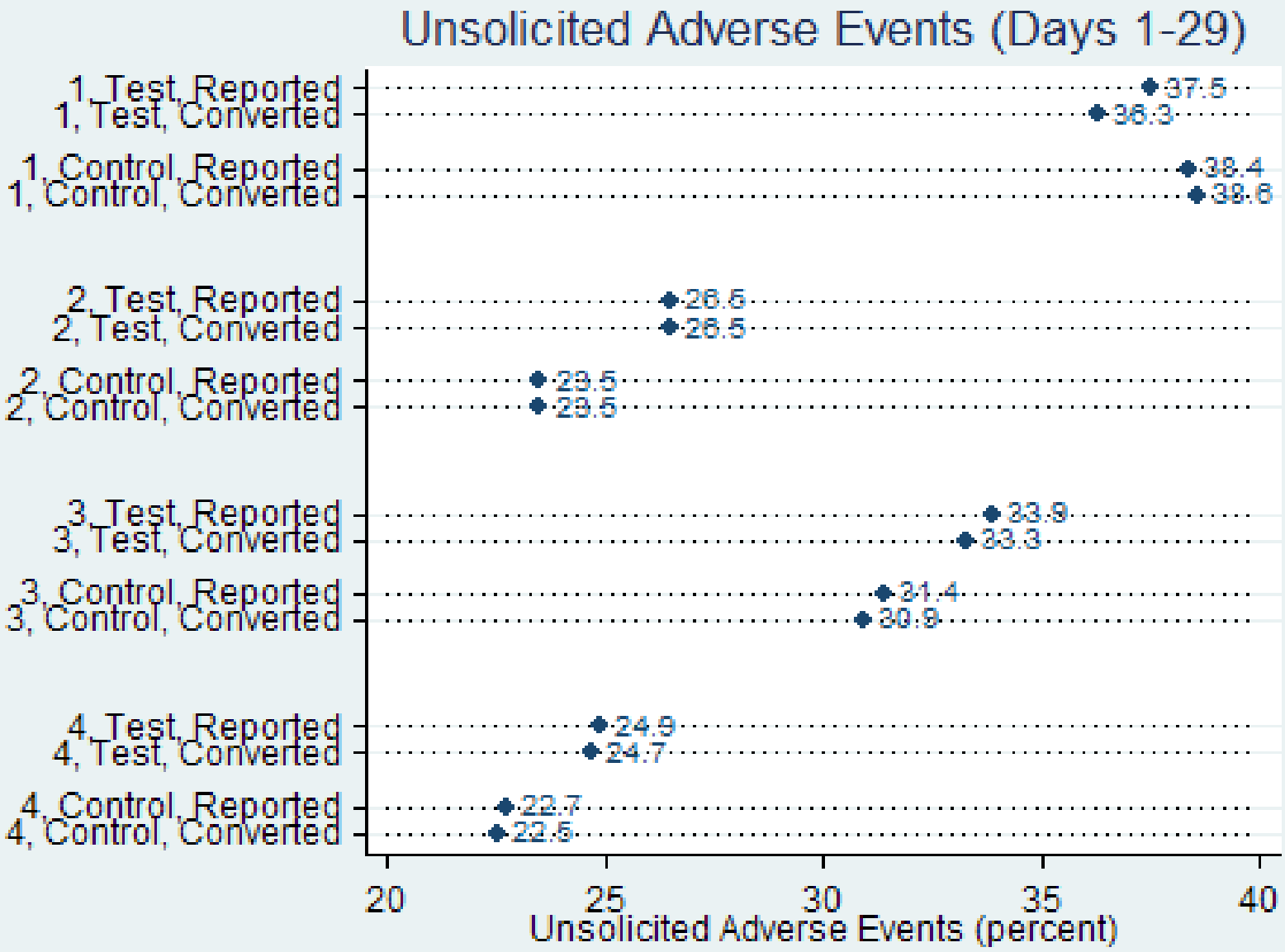
- Software: OpenCDISC
- Validation: to ensure compliance with CDISC standards
- Define file: contains the file names, the variable names, and their definitions

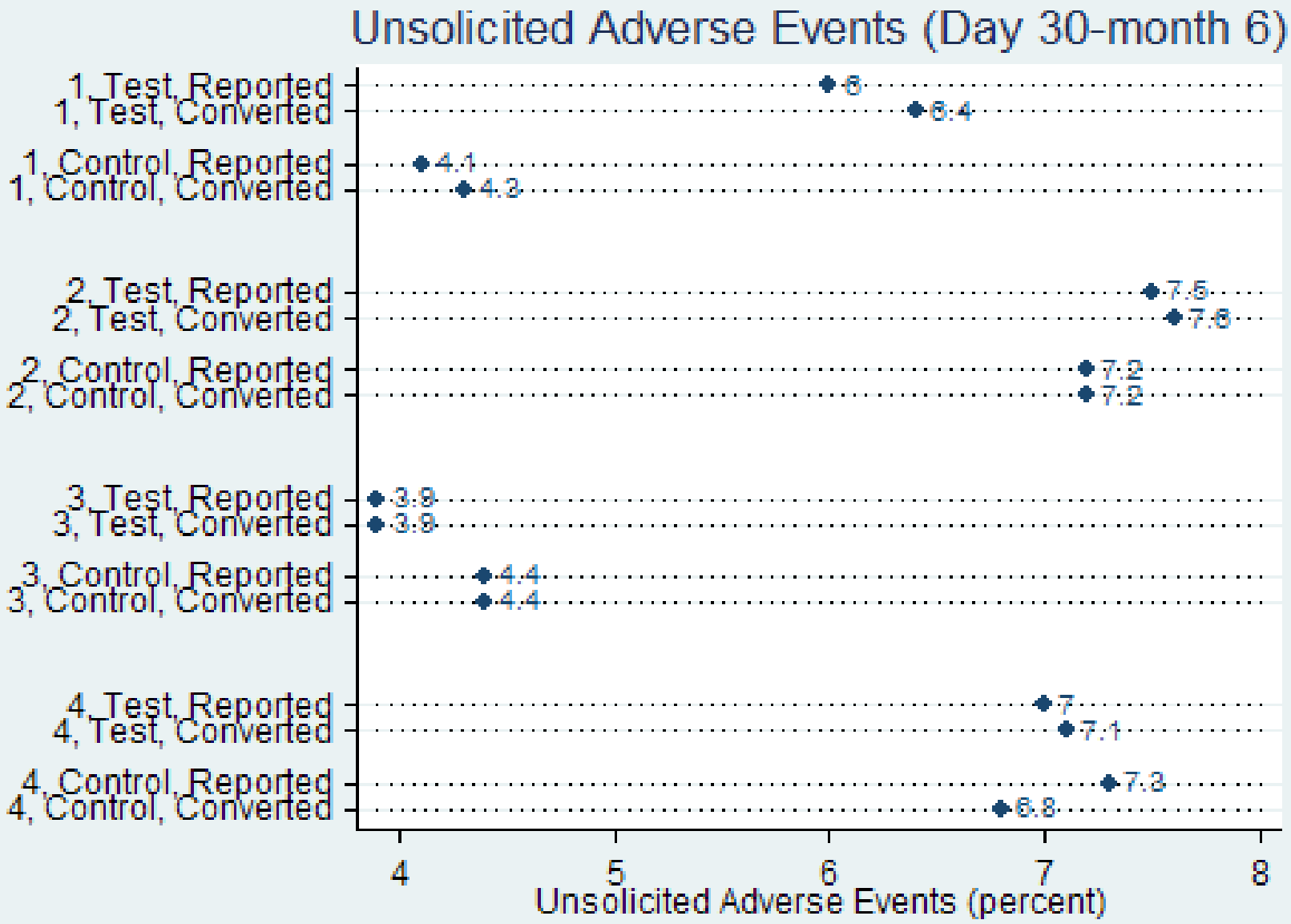
ADaM Datesets Created

- ADSL: Subject-Level Analysis Dataset
  - Including demographics, population indicators, treatment variables, trial dates, etc.
  - One line per subject
- ADAE: Analysis dataset for analyzing AE
  - ADSL
  - AE and SUPPAE
  - Multiple lines per subject

Reproducibility

- Repeat the tests reported in the original clinical study report to examine whether the conversion process has altered the data
- 100% match in the demographic profiles
- 100% match in the immediate reactions and all serious adverse events (day 1 – month 6) after the vaccination
- Small discrepancies in the unsolicited adverse event rate, differences mostly less than 1%

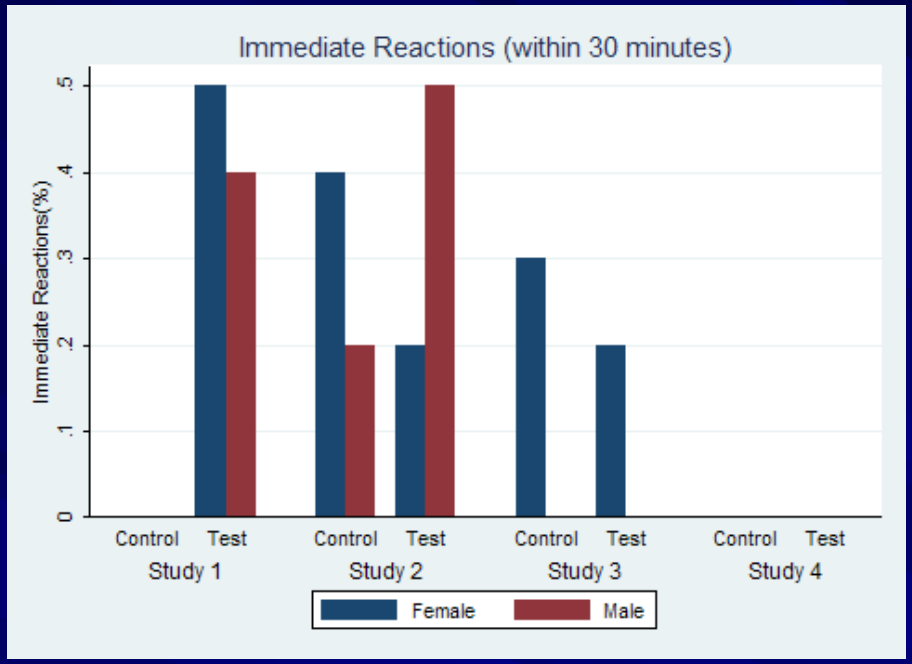

Unsolicited Adverse Events (Days 1-29)
1, Test, Reported
1, Test, Converted
1, Control, Reported
1, Control, Converted
2, Test, Reported
2, Test, Converted
2, Control, Reported
2, Control, Converted
3, Test, Reported
3, Test, Converted
3, Control, Reported
3, Control, Converted
4, Test, Reported
4, Test, Converted
4, Control, Reported
4, Control, Converted
37.5
36.3
38.4
38.6
26.6
26.5
23.5
23.5
33.9
33.3
31.4
30.9
24.9
24.7
22.7
22.6
20
25
30
35
40
Unsolicited Adverse Events (percent)

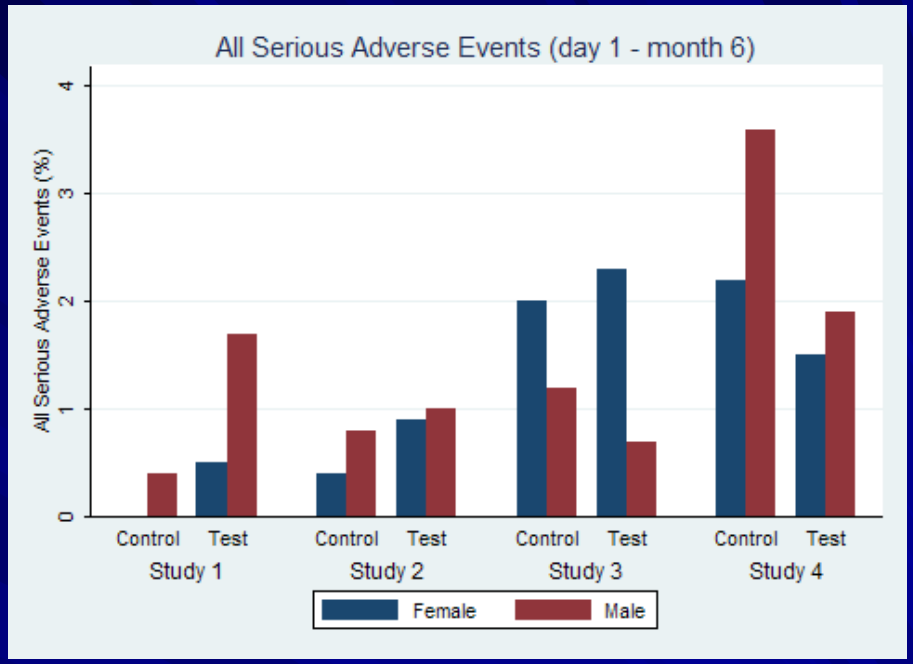

Unsolicited Adverse Events (Day 30-month 6)
1, Test, Reported
1, Test, Converted
1, Control, Reported
1, Control, Converted
2, Test, Reported
2, Test, Converted
2, Control, Reported
2, Control, Converted
3, Test, Reported
3, Test, Converted
3, Control, Reported
3, Control, Converted
4, Test, Reported
4, Test, Converted
4, Control, Reported
4, Control, Converted
6
6.4
4.1
4.2
7.5
7.6
7.2
7.2
3.8
3.8
4.4
4.4
7
7.1
7.3
6.8
4
5
6
7
8
Unsolicited Adverse Events (percent)

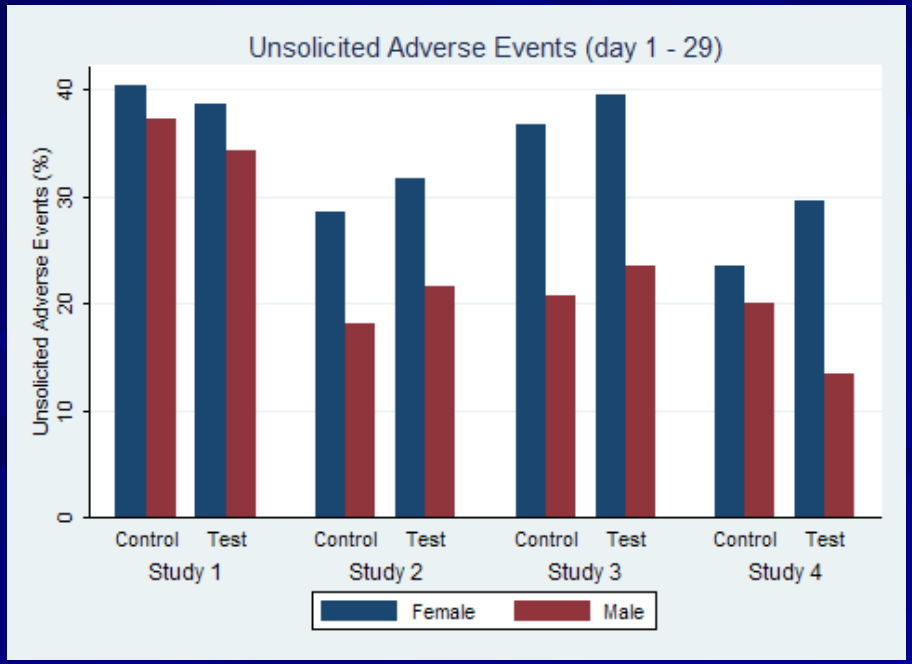
Issues in Analysis Datasets

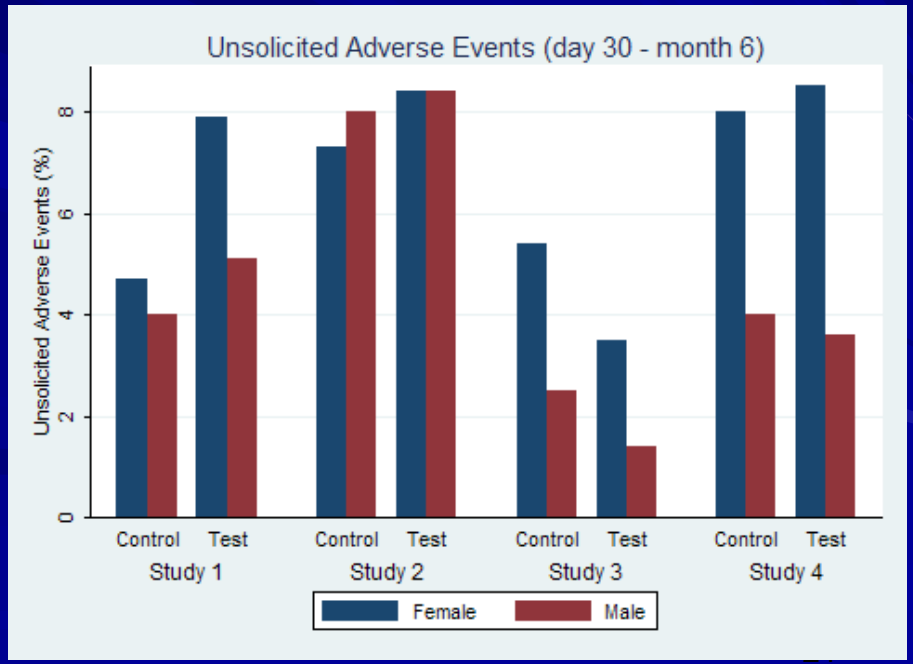
- Population flags
  - Usually defined in protocol
  - Protocol deviations were not in electronic form in the legacy datasets
  - Exceptions for protocol deviations also were not included in the electronic datasets
- Derived variables
  - Not well defined or referenced
  - Example: season

Results from the Pilot Sex Analyses


Immediate Reactions (within 30 minutes)
Immediate Reactions(%)
0
.1
.2
.3
.4
.5
Control
Test
Study 1
Study 2
Study 3
Study 4
Female
Male


All Serious Adverse Events (day 1 - month 6)
All Serious Adverse Events (%)
0
1
2
3
4
Control
Test
Study 1
Study 2
Study 3
Study 4
Female
Male


Unsolicited Adverse Events (day 1 - 29)
Unsolicited Adverse Events (%)
0
10
20
30
40
Control
Test
Study 1
Study 2
Study 3
Study 4
Female
Male


Unsolicited Adverse Events (day 30 - month 6)
Unsolicited Adverse Events (%)
0
2
4
6
8
Control
Test
Study 1
Study 2
Study 3
Study 4
Female
Male

Sex analysis

- None of the studies was powered for subgroup analysis
- It seems that female had higher AE than male for unsolicited adverse events
- It also seems that female had lower SAE than male for all serious AEs
- Hope the pooled study provides more info!

Future Possible Applications

- Subgroup analysis for sex, race, geographical regions, etc. on vaccine safety, efficacy, and immunogenicity

- Autoimmune diseases and genetic risk factors associated with autoimmune diseases following vaccination

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