Pooling, Grouping, Adjusting: A Statistician's Toolkit for Integrated Summary of Safety Development

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Operationalising ISS Reporting Sub-Team
(Safety Implementation Working Group)

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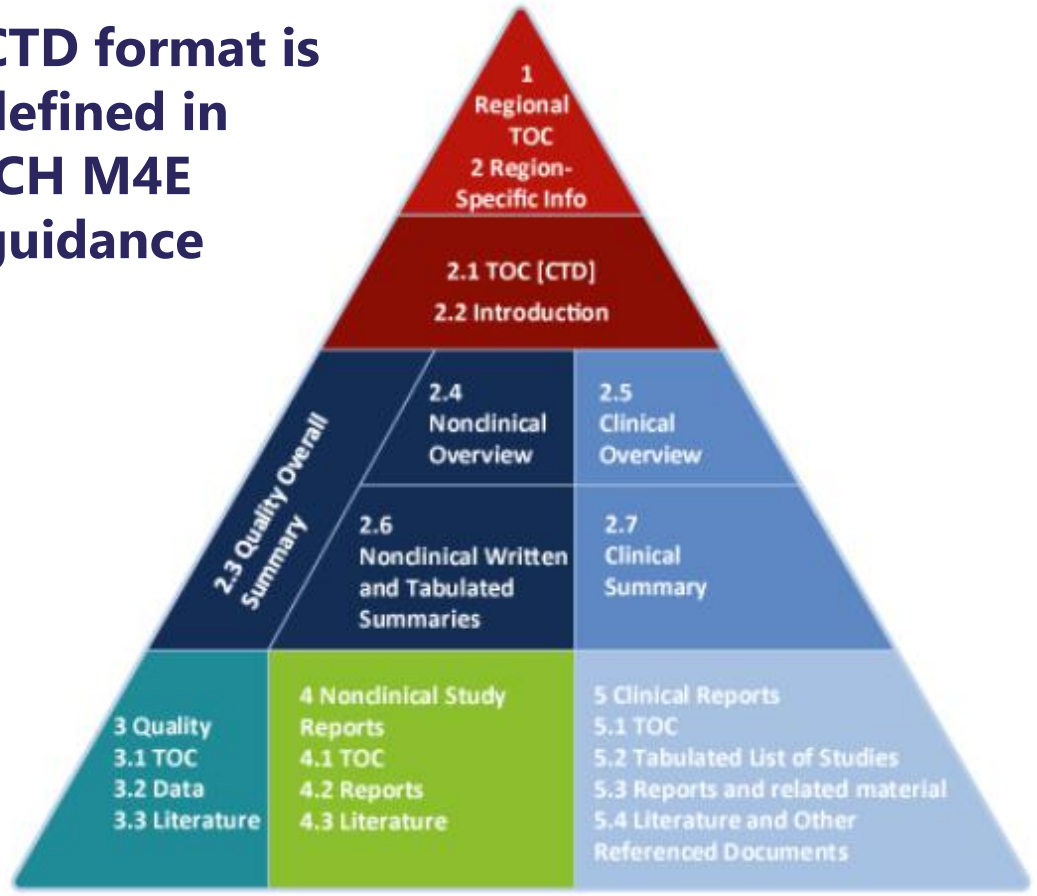
What is an Integrated Summary of Safety (ISS)

The Common Technical Document - Content

- CTD format is defined in ICH M4E guidance



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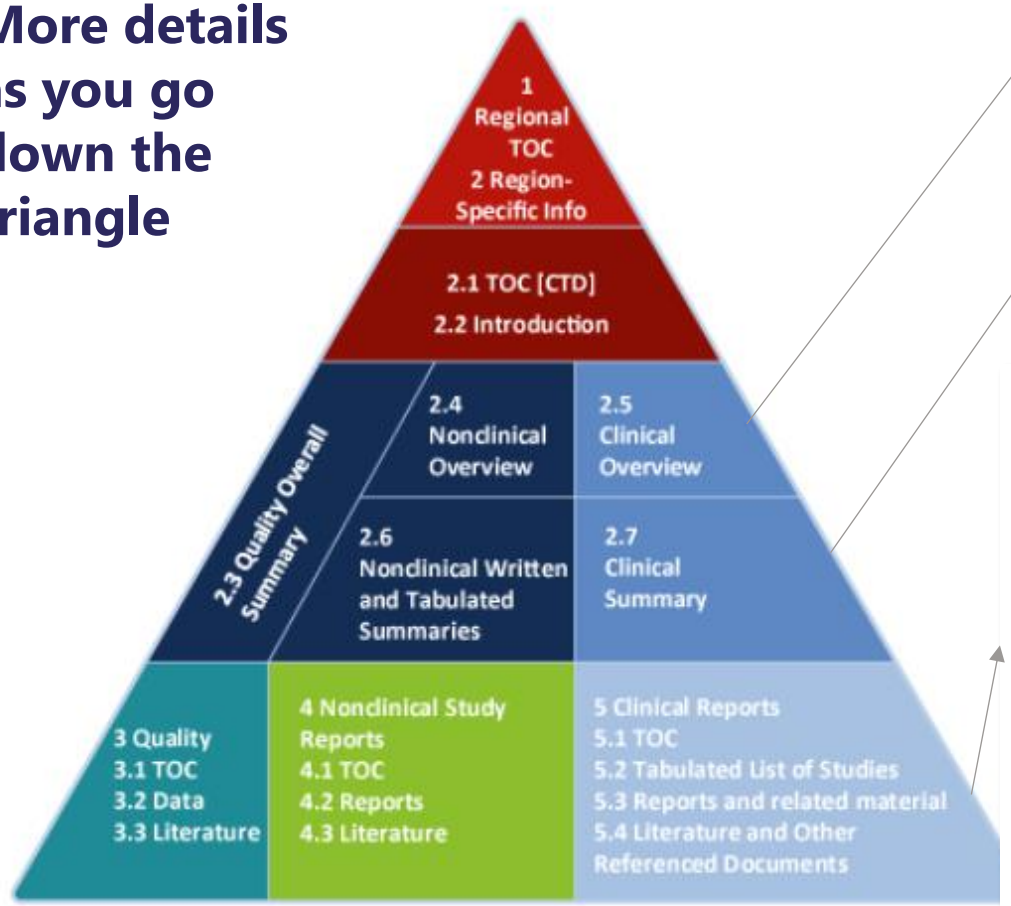
What is an Integrated Summary of Safety (ISS)

The Common Technical Document - Content

- **More details as you go down the triangle**



2.5 - Clinical Overview (CO)
- Critical summary of clinical data
- Benefits and Risks of new drug

2.7.4 - Summary of Clinical Safety
- Detailed factual summary of all the clinical information in the CTD (from individual reports or pooled/integrated analyses)

5.3.5.3 Reports of Analyses for more than one Study
→ Where the ISS goes

The ISS brings together in one place data and analyses pertinent to assess the safety of a new drug submitted to the regulatory authorities.

This often includes pooled analyses of safety data.

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Background to "Operationalizing ISS Reporting"

Florence Le Maulf,
Submissions Subject Matter Expert at Cytel

- Participated in > 25 submission projects within pharma or as CRO statistician
- ISS Statistical Analysis Plans for with many companies
  - Different methods across companies
  - Different requests from authorities
  - No guidance on best method for analyses/ situations
- No readily available info on how to implement in ISS SAP, SAS code, data displays…
- Every ISS SAP starting from scratch to decide how best to present/summarise integrated safety data

➔ Reached out to wider stats community via PSI

Operationalising ISS Reporting - Sub-team creation

- Outreach by **Naomi and Dooti** at PSI conference in Jun 2024 to start PSI Safety WG
- Safety Implementation Working Group started and introduced by Naomi at PSI 2025
- Operationalising ISS reporting introduced as sub-topic to be started after 2025
- Interest shown by PSI conference participants to participate in ISS sub-team to share best practice and develop guidance
- LinkedIn outreach to search for more volunteers, June 2025

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Operationalising ISS Reporting - Sub-team creation

Sub-team Kick Off Sept 2025

Katy White, UCB (UK)
Barbara Hendrickson, ex-AbbVie (US), safety physician
Ivana Lazik, GSK (UK)
Stéphanie Gautier, Cytel (France)
Elisa Cinconze, GSK (Italy)
Nancy Carpenter, MoonLake Immunotherapeutics (UK); participation on hold
Florence Le Maulf, Cytel (France)

Monthly meetings since Sept 2025

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Operationalizing ISS Reporting – List of Topics

Topics of Interest selected by sub-team

- What to Pool / **Pooling strategy**
- Why / How to calculate and present **study size adjusted AE** rates
- Why / How to calculate and present **exposure adjusted AE** rates
- Should **exposure adjustment** be done **for other safety data** (lab/vital signs)
- Recommendations for **grouping AE terms** / MedDRa versioning
- How to assess **trends over time/temporality**
- **Severity assessment** outside of oncology
- How to detect **rare events**
- How to define **Adverse Drug Reactions** / Quantitative methods for ADRs
- How to **leverage other data** (e.g. Other indications, external data …)
- **Safety estimands** recommendations

Operationalizing ISS Reporting – Step by Step

Step 1- For each topic, sub-team member regrouped literature/ guidelines relevant to topic and example ISS shells or SAP text

Step 2 – WG Review of available material

- **Many useful publications/ guidelines**
- **BUT very long** and **covering several topics** (e.g. ICH M4E guideline for the CTD content (section about Module 2.7.4, the Summary of Clinical Safety) and Phuse White paper on "Analysis and Displays Associated with Adverse Events: Focus on Adverse Events in Phase 2–4 Clinical Trials and Integrated Summary Documents").
- Available info **not always easy to find / visible** especially when looking into a single specific topic
- Often **no advice on best methods to use** but listing all possible methods and no **practical implementation** recommendations

Operationalizing ISS Reporting – Step by Step

Step 3- Decision to create a toolkit for ISS development for statisticians and clinicians

- **For each topic, the following is being done:**
  - Summary available literature/guidance (i.e. with refs, relevant sections/text extracts…)
  - Assess if there is already a consensus or methods. If not, summary of pros and cons of different options
  - Gather examples/recommended SAP text and shells/code to produce analysis/display
- **Summary docs to be reviewed by sub-team + Safety Implementation WG and maybe other groups before finalisation**

Step 4- Aim to share using PSI website (to be available to non-members) and inform community when ready

Example – Study Size Adjustment

STUDY SIZE ADJUSTMENT

Rationale for doing Study Size Adjustment in an ISS

Why do this at all

Explain why this may need to be done, focusing on the needs specific to ISS development; integration/pooling of safety data.

List available guidelines/industry recommendations to mention the need to do topic #1; include exact references e.g. guidelines/publications with exact section(s) where the need for <<topic #1>> is discussed so it can be used if required as reference/justification for example in ISS SAP or for discussion with the team working/deciding on the ISS.

When data are pooled from multiple studies to create an integrated summary and when the treatment-placebo randomization ratio is not constant across the studies included in the integrated summary and only crude percentages are calculated, then the review of data is subject to potential misinterpretations (eg. Simpson's paradox; [Crowe B. et al., 2016]). Creating visual displays or tables in which comparisons are confounded within study is discouraged. One method that has been proposed by Chuang-Stein and Beltangady [Chuang-Stein C et al., 2011] is to create "adjusted percentages". While there are multiple methods for creating adjusted percentages the inclusion of the study-size adjusted percentages in displays is encouraged [Crowe B. et al., 2016]. When the unadjusted percentages are impacted by such paradoxes, the adjusted percentages are likely to be more appropriate for summaries such as labeling.

Crowe B, Chuang-Stein C, Lettis S, Brueckner A. Reporting adverse drug reactions in product labels. Therapeutic Innovation & Regulatory Science, 2016, 50(4): 455-463.

Chuang-Stein C, Beltangady M. Reporting cumulative proportion of subjects with an adverse event based on data from multiple studies. Pharmaceutical Statistics, 2011, 10(1): 3-7.

Available methods and recommended approach for Study Size Adjustment in an ISS

What methods exists; best approach/consensus/ different scenarios

List publications/ guidelines for methods to do topic #1; include exact references.

Assess if there is already a consensus in the industry on best method to use depending on different scenarios for studies/data in ISS methods. If no consensus exists, summarise pros and cons of different options and provide recommendations.

Consider adding estimands considerations.

There are two primary approaches for reporting study-size adjusted cumulative proportions of subjects experiencing an adverse event (AE) when pooling data from multiple studies: the Cochran-Mantel-Haenszel (CMH) method and the study size-based (SS-based) method [Chuang-Stein C et al., 2011]. Both methods aim to address the potential impact of Simpson's Paradox, which can lead to misleading conclusions when naively pooling data.

CMH Method: this method utilizes weights that are proportional to the harmonic mean of the number of subjects in each treatment group within a study ($1/n_{1j} + 1/n_{2j}$).

Example – Study Size Adjustment

Example ISS SAP text for implementing Study Size Adjustment

5.X.X.2. Methodology for adjustment

Study-size adjusted cumulative proportions will be calculated for key adverse events and system organ classes (SOCs)/preferred terms (PTs) of interest. The primary method that will be considered for this adjustment is the Study Size-Based (SS-based) method. This method assigns weights to each study's observed AE proportion based on its total sample size. The adjusted cumulative proportion for treatment group *i* will be calculated as the weighted average of the study-specific proportions, where the weights are the percentages of participants in that study among the pooled population.

5.X.X.3. Analysis and Output

Study-size adjusted cumulative proportions will be calculated for all AEs of special interest (AESIs), all AEs leading to discontinuation, all serious adverse events (SAEs), and common AEs (occurring in ≥X% of any treatment group).

Tables will present the raw pooled cumulative proportions alongside the study-size adjusted cumulative proportions for each treatment group.

The tables will include the number of subjects at risk, the number of events and the unadjusted and adjusted percentages.

Example SAS code (and/or R code)

```
/* --- 1. Create Sample Data --- */
DATA ae_data;
   INPUT StudyID Treatment $ N_AE_Group N_Total_Group;
   DATALINES;
1 Drug_A 10 100
1 Placebo 5 100
2 Drug_A 20 500
2 Placebo 15 500
3 Drug_A 5 50
3 Placebo 3 50
;
RUN;

/* --- 2. Calculate Study-Specific Proportions (p_ij) --- */
DATA ae_data_props;
   SET ae_data;
   prop_ae_group = N_AE_Group / N_Total_Group; /* p_ij */
RUN;

/* --- 3. Calculate Total Subjects per Study (n_+j) --- */
PROC SQL;
   CREATE TABLE study_total_n_per_study AS
   SELECT
      StudyID,
      SUM(N_Total_Group) AS N_Total_Study
   FROM
      ae_data
   GROUP BY
      StudyID;
QUIT;
```

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Comments?

Suggestions?