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Enhancing ISS Analyses with Continuity-Corrected MH Method A SAS-Based Solution for Zero-Event Strata

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ABSTRACT

The Mantel–Haenszel (MH) method is a standard approach for estimating treatment effects in stratified analyses and is widely used in Integrated Summary of Safety (ISS) submissions. However, zero-event strata, common scenario in rare adverse, poses challenges, as SAS PROC FREQ does not natively support continuity correction, which potentially leads to biased risk differences and ultimately impact regulatory conclusions. To address this, we developed a custom SAS macro that applies the Haldane–Anscombe correction by adding 0.5 to all cells in any stratum with zero counts, with optional exclusion of double-zero event strata, and output more accurate CMH statistics. Applied to ISS datasets, this approach stabilized estimates of risk differences, reduced bias toward the null, and aligned with regulatory expectations. Our solution offers a practical, reproducible method for handling sparse data in safety analyses, bridging a critical gap in standard software and supporting robust regulatory reporting.

INTRODUCTION

In practice, the Integrated Summary of Safety (ISS) adopts the Mantel–Haenszel (MH) framework by treating each clinical study (STUDYID) as an independent stratum. This structure enables treatment comparisons to be conducted within individual strata and then combined across studies, while appropriately accounting for differences in baseline risk and sample size. Nevertheless, rare adverse events are common in clinical trials and frequently give rise to single- or double-zero cells in study-level 2×2 contingency tables. Such sparse event structures can undermine the stability of conventional stratified pooling procedures and substantially increase the complexity of quantitative evidence synthesis. Within this setting, the MH method remains a foundational approach for aggregating study-specific effects across predefined strata, yielding consistent pooled estimates while explicitly adjusting for stratification factors such as study identifier and treatment arm. Depending on the effect measure, the pooled estimate may be interpreted on an absolute scale—via the risk difference (RD)—or on a relative scale—via the risk ratio (RR) or odds ratio (OR).

A persistent methodological difficulty arises when one or both study arms contain zero events. Common meta-analytic practice often retains single-zero studies but excludes double-zero studies. However, excluding such studies reduces the total weight of the analysis without reducing the numerator, thereby systematically shifting the combined RD away from zero and causing first-order bias. Conversely, retaining these studies can render relative-scale estimators such as the RR and OR undefined, prompting routine use of continuity corrections—for example, adding 0.5 to all cells of a zero-event stratum.

In contrast, within the MH framework, the RD can be estimated without continuity correction when single- or double-zero cells occur, and zero-subject strata contribute no information (i.e., weight zero) to the pooled RD should be excluded. This observation motivates a careful examination of how continuity correction affects RD estimation in sparse-event meta-analyses. In MH analyses, omitting the continuity correction typically yields narrower confidence intervals relative to analyses that apply the correction. Although the continuity correction is computationally convenient, it artificially introduces data and can distort effect estimates, with particularly pronounced impacts on absolute-scale measures such as the risk difference.

MANTEL-HAENSZEL METHOD

The Mantel–Haenszel method is widely used in meta-analysis to estimate a pooled effect size—such as an odds ratio, risk ratio, or risk difference—across multiple studies [1]. The risk difference reflects the treatment effect on an absolute scale by comparing the event rates between two groups, whereas the risk or odds ratio quantifies the effect on a relative scale by taking the ratio of the event rates or odds.

	Event	No Event	sum
Active	A	B	A+B
Control	C	D	C+D

Effect Measures	Definition	Interpretation
Relative Risk (RR)	$\frac{\frac{A}{A+B}}{\frac{C}{C+D}}$	RR=1: No association between exposure and outcome. RR < 1: Exposure decreases risk (protective effect). RR > 1: Exposure increases risk (risk factor).
Odds Ratios (OR)	$\frac{\frac{A}{B}}{\frac{C}{D}}$	OR = 1: No association between exposure and outcome. OR < 1: Exposure is associated with lower odds (protective effect). OR > 1: Exposure is associated with higher odds (risk factor).
Risk Difference (RD)	$\frac{A}{A+B} - \frac{C}{C+D}$	RD = 0: No difference in risk between the exposed and control group. RD < 0: Exposure decreases risk (protective effect). RD > 0: Exposure increases risk (harmful effect).

Table 1 Pool Effect Estimates from 2×2 Tables, along with the Definitions and Interpretations of the corresponding Effect Measures.

CALCULATION PROCEDURE

The Mantel–Haenszel estimator can be expressed as a weighted average of the effect size estimates from the individual strata. Unlike the inverse-variance method, whose weights are derived from the reciprocals of the variances of the study-specific estimates, the Mantel–Haenszel weight reflects the amount of information each stratum contributes, typically driven by sample size and variability. The Mantel–Haenszel (MH) method provides a pooled estimate of the treatment effect across multiple strata while accounting for stratification factors [2,3]. To illustrate the procedure, we describe the calculation steps using the risk difference (RD) as the effect measure.

Stratum I	Event	No Event	Total
Active	a_i	b_i	n_{1i}
Control	c_i	d_i	n_{0i}
Total	m_i	n_i	T_i

Table 2 Stratified 2×2 Tables for Risk Difference Calculation

For each stratum, the stratum-specific risk difference is computed as $RD_i = \frac{a_i}{n_{1i}} - \frac{c_i}{n_{0i}}$, which represents the absolute difference in event probabilities between the treatment and control groups. The Mantel–Haenszel weight for risk difference is then calculated as $w_i = \frac{n_{1i} \cdot n_{0i}}{T_i}$, allowing each stratum to contribute proportionally based on the sizes of its treatment and control arms. The pooled Mantel–Haenszel risk difference is obtained as a weighted average of the stratum-specific estimates, $RD_{MH} = \frac{\sum_i w_i \left(\frac{a_i}{n_{1i}} - \frac{c_i}{n_{0i}}\right)}{\sum_i w_i}$, yielding an overall absolute effect estimate adjusted for stratification. The variance of the pooled estimate is computed using $Var(RD_{MH}) = \frac{\sum_i w_i^2 Var(RD_i)}{(\sum_i w_i)^2}$, where $Var(RD_i) = \frac{a_i b_i}{n_{1i}^3} + \frac{c_i d_i}{n_{0i}^3}$. The standard error follows as $SE(RD_{MH}) = \sqrt{Var(RD_{MH})}$, and the 95% confidence interval is constructed as $RD_{MH} \pm 1.96 \times SE(RD_{MH})$.

ZERO EVENT AND CONTINUITY CORRECTIONS

When event rates are low, it is common for studies to observe no events of interest in one or both study arms, resulting in so-called single- or double-zero events. Given the prevalence of such studies, their treatment in meta-analysis has been widely discussed, with common practice being to retain single-zero studies while excluding double-zero events from the analysis. However, excluding double-zero events can introduce first-order bias. On the other hand, the inclusion of single- or double-zero events in meta-analysis often leads to situations in which the denominator becomes zero when calculating pooled effect measures such as the odds ratio (OR) or risk ratio (RR), making the effect estimates impossible to compute directly. A commonly used approach to address this issue is to include zero-total-event trials by applying a standard continuity correction of 0.5 [4], a method more typically used for studies with zero events occurring in only one arm [5,6].

DOUBLE ZERO EVENT

The primary rationale for excluding double-zero events—those with no events in either the treatment or control arm—when pooling effect measures such as the risk difference (RD), risk ratio (RR) or odds ratio (OR) is that these trials do not contribute to the magnitude of the estimated treatment effect [5,6]. However, excluding these studies reduces the total weight without reducing the numerator, which systematically pushes the combined effect measures away from zero and introduces first-order bias. As a result, some researchers argue that zero-total-event trials should be included in meta-analyses “to account for the sample sizes of these studies” [7].

ZERO SUBJECT

A zero-subject stratum refers to a stratum in which the total number of participants in one or both treatment arms is zero. In such cases, the stratum should be removed from the analysis for two reasons. First, when a continuity correction is applied—such as adding 0.5 to all cells, the procedure effectively fabricates information. This can produce an artificial risk difference of approximately 0.5 for the active arm, which is entirely spurious given that the true number of subjects in the stratum is zero, which is shown in following table 3. Second, before continuity correction is applied, the stratum receives a weight effector of zero because its total sample size is zero for Active. As shown in the CALCULATION PROCEDURE section above, it therefore contributes no information to the estimation of the effect measures.

Stratum I	Event/ with continuity correction	No Event/ with continuity correction	Sum/ with continuity correction
Active	0/0.5	0/0.5	0/0.5+0.5=1
Control	C	D	C+D

Table 3 Stratified 2×2 Tables for Zero Subject on Active Arm.

SAS BASED MACRO

To illustrate this topic, we constructed an example dataset as a dummy CDISC ADAM ADAE dataset (see Table 4). The variable TRT01A was used to store treatment assignments and delineate analysis groupings, while stratification attributes were operationalized through the study identifier (STUDYID). To simplify exposition, we assumed Headache as the sole preferred term (PT). Notwithstanding this simplification, the provided SAS code remains applicable without modification to analyses involving more than one preferred term.

	STUDYID	SUBJID	TRT01A	AEDECOD	AEBODSYS	ASTDT	AENDT	GRP	TRT01AN
1	101	0001	Treatment1	Headache	Nervous system disorders	08FEB2018	11FEB2018	1	1
3	101	3030	Treatment3	Headache	Nervous system disorders	14AUG2018	14AUG2018	3	3
4	101	3030	Treatment3	Headache	Nervous system disorders	16AUG2018	16AUG2018	3	3
5	101	3090	Treatment3	Headache	Nervous system disorders	21AUG2018	21AUG2018	3	3
6	101	3120	Treatment3	Headache	Nervous system disorders	23AUG2018	23AUG2018	3	3
7	102	1002	Treatment4	Headache	Nervous system disorders	11SEP2019	12SEP2019	4	4
8	102	1005	Placebo	Headache	Nervous system disorders	14SEP2019	14SEP2019	5	5
9	102	2003	Treatment4	Headache	Nervous system disorders	05OCT2019	06OCT2019	4	4
10	102	3002	Placebo	Headache	Nervous system disorders	22OCT2019	22OCT2019	5	5
11	102	3004	Treatment4	Headache	Nervous system disorders	26OCT2019	26OCT2019	4	4
12	107	0002	Treatment3	Headache	Nervous system disorders	30JUL2021	30JUL2021	3	3
13	108	0023	Treatment3	Headache	Nervous system disorders	24FEB2022	24FEB2022	3	3
14	109	1014	Treatment4	Headache	Nervous system disorders	05APR2023	05APR2023	4	4
15	109	2024	Treatment4	Headache	Nervous system disorders	26MAY2023	27MAY2023	4	4
16	109	2027	Treatment4	Headache	Nervous system disorders	23JUN2023	24JUN2023	4	4
17	109	2028	Treatment4	Headache	Nervous system disorders	26MAY2023	26MAY2023	4	4
18	110	1051	Treatment3	Headache	Nervous system disorders	12JAN2022	13JAN2022	3	3
19	110	1064	Treatment3	Headache	Nervous system disorders	28JAN2022	28JAN2022	3	3
20	110	1084	Treatment4	Headache	Nervous system disorders	25FEB2022	25FEB2022	4	4

Table 4 ADAE Dataset with Stratification Variable

Step1: Create dummy table with total subjects in different STUDYID.

To enable the construction of the final 2×2 contingency table, we first computed the count of distinct subjects (USUBJID) by treatment and study (STUDYID) from Adam ADSL and then generated a bridging dummy dataset (dummy6) as it is shown in following Table 5. The motivation for creating this dummy dataset arises from the fact that certain studies may exhibit no adverse events, as illustrated by Studies 103 and 104 in Table 5. Despite the absence of events, these studies have non-zero sample sizes and should be incorporated into the analysis. Failure to include them would result in the exclusion of entire studies, thereby introducing bias into the pooled estimates.

DEN1	DEN2	DEN3	DEN5	DEN4	N1	N2	N3	N4	N5	TEXT	STUDID
44	6	18	16	0	0	0	0	0	0	Headache	101
0	0	0	12	30	0	0	0	0	0	Headache	102
0	0	6	0	0	0	0	0	0	0	Headache	103
0	0	24	0	0	0	0	0	0	0	Headache	104
0	0	26	0	0	0	0	0	0	0	Headache	107
0	0	36	0	0	0	0	0	0	0	Headache	108
0	0	0	28	36	0	0	0	0	0	Headache	109
0	20	18	18	18	0	0	0	0	0	Headache	110

Table 5 Dummy Dataset

Step2: In the subsequent step, the ADAE dataset is parsed to compute, for each STUDYID, both the total number of events and the total number of subjects.

	STAT	N1	N2	N3	N4	N5	DEN1	DEN2	DEN3	DEN4	DEN5	TEXT
1	stat_n__1-101	1		4			44	6	18	0	16	Headache
2	stat_n__1-102				3	2	0	0	0	30	12	Headache
3	stat_n__1-107			1			0	0	26	0	0	Headache
4	stat_n__1-108			1			0	0	36	0	0	Headache
5	stat_n__1-109				4		0	0	0	36	28	Headache
6	stat_n__1-110			2	1		0	20	18	18	18	Headache

Table 6 Counting Result for Each STUDYID

Step3: Create 2*2 analysis table with continuity correction for zero events. The pooled estimates for Treatment 1 vs Placebo, as well as the results obtained after applying the continuity correction, are summarized in Table 7.

```
%let ntrt=5;
%let nloop=%eval(&ntrt-1);
%macro pci;
 %do i=1 %to &nloop.;
   data cnt_all; set stat_n__:;
      if n&i=. then n&i=0;
      if n&ntrt.=. then n&ntrt.=0;
      keep STUDYID text n&i n&ntrt. den&i den&ntrt.;
      proc sort;
        by STUDYID TEXT n&i n&ntrt. den&i den&ntrt.;
      run;
    data cnt_all3;
        set cm_all_.
        if den&i.=0 or den&ntrt. =0 then delete;
        if n&i.=0 or n&ntrt. =0 then do;
          n&i.=n&i.+0.5; n&ntrt. =n&ntrt. +0.5;
          den&ntrt. =den&ntrt. +1; den&i.=den&i.+1;
             grp=1; count=n&i.;       aval=1; output;
             grp=1; count=den&i.-n&i.; aval=2; output;
             grp=2; count=n&ntrt.;       aval=1; output;
             grp=2; count=den&ntrt. -n&ntrt.; aval=2; output;
        end;
        else do;
             grp=1; count=n&i.;          aval=1; output;
             grp=1; count=den&i.-n&i.;   aval=2; output;
             grp=2; count=n&ntrt.; aval=1; output;
             grp=2; count=den&ntrt. -n&ntrt.; aval=2; output;
        end;
      run;
 %mend;
```

DEN1	DEN5	N1	N5	TEXT	STUDID
44	16	1	0	Headache	101
0	12	0	2	Headache	102
0	0	0	0	Headache	103
0	0	0	0	Headache	104
0	0	0	0	Headache	107
0	0	0	0	Headache	108
0	28	0	0	Headache	109
0	18	0	0	Headache	110

	DEN1	DEN5	N1	N5	TEXT	GRP	COUNT	AVAL	STUDID
1	45	17	1.5	0.5	Headache	1	1.5	1	101
2	45	17	1.5	0.5	Headache	1	43.5	2	101
3	45	17	1.5	0.5	Headache	2	0.5	1	101
4	45	17	1.5	0.5	Headache	2	16.5	2	101

Table 7 Pooled estimates for Treatment 1(up) and corresponding continuity-corrected estimates(down)

Step4: Estimate effect size measurements.

```
ods output CommonRelRisks=cmh_rr commonpdiff=cmh_rd
CommonPdiffTests=cmh_pval;
proc freq data=cnt_all3 order=data; by text;
   tables STUDYID*grp*aval/ nocol nopercent cmh relrisk riskdiff(common)
   commonriskdiff(TEST=MH CL=MH);
   weight count/zeros;
run;
```

CONCLUSION

For the estimation of odds ratios (OR) and risk ratios (RR), a continuity correction—typically the addition of 0.5—is commonly applied to address zero-event issues and enable subsequent pooled-effect calculations. However, as

indicated in the CALCULATION PROCEDURE section, the Mantel–Haenszel approach can incorporate studies with single-zero cells even without applying a continuity correction, and studies with double-zero cells do not affect the inference for the risk difference (RD).

Treatment 1-4	With Continuity Correction	Without Continuity Correction	Risk difference CI Range with(L) and without(R) Continuity Correction
1	0.4 (-9.2, 10.0)	2.3 (-2.1, 6.7)	19.2/8.8
2	1.2 (-8.0, 10.4)	0.0 (0.0, 0.0)	18.4/0
3	15.5 (2.1, 28.9)	16.5 (4.4, 28.6)	26.8/24.2
4	4.7 (-4.2, 13.6)	5.0 (-3.2, 13.3)	17.8/16.5

Table 7 Risk Differences and CI Range for Different Treatments with and without Continuity Correction

In this study, we compared pooled estimates of the risk difference (RD) with and without continuity correction under scenarios involving single- or double-zero-event data to evaluate the impact of this adjustment in sparse-event settings. In Mantel–Haenszel meta-analyses, omitting the continuity correction yields a narrower confidence interval, relative to analyses that apply the correction. Because a narrower confidence interval reflects greater stability of the RD estimate, smaller variance, higher statistical efficiency, and clearer clinical interpretability, investigators generally prefer the interval to be as narrow as possible. Accordingly, when using the Mantel–Haenszel method, the need for a continuity correction in RD analyses should be considered with caution.

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