

Electronic Supplemental Material (ESM)

Article Title:

Individual Case Safety Report Replication: An Analysis of Case Reporting Transmission Networks

Journal Name:

Drug Safety

Authors:

John van Stekelenborg, PhD¹

Vijay Kara, MSc²

Roman Haack, MaHM³

Ulrich Vogel, MD⁴

Anju Garg, MD⁵

Markus Krupp, PhD⁶

Kate Gofman, MD, PhD⁷

Brian Dreyfus, MPH⁸

Manfred Hauben, MD, MPH⁹

Andrew Bate, PhD¹⁰

Author Affiliations:

¹Global Medical Safety, Janssen, the Pharmaceutical Companies of Johnson & Johnson, Horsham, Pennsylvania, United States

²Global Safety, GSK, 980 Great West Road, Brentford, UK

³Bayer AG, Pharmacovigilance Analytics, Berlin, Germany

⁴Global Patient Safety & Pharmacovigilance, Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany

⁵Safety Analyses Innovation and Submission Readiness Lead, Global Pharmacovigilance, Sanofi, Bridgewater, New Jersey, United States

⁶Merck Healthcare KGaA, Global Patient Safety, Darmstadt, Germany

⁷Global Patient Safety Physician, CMO Patient Safety, CVRM Unit, AstraZeneca, Gaithersburg, MD, USA

⁸Epidemiology Lead for Integrated Oncology, Bristol-Myers Squibb Company, Princeton, New Jersey, United States

⁹Pfizer Inc, New York, NY, USA; NYU Langone Health, Department of Medicine, New York, NY, USA; and Pfizer Inc, New York, NY, USA

¹⁰Global Safety, GSK, Brentford, UK; Department of Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, UK; Department of Medicine at NYU Grossman School of Medicine, New York, USA

Corresponding Author:

John van Stekelenborg, PhD (ivanstek@its.inj.com)

Additional Results – Table ESM1

Mean Average Number of Recipients by Case Version Number and Specific Case Attributes

Version	Mean ANR*					
	ALL	Spontaneous	HCP Confirmed	Serious	Unlisted	Literature
1	2.90	2.95	3.22	4.33	3.46	4.01
2	3.31	3.38	3.67	4.33	3.85	4.40
3	3.30	3.40	3.73	4.00	3.78	4.83
4	3.31	3.43	3.65	3.95	3.76	5.13
5	3.30	3.43	3.57	3.82	3.78	5.66
>5	3.55	3.91	3.72	3.88	3.98	6.09

ANR = average number of recipients; HCP = health care professional; MAH = marketing authorization holder.

*Mean of the 7 MAH ANR values

Additional Results – Table ESM2

Median Percentage of Case Versions by Case Attribute for 7 TransCelerate MAHs

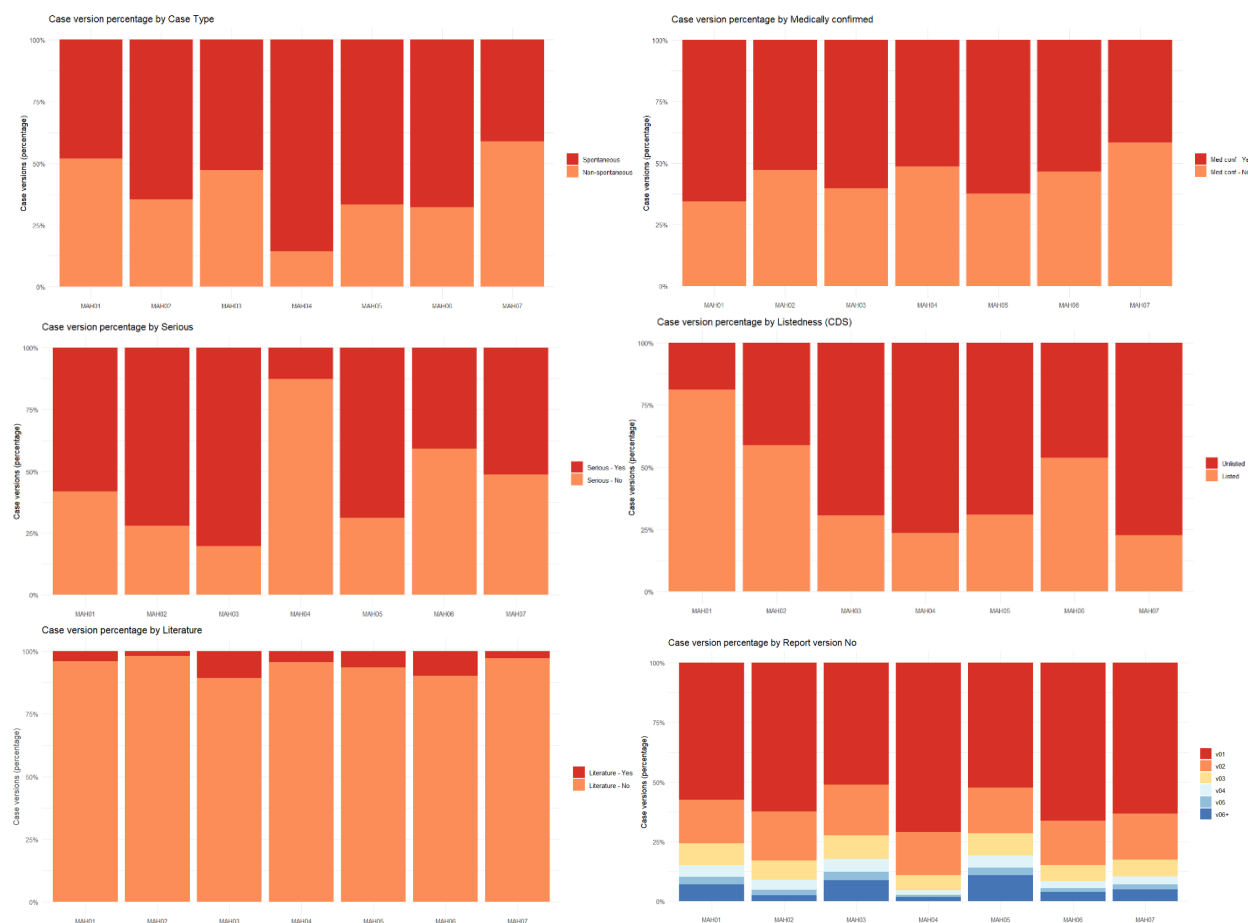
Case Attribute	Median Percentage
Case Type - Spontaneous	64.6%
Case Type – Non-spontaneous	35.4%
HCP Confirmed - Yes	53.3%
HCP Confirmed - No	46.7%
Seriousness – Serious	58.1%
Seriousness – Non-serious	41.9%
Listedness - Listed	30.9%
Listedness – Unlisted	69.1%
Literature – Yes	5.4%
Literature - No	94.6%
Version 1	62.4%
Version 2	19.2%
Version 3	8.2%
Version 4	4.2%
Version 5	2.3%
Version 6+	4.9%

HCP = health care professional; MAH = marketing authorization holder.

Note: These are medians taken across 7 MAHs and do not necessarily add up to 100%.

Additional Results – Figure ESM1

Case Version Percentage for the 7 TransCelerate MAHs Stratified by Case Attribute



CDS = core data sheet; HCP = health care professional; MAH = marketing authorization holder; v = version.

Additional Results – Table ESM3

Qualitative Summary of Case Version Volume and Extent of Replication (ANR) by Case Attribute

TYPE	Extent of replication
SPONTANEOUS	MEDIUM
NON-SPONTANEOUS	MEDIUM
MEDICALLY CONFIRMED - YES	MEDIUM
MEDICALLY CONFIRMED - NO	LOW
SERIOUS	HIGH
NON-SERIOUS	LOW
UNLISTED	HIGH
LISTED	LOW
LITERATURE - YES	HIGH
LITERATURE - NO	MEDIUM

DEFINITION:

HIGH: > 3.5 recipients

MEDIUM: between 3 and 3.5 recipients

LOW: < 3 recipients

ANR = average number of recipients.

Mathematical Details of the Submission Selectivity Measure

- **Rmax:** the maximum number of recipients for a case version, e.g., for a given case, 5 recipients received version 3, which is the highest submission number (Rmax = 5).
- **R_i:** Number of HA recipients for version i, e.g., version 1 was submitted to 3 HAs (R₁ = 3).
- **DR_i = Rmax - R_i:** the difference between the maximum number of recipients and recipient of version i. Continuing the example, DR₁ = 2, as version 1 was received by 3 HAs, which is 2 less than the maximum of 5 recipients for version 3.
- **v_i = DR_i/Rmax:** This is the single case variation for version i. In the example, v₁ = 2/5 = 40%. This means that version 1 for the case of interest was received by 40% fewer recipients than the version sent to the highest number of HAs.
- The submission selectivity **S_i** for version i for all cases is calculated as:

$$S_i = \sum_{j=1}^N \frac{\Delta R_{ij}}{R_{\max_j}} / N$$

where the subscript j denotes the case, running from 1 to N; N is the number of cases, and i denotes the version.

Note that non-submitted versions are excluded from the calculation.

Data Collection Table 1: Descriptive Submitted Case Version Volume Statistics

	MAH ₀₁	MAH ₀₂	MAH ₀₃	MAH ₀₄	MAH ₀₅	MAH ₀₆	MAH ₀₇
Total Number of Case Versions							
Number of Case Versions by Case Type							
Spontaneous							
Non-Spontaneous							
Number of Case Versions Confirmed by HCP							
Yes							
No							
Number of Case Versions by Seriousness							
Yes							
No							
Number of Case Versions by Listedness (CDS)							
Unlisted							
Listed							
Number of Case Versions by Literature							
Yes							
No							
Number of Case Versions by Version							
1							
2							
3							
4							
5							
>5							

The above table is referred to in the paper as **Data output 1** (case version volume), which includes:

- Number of case versions, stratified by the 5 stratification variables
- Number of case versions by version number from version 1 through 5 and aggregated for versions higher than 5.

Table Collection Table 2: Average Number of Recipients per Submission by Version

Version	1	2	3	4	5	>5
Average No of Health Authority (HA) Recipients						
Average No of HA Recipients by Case Type						
Spontaneous						
Non-Spontaneous						
Average No of HA Recipients Confirmed by HCP						
Yes						
No						
Average No of HA Recipients by Seriousness						
Yes						
No						
Average No of HA Recipients by Listedness (CDS)						
Unlisted						
Listed						
Average No of HA Recipients by Literature						
Yes						
No						

The above table is referred to in the paper as **Data output 2** (replication), which includes:

- The average number of HA recipients of submissions by case version, for versions 1 through 5
- The average number of HA recipients of submissions for versions 6 or higher
- The average number of HA recipients as above, stratified by the 5 case attributes.
- Full distribution: count of case versions submitted as a function of the number of HA recipients (note: 5 of 7 MAHs provided this data)

Data Collection Table 3: Variation Relative to Most Widely Distributed Version

MAH #	Report Version	1	2	3	4	5	6	7	8	9	10
MAH ₀₁	Variation (%)										
MAH ₀₂	Variation (%)										
MAH ₀₃	Variation (%)										
MAH ₀₄	Variation (%)										
MAH ₀₅	Variation (%)										
MAH ₀₆	Variation (%)										
MAH ₀₇	Variation (%)										

The above table is referred to in the paper as **Data output 3** (submission selectivity), which includes:

- Submission Selectivity Measure by case version

Data Collection Table 4: Overlap of Company Safety Databases

Unique Case Count	Percent of Unique Cases	Case Count (i.e., Number of Unique Cases x Number of Databases)	Percent of Cases

The above table is referred to in the paper as **Data output 4** (MAH overlap), which includes:

- Percentage of case versions residing in 2 or more participating MAH Safety Databases (see section 3.5 below)