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REVIEW

A Risk-Based Approach for Safety Case Follow-up of Adverse Event Reports in Pharmacovigilance

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ABSTRACT

This study presents an analysis of follow-up attempts for adverse event (AE) reports, shedding light on the characteristics of a risk-based approach to Individual Case Safety Report (ICSR) follow-up by Marketing Authorization Holders (MAH). The analysis primarily focuses on Spontaneous Reports (SR), reports from Patient Support Programs (PSPs), and literature, utilizing data from safety reports sourced from the European Economic Area (EEA) during the pre-pandemic period. Through descriptive statistics, we examine response rates spanning 1 year and compare various types of cases based on distinct ICSR features, including serious vs non-serious, listed vs unlisted, suspected vs not-suspected, SR vs PSP vs literature, as well as comparisons between different product categories (innovator, biological, generics, and combinations). The objective of this report is to stimulate further dialogue within the industry and regulatory authorities regarding the adoption of a risk-based approach to ICSR follow-up procedures.

Keywords: Adverse drug reaction; Adverse event; Causality; Council for International Organizations of Medical Sciences; Good Pharmacovigilance Practices; Listedness; Pharmacovigilance; Seriousness

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Key Summary Points

Globally, pharmacovigilance (PV) regulations offer only a limited framework for conducting follow-up activities on ICSRs. While the field of PV has seen advancements over time, including the emergence of new sources for solicited data collection, recommendations regarding the collection of follow-up information for ICSRs have not progressed at the same rate.

Given the limited ICSR follow-up framework available, MAHs are compelled to develop their follow-up procedures based on existing guidance and previous PV inspections.

The primary goal of this study is to catalyze discussions among industry stakeholders and regulatory authorities. We aim to foster conversations about the diverse approaches adopted by different companies, emphasizing the need to consider qualitative aspects in follow-up attempts and advocating for a risk-based approach to ICSR follow-ups, guided by our observations.

INTRODUCTION

In the field of pharmacovigilance (PV), adverse event (AEs), or adverse drug reactions (ADRs) encompass any untoward medical occurrence in a patient or clinical investigation subject who has been administered a pharmaceutical product, even if it does not necessarily have a causal relationship with the treatment received [1]. An Individual Case Safety Report (ICSR) serves as the standardized format for submitting individual reports of AEs or ADRs associated with medicinal products that occur in a single patient at a specific point in time. A valid ICSR should encompass at least one identifiable reporter, one single identifiable patient, at least one suspected adverse reaction, and at least one suspected medicinal product [2].

The procedures for handling ICSRs typically include the elements shown in Fig. 1.

Data Collection

The process begins with the collection of relevant information related to the AE. This includes details about the patient (age, gender, medical history), the suspected medicinal product, the AE itself (description, date of onset, severity), and the reporter's contact information.

Triage and Initial Assessment

Upon receipt of an ICSR, there is often a triage and initial assessment step to determine its seriousness and whether it requires immediate attention. Serious events, such as those leading to hospitalization or death, are typically prioritized.

Full Data Entry

The collected information is entered into a PV database or system. This data entry must be accurate and standardized to ensure consistency and enable efficient analysis. This includes specific medical coding systems, such as drug dictionaries and the Medical Dictionary for Regulatory Activities (MedDRA) used to classify and code the AE terms and medical conditions reported in the ICSR. A narrative description of the AE is generated. This narrative provides a detailed account of the event, including its timeline and relevant clinical information.

Quality Check

A quality check as needed is performed to ensure that all required information has been captured accurately and that there are no data entry errors.

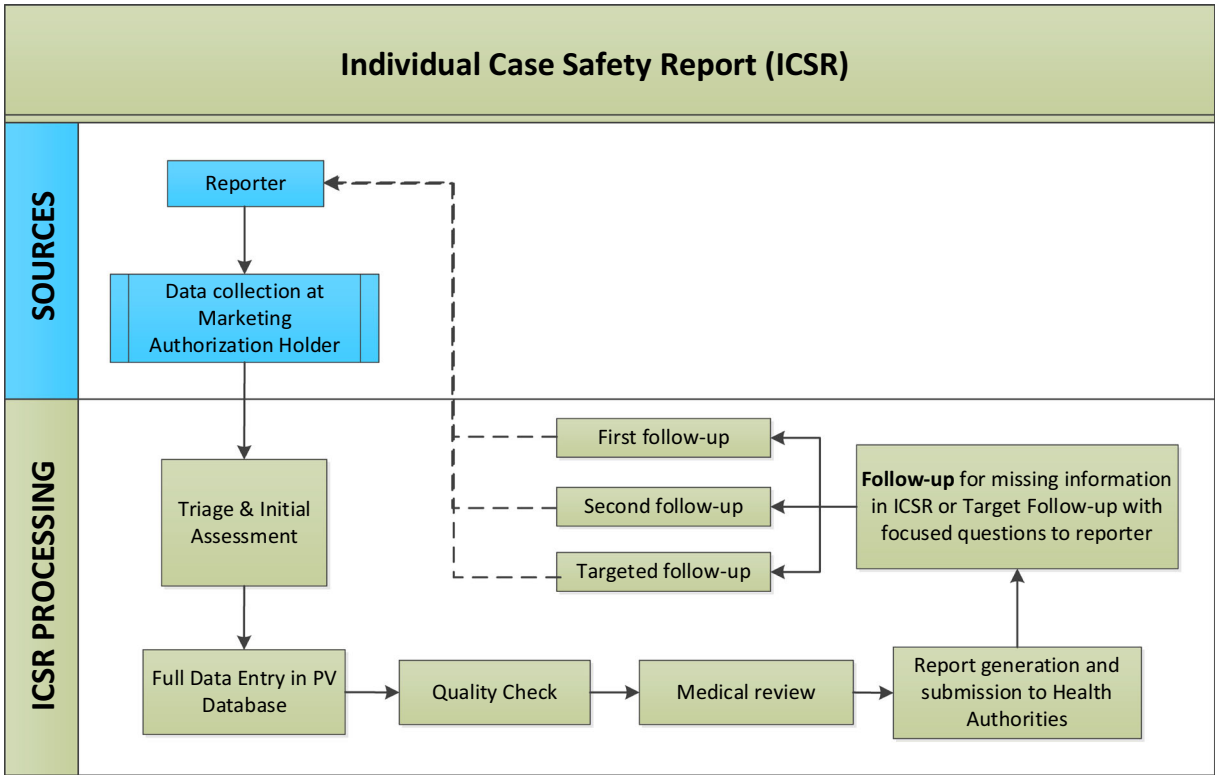

Fig. 1 Procedures for handling ICSRs

Medical Review

A healthcare professional or medical reviewer evaluates the ICSR to assess its clinical relevance, causality, and seriousness. This step helps determine whether the event is consistent with known product safety information. This includes causality assessment which involves evaluating the likelihood that the reported AE is related to the use of the medicinal product.

Regulatory Reporting

If the ICSR meets regulatory criteria for expedited or periodic reporting, it is submitted to the relevant Health Authorities (HAs) in accordance with regulatory requirements and timelines.

ICSR Follow-up

Marketing Authorization Holders (MAHs) play a crucial role in collecting and submitting ICSRs, generating periodic safety reports for HAs, and conducting benefit–risk analyses for pharmaceutical products to ensure their ongoing safety profile. ICSRs form the foundation for creating periodic safety reports and establishing the benefit–risk profile of medicinal products. Therefore, it is imperative for MAHs to have medically relevant information available when assessing serious and non-serious or ICSRs missing key information and there may be a need for follow-up with the reporter or healthcare provider to gather more details about the ICSR. However, in practice, since there are no incentives or obligations tied to reporting ICSRs by reporters, approximately 65% of initially received ICSRs lack sufficient information for meaningful medical assessment. To obtain the necessary information, MAHs undertake

structured follow-up efforts with reporters, with a reasonable number of follow-up attempts [2, 3].

Novartis has adopted the recommendations of the Council for International Organizations of Medical Sciences (CIOMS) V [4], which involve performing two follow-up attempts in general, utilizing appropriate formats and communication methods based on local practices. Additionally, case-by-case judgment is exercised, considering initial information reported, the specific product and event combination, and compliance with the Risk Management Plan (RMP). Follow-up becomes especially vital when the information provided is insufficient to determine the underlying cause of the event or the nature of the reported condition, hindering appropriate medical assessment.

PV regulations suggest that follow-up methods should be tailored to optimize the collection of missing information, with a focus on encouraging primary sources to submit new information relevant to the scientific evaluation of a specific safety concern [2, 3]. Nevertheless, there are instances where follow-up is unfeasible, such as when the reporter does not consent to contact, and their contact details are not provided, which accounts for 25% of cases in the overall sample.

- *First follow-up attempt (FU1)*: This is the initial follow-up conducted after the receipt of an ICSR. It aims to collect essential information that may be missing from the initial report.
- *Second follow-up attempt (FU2)*: If the response for FU1 attempt is not received, a FU2 will be conducted.
- *Targeted follow-up*: RMP/non-RMP "AEs of special interest (AESI)" require high priority handling. Targeted follow-up attempts are conducted based on the risk assessment of the case. These are typically performed when there is a specific need for additional information due to the seriousness or complexity of the AE or AESI or suspect product. Targeted follow-up questions are tailored to the specific characteristics of the case, and the inquiry is focused on collecting data that are critical for assessing the event's causality and severity. Targeted follow-ups are used strategically for cases where more in-depth investigation is warranted.

The rest of the paper is organized as follows: "Background" and "Purpose" sections provide information on current ICSR follow-up standards and the key issues involved in it and presents a purpose of the analysis on real-time data reported to Novartis. The "Methods" section discusses the adopted methodology including type of data used. The "Results" section presents the findings of the study. The "Discussion" section presents a detailed evaluation performed on the success rates of different ICSR follow-up attempts. The "Conclusion and Recommendations" section concludes the paper and highlights the need for further discussions among pharmaceutical industry and regulatory authorities.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

BACKGROUND

Globally, PV regulations provide a limited framework for follow-up activities. While they describe what information to seek, they also detail how to collect, manage, and submit selected outputs of this information to HAs. Guidelines, particularly those provided by CIOMS, which have mostly been developed within the last two decades, and Good Pharmacovigilance Practices (GVP), serve as critical guides for collecting missing safety information within ICSRs.

While advancements in PV have evolved the landscape of safety data management, with potential new sources and solicited data collection systems emerging, recommendations regarding the collection of ICSR follow-up information have not progressed at the same rate. As a result, MAHs often adapt their follow-up procedures based on available guidance and past PV inspections.

PURPOSE

The purpose of this analysis is to evaluate real-time data reported to Novartis, with a focus on Spontaneous Reports (SR), reports from Patient Support Programs (PSPs), and literature. We aim to compare different ICSR features using a data-driven statistical approach. On the basis of our findings, we intend to illustrate the limited benefits of the current follow-up approach, which relies on guidelines created two decades ago. Despite the evolution of PV, these guidelines remain largely unchanged. Additionally, we aim to describe the characteristics of a risk-based targeted follow-up approach for ICSRs conducted by MAHs.

METHODS

- *Report types included*: SR, reports from PSP, and literature.
- *Period analyzed*: 1 October 2018 to 30 September 2019 (33,133 unique cases).
- *Countries analyzed*: European Economic Area (EEA; Austria, Belgium, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, and Sweden).
    - Cases are labelled into five categories:
        - *Case complete at initial report*: This is indicated when case is assessed as complete at initial report (as per requirements specified in Novartis working procedure, including information on CIOMS A, B and/or C lists present in the procedure).
        - *Follow-up not possible*: This is indicated when Novartis is not allowed to perform follow-up with the reporter.
        - *FU1 success*: FU1 attempt, and its success rate: successful or not successful.
        - *FU2 success*: FU2 attempt, and its success rate: successful or not successful.
        - *Targeted follow-up success*: Targeted follow-up, successful or not successful.

Successful/unsuccessful: A case will be considered as successful if response is received from a reporter/author because of follow-up attempt performed by Novartis, otherwise considered as unsuccessful. Note that the success rate in this analysis report is quantitative and not qualitative, i.e., this analysis does not measure the content of the information received.

RESULTS

The following section provides a summary of the results, focusing on statistical correlations between follow-up success rates and various ICSR features, including seriousness, listedness, causality, report type, and product category, using real-time data reported to Novartis.

Distribution of Follow-ups in Cases

- A total of 33,133 unique cases were received during the analyzed period.
- 34.68% (11,490) of cases were completed at the initial report (Fig. 2).
- For 25.1% (8317) of cases, follow-up was not possible.
- FU1 was performed on 36.16% of the cases, and a FU2 on 21.23% of the total cases.
- Targeted follow-up was performed on 7.7% of total cases, either as part of the FU1 or FU2.

Success of Follow-ups

- FU1 was performed on 11,980 cases, with a success rate of 32.7% (Fig. 3).
- The success rate of the FU2 is 19.04%.
- Targeted follow-up was performed for 2550 cases with a success rate of 30.94%.

Follow-up Success Rate vs Case Seriousness

- In the FU1, the success rate for serious cases (34.16%) is statistically higher (p value 0.000028) than non-serious cases (30.49%).
- In the FU2, there is no statistically significant distinction (p value 0.952) between the

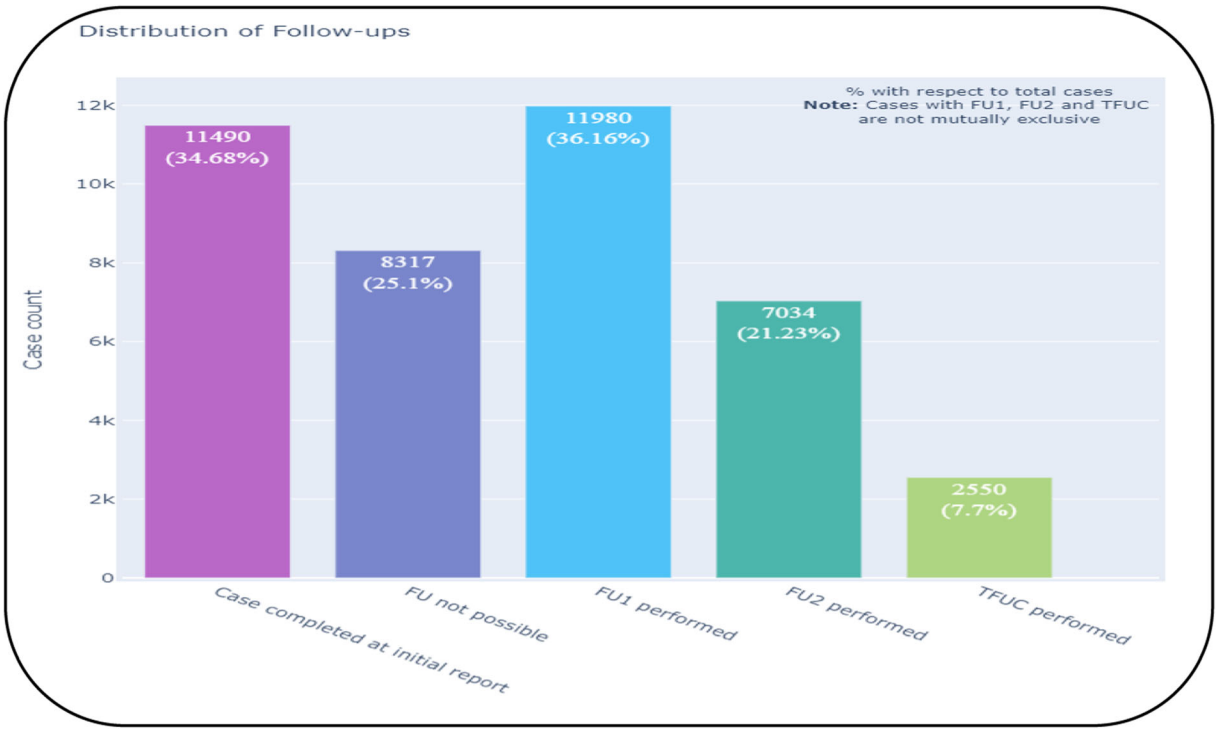

Fig. 2 Distribution of follow-ups

success rate of serious (19.05%) and non-serious cases (18.98%).
- Follow-up with targeted follow-up shows a higher success rate for serious cases (32.97%) than non-serious cases (23.7%).

Follow-up Success Rate vs Case Listedness

- In the FU1, there is a higher success rate (*p* value 0.00001) for unlisted cases (34.62%) than listed cases (29.27%).
- In the FU2, there is a higher success rate (*p* value 0.001) for unlisted cases (20.21%) than listed cases (17.08%).
- Follow-up with targeted follow-up shows no statistically significant distinction (*p* value 0.333) between the success rate of unlisted (31.67%) and listed cases (29.86%).

Follow-up Success Rate vs Case Causality

- In the FU1, there is a higher success rate (*p* value 0.00001) for "not suspected" cases (39.58%) than "suspected" cases (36.03%) and "not assessable" cases (25.49%).
- In the FU2, there is a higher success rate (*p* value 0.00001) for "not suspected" cases (21.92%) than "suspected" cases (21.51%) and "not assessable" cases (13.01%).
- Follow-ups with targeted follow-up indicate a higher success rate (*p* value 0.00001) for "suspected" cases (36.71%) than "not suspected" cases (35.99%) and "not assessable" cases (18.7%).

Follow-up Success Rate vs Case Report Type

- In the FU1, there is a higher success rate (*p* value 0.00001) for "PSP" reports (41.26%) than "SR" (36.21%) and "literature" reports (21.36%).
- In the FU2, there is a higher success rate (*p* value 0.00001) for "SR" reports (26.17%) than "PSP" reports (23.86%) and "literature" reports (8.46%).

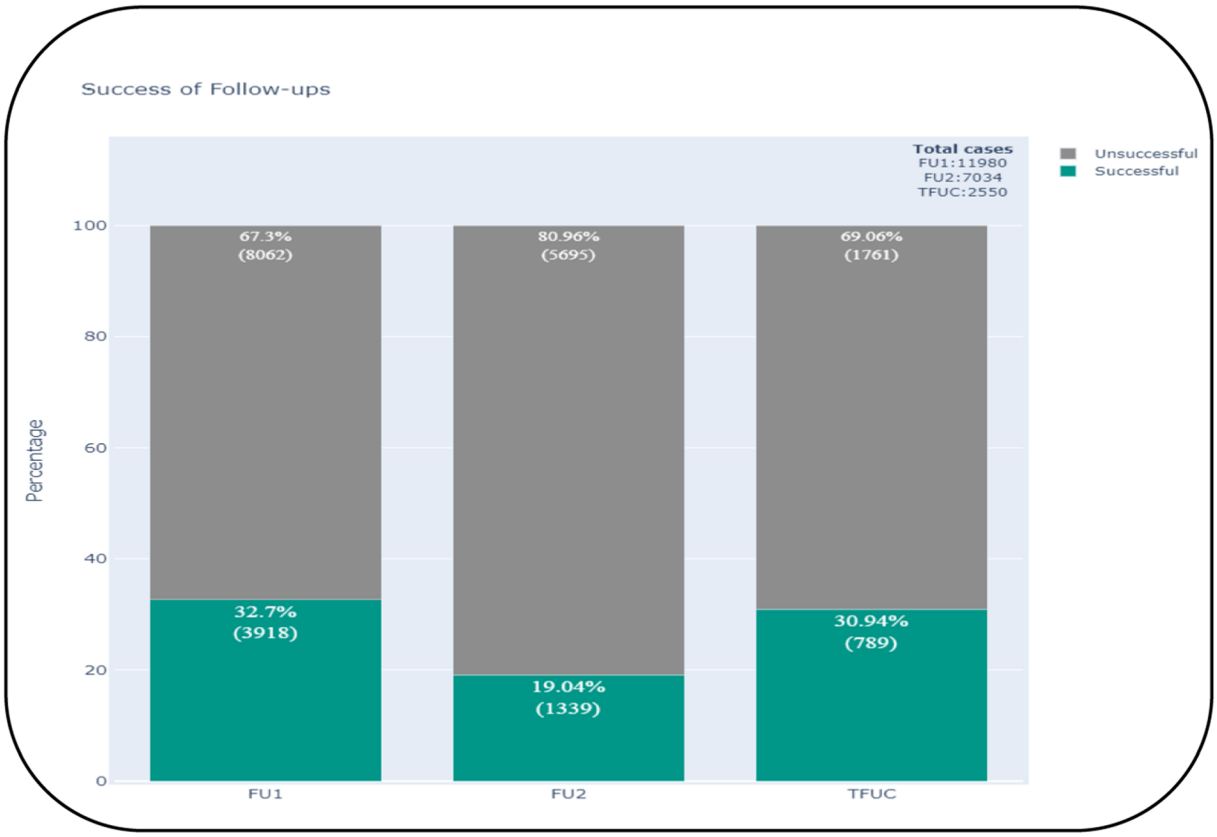

Fig. 3 Success of follow-ups

- Follow-up with targeted follow-up indicates a higher success rate (p value 0.00001) for "SR" reports (34.56%) than "PSP" reports (34.45%) and "literature" reports (13.36%).

Success Rate vs Product Category

- In the FU1, there is a higher success rate for "non-innovator" product type (37.86%) than "innovator" (33.7%), "biologicals" (33.42%), and "generics" (26.85%).
- In the FU2, there is a higher success rate for "biologicals" product type (23.52%) than "innovator" (19.92%), "non-innovator" (17.45%), and "generics" (12.49%).
- Follow-up with targeted follow-up indicates a higher success rate for "biologicals" product type (34.87%) than "non-innovator" (30.84%), "innovator" (27.17%), and "generics" (26.88%).

FU1 Vs FU2

FU2 success	Successful	Unsuccessful	Total
FU1 success			
Successful	1017	920	1937
Unsuccessful	302	4725	5027
Total	1319	5645	6964

FU2 success	Successful	Unsuccessful	Total
FU1 success			
Successful	14.6	13.2	27.8
Unsuccessful	4.3	67.8	72.2
Total	18.9	81.1	100

Fig. 4 FU1 success rate vs FU2 success rate

FU1 success	Successful		Unsuccessful		na		
FU2 success	Successful	Unsuccessful	Successful	Unsuccessful	Successful	Unsuccessful	Total
TFU success							
Successful	299	8	116	2	11	2	438
Unsuccessful	8	248	1	849	0	19	1125
Total	307	256	117	851	11	21	1563

FU1 success	Successful		Unsuccessful		na		
FU2 success	Successful	Unsuccessful	Successful	Unsuccessful	Successful	Unsuccessful	Total
TFU success							
Successful	19.1	0.5	7.4	0.1	0.7	0.1	28.0
Unsuccessful	0.5	15.9	0.1	54.3	0.0	1.2	72.0
Total	19.6	16.4	7.5	54.4	0.7	1.3	100.0

Fig. 5 FU1 success rate vs FU2 success rate vs follow-up with targeted follow-up success rate

FU1 vs FU2

- 67.8% (4725) of cases were unsuccessful in which both FU1 and FU2 were performed (Fig. 4).
- 14.6% (1017) of cases that were successful in the FU1 were also successful in the FU2.
- 13.2% (920) of cases that were successful in the FU1 were unsuccessful in the FU2.

FU1 vs FU2 vs Follow-ups with Targeted Follow-up

- 54.3% (849) of cases were unsuccessful in which FU1, FU2, and targeted follow-up were performed (Fig. 5).

DISCUSSION

During the era of the COVID-19 outbreak, multiple MAHs, including Novartis, adjusted their company follow-up procedures to support healthcare professionals (HCPs). This analysis focused on pre-Covid data from EEA countries to assess the effectiveness of these follow-up procedures and draw evidence-based recommendations for ICSR follow-up.

The response rate to follow-up requests was found to be low, with two-thirds of reporters not providing responses for cases where follow-ups were performed. Different follow-up attempts (first, second, and targeted follow-up) yielded varying success rates, and the analysis revealed several interesting trends. The success rates of follow-up attempts vary depending on the seriousness of the cases. While FU1 show promise in obtaining responses for serious cases, FU2 seem to have more uniform success rates. Additionally, targeted follow-ups stand out as a valuable strategy for improving response rates, especially for serious cases. These findings provide insights into optimizing follow-up procedures to enhance the quality of safety data collection. Unlisted cases demonstrate a notably higher success rate during both FU1 and FU2 attempts, underscoring the importance of thorough follow-up for cases with unlisted events. However, when targeted follow-up is applied, there is no significant difference in success rates between unlisted and listed cases, suggesting the effectiveness of tailored follow-up strategies in gathering crucial data, irrespective of listedness. Across all follow-up attempts, cases categorized as “not suspected” consistently yield the highest success rates, underscoring the importance of targeting these

cases also for thorough follow-up. Conversely, "not assessable" cases generally have lower success rates, emphasizing the need for more tailored follow-up strategies to enhance their response rates. The success rates of follow-up attempts varied between different report types. The FU1 showed higher success rates for PSP reports, emphasizing the need for efficient follow-up in this category. Surprisingly, in the FU2, SR exhibited higher success rates than PSP reports, highlighting the importance of follow-up strategies for SR. However, when employing targeted follow-up, success rates were similar across report types, indicating their effectiveness in improving response rates regardless of the report type. Generic product reports had a lower success rate compared to innovator and biological product reports. The study also found that many cases did not receive responses for follow-up attempts. Recommendations were made to improve response rates, including using more focused questions for medical assessment and considering a risk-based approach for FU2 attempts. The study concludes by emphasizing the need for HCPs to provide sufficient information for ethical medical assessment of ICSRs.

CONCLUSION AND RECOMMENDATIONS

Follow-up for ICSRs is mandated by regulations such as GVP and the CIOMS. However, there is limited guidance available from HAs regarding best practices for these follow-up procedures. The analysis results presented in this manuscript are believed to be valuable for developing effective follow-up procedures. The goal is to stimulate further discussions among industry stakeholders and regulators to consider qualitative aspects in follow-up attempts and adopt a risk-based approach. Here are the key recommendations:

- *Modulated FU2*: Instead of a standard FU2 for all cases, a more modulated approach should be considered. FU2 attempts should be performed on a case-by-case basis when identified risks necessitate additional information. A blanket FU2 is not recommended by default.
- *Literature cases*: For literature cases, where there is a substantial time lag between the AE occurrence and report publication, a single follow-up attempt is generally sufficient.
- *Influence HCPs*: Given the high percentage of cases where follow-up is not possible, it is recommended that HAs initiate activities to influence HCPs to provide sufficient information to MAHs. This should be framed as an ethical recommendation for the medical assessment of ICSRs.
- *Focused Questions*: A more effective approach to follow-up is to use targeted and focused questions for appropriate medical assessment rather than relying on a long list of standard items. This strategy can encourage reporters to provide responses, thereby increasing the overall response rate for follow-up attempts performed by MAHs.

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Data Availability. The authors confirm that the data supporting the findings of this study are available within the article. The supplementary materials can also be provided where needed.

Declarations

Conflict of Interest. All authors (Ganesh Kumar Vemula, Pavan Badale, Petros Mavrogenis, Isabelle Lalande-Luesink, Michal Borkowski, and David John Lewis) declare no conflicts of interest.

Ethical Approval. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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