Therapeutic Innovation
& Regulatory Science
2016, Vol. 50(4) 464-471

DOI: 10.1177/2168479016634766
tirs.sagepub.com

Best Practices for Improving the Quality of Individual Case Safety Reports in Pharmacovigilance

Rishi Kumar, MPharm[1], Pranay Kumar, MPharm[1], Vivekanandan Kalaiselvan, MPharm, PhD[1], Ismeet Kaur, MPharm[1], and G. N. Singh, MPharm, PhD[1]

Abstract

Background: The quality of individual case safety reports (ICSRs) plays a vital role in identifying new safety signals in pharmacovigilance. This article focuses on establishing a method for ensuring the quality data. *Objective:* To develop an in-house method for assessing the documentation grading and completeness score of ICSRs. *Methods:* In the proposed method, 16 parameters, from report title to case narrative, are adopted to assess the quality of ICSRs. The in-house method ensures the completeness of the data and enhances the quality of ICSRs. *Results:* The in-house method was found effective in calculating the completeness score of ICSR ranges from 0.05 to 1. Indian ICSR completeness scores significantly improved after the implementation of the proposed method in the third quarter of 2013. In 2014 and until the third quarter of 2015, the score was found to be 0.91 and 0.93 out of 1, respectively. *Conclusion:* The higher quality ICSRs aids in more effective identification of new drug safety alerts and provides evidence-based information for regulating the drug safety.

Keywords

pharmacovigilance, Completeness score, adverse drug reactions, safety signals

Introduction

Adverse drug reactions (ADRs) are a major cause of concern for morbidity and mortality, and hence their monitoring becomes a major element of pharmacovigilance for ensuring medicine safety.[1–4] In 2010 in India, the Ministry of Health and Family Welfare launched the Pharmacovigilance Programme of India (PvPI) to monitor ADRs. The PvPI is coordinated by the Indian Pharmacopoeia Commission as a National Coordination Centre (NCC).[3–6] The PvPI aims to generate reports through ADR monitoring centers (AMCs) and other stakeholders to identify new sources of suspected ADRs.[7] The information gathered therein is reviewed and assessed to provide inputs to the Central Drugs Standard Control Organisation (CDSCO) for appropriate regulatory intervention.

The NCC plays a pivotal role in creating awareness in the health care profession to understand the concept of pharmacovigilance and report ADRs. Also, regular hands-on training is imparted to the stakeholders, contributing to skill development. As a member of the World Health Organization (WHO) Programme for International Drug Monitoring, India through the PvPI has made a significant contribution to the WHO international database of suspected ADRs at the Uppsala Monitoring Centre (WHO-UMC) in Sweden. The major challenge for the NCC is to assess the quality of individual case safety reports (ICSRs) through spontaneous reporting. The quality of ICSRs is addressed by ensuring the completeness of the information provided by the reporter, such as suspected medicine, causality, patient details, case narrative, outcome, seriousness of the event, etc. Initially, there was a dearth of ICSRs, as the above components were not minutely addressed by the reporter.[8,9,11] This signified the need to develop a method to assess the quality of ICSRs, which helps in identifying signals. The completeness score for Indian ICSRs in the global database is encouraging.[3]

Methodology

Documentation grading is a system used to measure the quality and quantity of the information provided on the ICSRs by the AMCs. To ascertain the degree of completeness of an ICSR, a

[1] Ministry of Health and Family Welfare, Indian Pharmacopoeia Commission, Ghaziabad, Uttar Pradesh, India

Submitted 27-Oct-2015; accepted 29-Jan-2016

Corresponding Author:
Rishi Kumar, MPharm, Ministry of Health & Family Welfare, Indian Pharmacopoeia Commission, Sector 23, Rajnagar, Ghaziabad, Uttar Pradesh 201002, India.
Email: tawar.rishi@gmail.com

Table 1. Scoring Pattern of Important Fields in ICSRs.

S. No.	Field	Score Description	Weight Given by NCC-PvPI
1	Report title	A full score is given if an allowed value has been entered.	0.05
2	Seriousness	A full score is given if an allowed value has been entered.	0.1
3	Primary source	A change in score might be due to a change in information of the following fields: primary source, reporter's qualification.	0.1
4	Patient information	A change in score might be due to a change in information of the following fields: age at time of onset, patient initials.	0.4
5	Patient sex	A full score is given if an allowed value has been entered.	0.35
6	Free text	A change in score might be due to a change in information of the following fields: results of test and procedures, relevant medical history, reporter's comments, additional information (drug), sender's comment.	0.05
7	Reaction(s)/event (s)	A full score is given if an allowed value has been entered through WHO-ART.	0.05
8	Outcome	A full score is given if an allowed value has been entered.	0.01
9	Drug name	A full score is given if an allowed value has been entered through WHO-DD	0.05
10	Drug information	A change in score might be due to a change in information of the following fields: pharmaceutical form, route of administration, authorization holder, dose, dosage regimen.	0.05
11	Action taken	A full score is given if an allowed value has been entered	0.35
12	Indication	A full score is given if an allowed value has been entered. Since indication is reported on drug level, the score per ICSR is the average score of all suspected/interacting drugs.	0.5
13	Time on set	A change in score might be due to a change in information of the following fields: drug start date, ADR date of on set.	0.15
14	Causality assessment	A full score is given if an allowed value has been entered as per WHO causality scale.	0.05
15	Case narrative	A full score is given if an allowed value has been entered.	0.05
16	Compliance of in-house standard operating procedures	A full score is given if no query or resolve the query within 10 days by AMC.	0.01
17	Completeness	Calculated on the basis of formula given in Equation 1	—

Abbreviations: ADR, adverse drug reaction; AMC, ADR monitoring center; ICSR, individual case safety report; NCC-PvPI, National Coordination Centre–Pharmacovigilance Programme of India; WHO-ART, WHO Adverse Drug Reaction Terminology; WHO-DD, WHO Drug Dictionary; WHO, World Health Organization.

quantitative measure was defined. The weight for each reporting element is fixed on the basis of the gravity of information required for ensuring the quality of ICSRs. To assign weight in multiple drug-ADR combinations, the score for a particular field is divided equally for each drug-ADR pair. The score description and weight of each parameter considered for its completeness is given in Table 1.

The total completeness score of an ICSR is calculated from several field scores. The data fields that are implemented in the completeness score include report title, seriousness, primary source, patient information, patient sex, free text, reaction term, outcome, drug name, drug information, action taken, indication, time onset, causality assessment, case narratives, and compliance of in-house standard operating procedures. Of these parameters, the following are in addition to the parameters used by WHO-UMC: report title, seriousness, patient information (including patient initials and age), free text (including 5 subparameters: results of test and procedure, patient medical history, additional information, reporter's comment, sender's comment), drug name, drug information (including 5 subparameters: pharmaceutical form, route of administration, authorization holder, dose, dosage regimen), causality assessment, case narrative, and response to NCC. Informative values of the fields, as described below, are derived based on ICH E2B Guidelines.

A score is calculated for each drug-ADR combination separately, and the mean of all these forms the completeness score. Only suspected and interacting drugs are included in the calculations. The completeness of ICSRs is required to be graded to enable their quality assessment by applying the following multiplicative model:

$$\text{Completeness score} = \prod_{(i=1)}^{n}((1 - w_i) + (w_i * f_i)) \qquad (1)$$

where i indicates the field included in the score, w_i is the field weight, and f_i is the field score.

Report Title

The ICSR sections begin with the report title, which gives the uniqueness and identity. The report title should emphasize the combination of ADR and drug. An example is given in Table 2.

Seriousness

Seriousness is classified as *yes* or *no*. If *yes*, the reason must be specified, as shown in Table 3.

Table 2. The Score Calculation for the Report Title Section of ICSRs.

Report ID	Report Title	Score
R1	Haematoma: Clopidogrel	1
R2	Clopidogrel	0
R3	Haematoma	0
R4	No title given	0

Abbreviation: ICSRs, individual case safety reports.
Note: In the case of multiple drugs and adverse drug reactions, suspected drug needs to be demarcated from the concomitant drugs.

Table 3. The Score Calculation Information to Assess the Seriousness of ICSRs.

Report ID	Seriousness	Reason for Seriousness		Score
R1	Yes	Death Life threatening Congenital anomaly Hospitalization—initial or prolonged Disability Other	Any one should be marked	1
R2	Yes	Reason of seriousness not selected		0
R3	No	No need of reason		1
R4	Not mentioned	Not mentioned		0

Abbreviation: ICSR, individual case safety report.

Primary Source

The primary source section consists of details of the reporter, such as name, qualification, department, and contact details. Primary source information is considered as one of the vital parts of an Adverse Drug Reaction (ADR) to ensure quality because the source reporter is the witness of the event. As per the pharmacovigilance standards, reporter identity is among the 4 mandatory elements to assess the relatedness of the event. The details of the primary source section are given in Table 4.

Patient Information

Patient information details, such as age at time of onset of reaction/event and patient initials (patient name and identifying information are not reported) are mentioned in the field. The informative values for patient information scoring are given in Table 5.

Patient Sex

A full score is given if the patient's sex is categorized as male, female, and other (transgender) in the field.

Free Text

This section consists of 5 subsections, the details of which are given in Table 6. The relevant information on relatedness of the

Table 4. The Score Calculation for the Primary Source Section of ICSRs.

Report Id	Primary Source	Reporter Qualification	Primary Source Score
R1	Yes	Yes	1
R2	Yes	Not mentioned	0.5
R3	Not mentioned	Yes	0.5
R4	Not mentioned	Not mentioned	0

Abbreviation: ICSRs, individual case safety reports.

Table 5. The Score Calculation for the Patient Information Section of ICSRs.

Report ID	Age at time of onset	Patient initial	Score
R1	50	RKV	1
R2	Not mentioned	RKV	0.5
R3	50	Not mentioned	0.5
R4	Not mentioned	Not mentioned	0

Abbreviation: ICSRs, individual case safety reports.

Table 6. Components to be Described in the Free Text to Improve the Quality of ICSRs.

Field for Free Text	Description
Result of test procedure	This section should capture the tests and procedures performed to diagnose or confirm the reaction/event, including those tests done to investigate (exclude) a nondrug cause (eg, serologic tests for infectious hepatitis in suspected drug-induced hepatitis). Both positive and negative results should be reported.
Relevant medical history	This field should be used for providing information pertinent to understanding the case is desired such as diseases, conditions such as pregnancy, surgical procedures, psychological trauma, etc. and concurrent condition can be described in this section.
Reporter's comments	This field should be used for comments from the primary source that are relevant for all reactions like diagnosis, causality assessment, treatment and other issues related to the reaction.
Additional information (drug)	This field should be used to describe the information of fixed dose combination/ medical treatment/date of rechallenge/dose reduces/labeling of drug and indication if no suitable indication found.
Sender Comment	This field should be used for any discussion or alternative diagnoses from the sender (person who sent the ICSR to the NCC). This section provides the sender with an opportunity to combine signs and symptoms that were reported into a succinct diagnosis and the reasoning.

Abbreviations: ICSRs, individual case safety reports; NCC, National Coordination Centre.

Table 7. Procedure for Calculating the Score of the Free Text Section in ICSRs.

	Free Text					
Report ID	Result of Test Procedure	Relevant Medical History	Reporter's Comments	Additional Information (Drug)	Sender Comment	Score
R1	Yes	Yes	Yes	Yes	Yes	1
R2	Yes	Yes	Yes	Yes	Not mentioned	0.8
R3	Yes	Yes	Yes	Not mentioned	Not mentioned	0.6
R4	Yes	Yes	Not mentioned	Not mentioned	Not mentioned	0.4
R5	Yes	Not mentioned	Not mentioned	Not mentioned	Not mentioned	0.2
R6	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned	0

Abbreviation: ICSRs, individual case safety reports.

Table 8. The Score Calculation for the Reaction(s)/Events Section of ICSRs.

Report ID	Reaction/Event	WHO-ART	Score
R1	A1	0030 PT/HLT/IT	1
R2	A2	Uncoded	0
R3	A1	0030 PT/HLT/IT	0.5
	A2	Uncoded	
R4	Not mentioned	Not mentioned	0

Abbreviations: ICSR, individual case safety report; WHO-ART, WHO Adverse Drug Reaction Terminology; WHO, World Health Organization.
Note: Free text was referred to obtain the information of event/reaction coding if not coded in WHO-ART.

reaction/event is provided in these fields. The score for these fields is calculated by taking into account the 5 related components as given in Table 7.

Adverse Drug Reactions/Events

Coding of ADRs is one of the important compliance in ensuring the quality of ICSRs as potential evidence in data mining and signal detection.[10] The reaction term and coding is done as per WHO Adverse Drug Reaction Terminology (WHO-ART), as given in Table 8.

Outcome

Whether the outcome of the reaction/event can be explained depends on the appearance as given in Table 9; scores are provided accordingly.

Drug Name

The suspected drug for the reasonable possibility of adverse event is mentioned. This is judged by the clinical relevance and experience of the reporter. Evidence-based information is also referred to identify the suspected drug. The coding of drug is done per the WHO Drug Dictionary (WHO-DD), as given in Table 10.

Table 9. The Score Calculation for the Outcome Section of ICSRs.

Report ID	ADR	Outcome	Option Selected	Score
R1	A1	Recovered/resolved	Anyone	1
		Recovering/resolving		
		Not recovered/not resolved		
		Recovered/resolved with sequelae		
		Fatal		
R2	A1	Unknown[a]		0
R3	A1	Anyone has marked		0.5
	A2	If left unmarked		

Abbreviations: ADR, adverse drug reaction; ICSRs, individual case safety reports.
[a]The value "unknown" is not considered (for information only).

Table 10. The Score Calculation for the Drug Name Section of ICSRs.

Report ID	Suspected/Concomitant Drug	WHO-DD	Score
R1	D1	Coded	1
R2	D1	Uncoded	0
R3	D1	Coded	0.5
	D2	Uncoded	

Abbreviations: ICSR, individual case safety report; MA, market authorization; WHO-DD, WHO Drug Dictionary; WHO, World Health Organization.
Note: The name of the product pharmaceutical form, MA holder, etc, are suggested if the suspected drug is not available with the WHO-DD.

Drug Information

Drug information details such as pharmaceutical form, route of administration, authorization holder, dose, and dose regimen are used for scoring in this field. Although it is not mandatory to provide this information in VigiFlow, it is adopted at NCC-PvPI as an improvement. The drug information scoring values are given in Table 11.

Action Taken on Adverse Drug Reactions

The score for this section is calculated per the details given in Table 12.

Table 11. The Score Calculation for the Drug Information Section of ICSRs.

Report ID	Pharmaceutical Form	Route of Administration	Market Authorization Holder	Dose	Regimen	Score
R1	Injection	Intravenous	–	250 mg	OD	1
R2	Injection	Intravenous	–	250 mg	Not provided	0.8
R3	Tablet	Oral	–	Not provided	Not provided	0.6
R4	Injection	Intravenous	Not provided	Not provided	Not provided	0.4
R5	Injection	Not provided	Not provided	Not provided	Not provided	0.2
R6	Not provided	Not provided	Not provided	Not provided	Not provided	0

Abbreviation: ICSR, individual case safety report; OD, overdose.
Note: Batch number of the pharmaceutical product is necessary in case of serious adverse event.

Table 12. The Score Calculation for the Action Taken on Adverse Drug Reactions Section of ICSRs.

Report ID	Drug	Action Taken		Score
R1	D1	Drug withdrawn Dose reduce Dose does not change Not applicable Unknown[a]	Any one should be marked	1
R2	D1	Not mentioned		0
R3	D1	Drug withdrawn Dose reduce Dose does not change Not applicable Unknown[a]	Any one should be marked	0.5
	D2	Not mentioned		

Abbreviation: ICSRs, individual case safety reports.
[a]The value "unknown" is not considered (for information only).

Indication

The informative values are calculated as per the guidelines of International Classification of Diseases (ICD) 8, ICD9 (including supplementary codes), and ICD10. The informative values are calculated as shown in Table 13.

Time Onset

Temporal relationship is one of the important criteria of assessment of the causality of the adverse event. Time onset comprises drug start date and adverse event onset date. The informative values are calculated as per Table 14.

Causality Assessment

Causality assessment (relatedness of drug and ADR) is carried out according to the WHO causality scale, as per Table 15.

Case Narrative

If the reporter has less scope to enter the data in the above-mentioned fields, opportunity is given to provide additional information, which is required to establish causality and to ensure quality of ICSRs. The reporters are followed up by

Table 13. The Score Calculation for the Indication Section of ICSRs.

Report ID	Drug	Indication Code	Score
R1	D1	486[a]	1
R1	D1	Not mentioned	0.67
	D2	486[a]	
	D3	486[a]	
R2	D1	3004[a]	0.50
	D2	Not mentioned	
R3	D1	Uncoded	0
R4	D1	Not mentioned	0

Abbreviations: ICD, International Classification of Diseases; ICSRs, individual case safety reports.
[a]Disease indication code as per the guideline of ICD.

Table 14. The Score Calculation for the Time Onset Section of ICSRs.

Report ID	Drug Start Date	ADR Onset Date	Time to Onset Score
R1	2010-08-08	2010-10-11	1
R2	2011-05-07	Not mentioned	0
R3	Not mentioned	2011-09-13	0
R4	2013-08-11	2010-11-11	0[a]
R5	Not mentioned	Not mentioned	0

Abbreviations: ADR, adverse drug reaction; ICSRs, individual case safety reports.
[a]Date of ADR supersedes the date of drug start; therefore, a score of 0 is given.

Table 15. The Score Calculation for the Causality Assessment Section of ICSRs.

Report ID	Drug	ADR	Perform Causality (WHO Causality Scale)	Score
R1	D1	A1	Yes	1
R2	D1	A1	Not mentioned	0
R3	D1	A1	Yes	1
	D2	A2		
	D1	A2		
	D2	A1		
R4	D1	A1	Yes	0.5
	D2	A2	Yes	
	D1	A2	Not mentioned	
	D2	A1	Not mentioned	

Abbreviations: ADR, adverse drug reaction; ICSRs, individual case safety reports; WHO, World Health Organization.

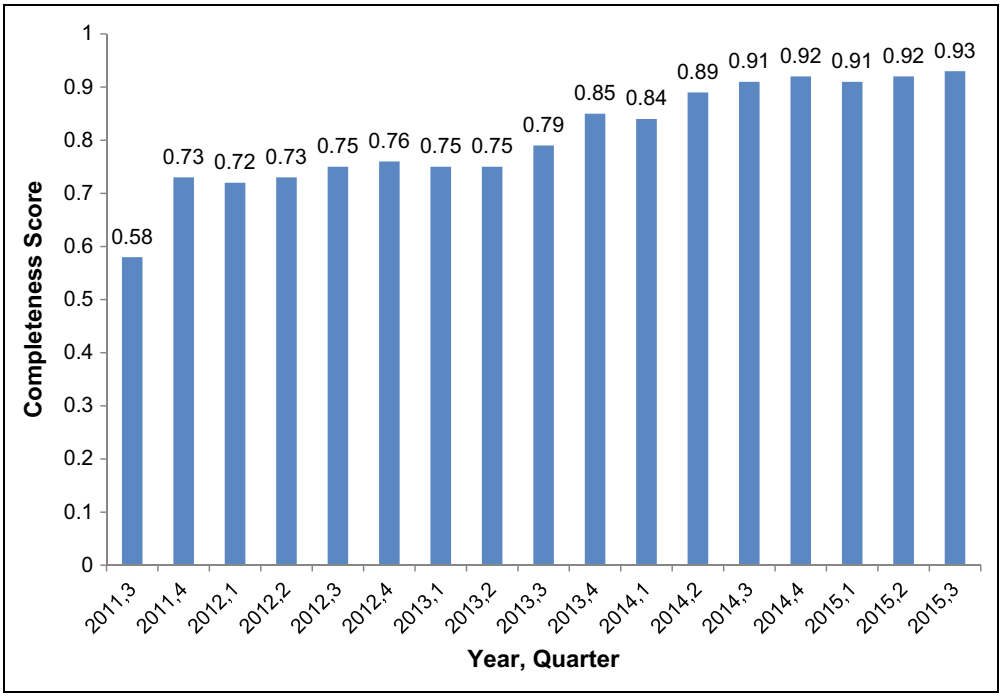

Figure 1. Completeness scores of Indian individual case safety reports by year and quarter.

NCC-PvPI for a complete case narrative. The full score of 1 for case narrative is given if information for all of the above-discussed fields is entered. In addition, NCC-PvPI might seek more information in specific cases.

Compliance of In-House Standard Operating Procedures

The full score is given to this field if the reporter responds to the query or comments raised by the NCC within 10 calendar days.

Completeness Score

The completeness score of an ICSR is calculated from the information obtained regarding the above-mentioned 16 parameters by using Equation 1.

Results

The above methodology was adopted and implemented by NCC-PvPI in September 2013 to assess the completeness of ICSRs received from AMCs across the country. The completeness score was increased or sustained in every quarter until the third quarter of 2015. The completeness score for Indian ICSRs received from WHO-UMC is given in Figure 1. Specifically, the score of comments, dosage, indication, time to onset, and outcome increased after implementation of the adopted method. The WHO-UMC is considering the 10 parameters (age at onset, patient sex, country, report type, primary reporter, comments, dosage, indication, time to onset, outcome) for providing the completeness score for the National Pharmacovigilance Centres. The NCC considers the above-mentioned 16 parameters in preparing the completeness score, and based on this there has been a gradual increase in the completeness score of NCC-PvPI.

Discussion

A robust PvPI has been established in the country.[1-7] Several initiatives have been taken to foster the culture of reporting. As a result, India is the first country to report more than 100,000 ICSRs in VigiFlow.[12] NCC-PvPI is also taking several measures to enhance the quality of ICSRs, such as advance level training and skill development for PvPI personnel. The Quality Review Panel (QRP) of PvPI is constituted by Ministry of Health and Family Welfare, Government of India, to review the quality of ICSRs. The panel also reviews and approves the proposed methodology to implement in PvPI. The criteria laid down in the methodology are in line with those of WHO-UMC, such as age at onset, patient sex, country, report type, primary reporter, comments, dosage, indication, time to onset, and outcome. In addition to these, NCC has made it mandatory for the AMCs to provide information on manufacturer details, free text (with emphasis on laboratory findings if any, medical history, additional information, reporters comment and sender's comment), drug information (this part includes formulation type, dose, dosage regimen, route of administration and authorization holder), action taken, causality assessment, case narrative, and response to NCC. NCC-PvPI has also given different weights to all 16 parameters adopted, as recommended by the Quality Review Panel (see Table 1).

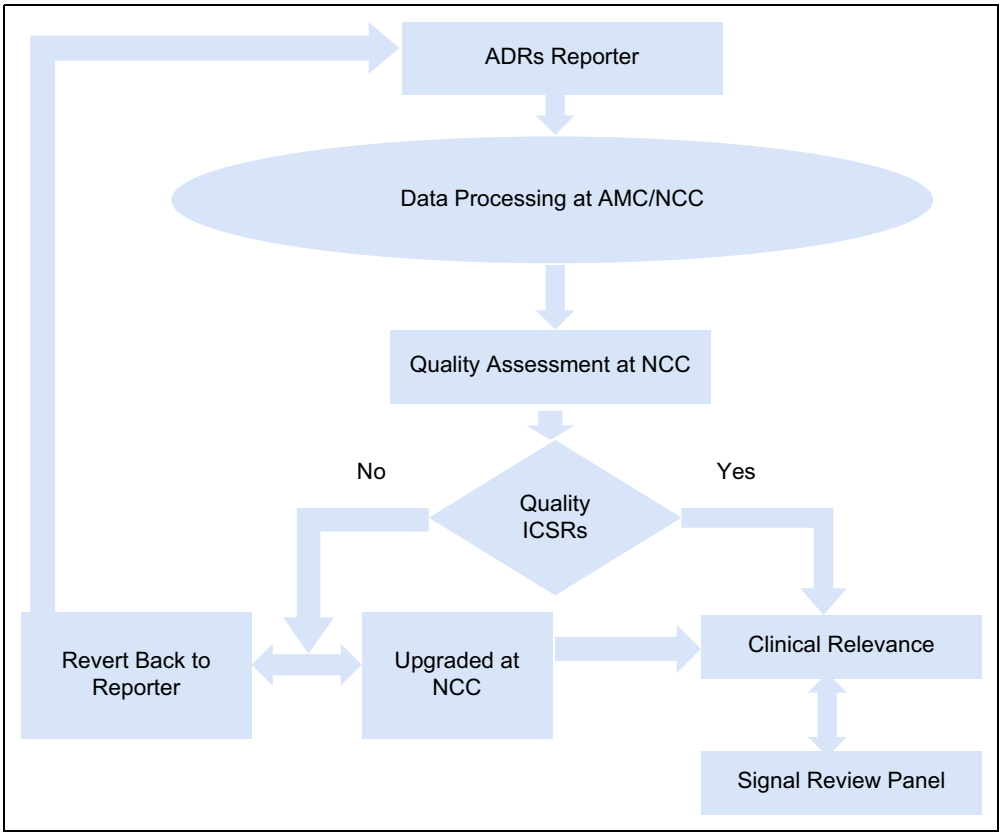

Figure 2. Flow of individual case safety reports under the pharmacovigilance program of India and proposed method.

The completeness score of ICSRs reported from India is improving, in spite of the high volume of data. Since WHO requires middle- and low-income countries to establish their own signal detection system, a Signal Review Panel (SRP) has been constituted under PvPI. The SRP consists of high-level experts in India, including academicians and clinicians working for pharmacovigilance, and was formed under the PvPI in order to analyze and review the identified signals proposed to the panel members for final decision and submission to the CDSCO for potential regulatory interventions. The function of the SRP is expressed in Figure 2. The SRP and QRP contribute significantly to enhance the quality of ICSRs. These quality reports help the process of signal review activities in India, and several recommendations are made on regulatory interventions on medicine to the Indian National Regulatory Authority.[13] This method may be implemented in low- and middle-income country members of the WHO Programme for International Drug Monitoring. It will strengthen their pharmacovigilance systems for generation of qualitative output. For any regulatory intervention, a high-quality ICSR is of prime importance to analyze the data.

Conclusion

The method described in this article aims to improve the quality of ICSRs. In the proposed method, the completeness score can be calculated based on the provided information in 16 fields of ICSRs. All the relevant fields are taken into consideration to establish the causal relationship between the drug and ADRs, as it plays a crucial role in ensuring quality ICSRs. The gravity of the completeness score, which varies from 0.05 to 1.0, depends on the amount of information provided in the ICSRs.

Acknowledgment

The authors are thankful to the Indian Pharmacopoeia Commission for providing support.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Dhikav V, Singh S, Anand KS. Adverse drug reaction monitoring in India. *J Indian Acad Clin Med*. 2004;5:27-33.

2. Norén GN, Edwards IR. Modern methods of pharmacovigilance: detecting adverse effects of drugs. *Clin Med*. 2009; 9(5):486-89.
3. Kalaiselvan V, Kumar R, Thota P, Tripathi A, Singh GN. Status of documentation grading and completeness score for Indian individual case safety reports. *Indian J Pharmacol*. 2015;47:325-327.
4. Kalaiselvan V, Sharma S, Singh GN. Adverse reactions to contrast media: an analysis of spontaneous reports in the database of pharmacovigilance programme of India. *Drug Saf*. 2014;5:70-78.
5. Kalaiselvan V, Prakash Jai, Singh GN. Pharmacovigilance programme of India. *Arch Pharm Pract*. 2012;3:229-232.
6. Kalaiselvan V, Thota P, Singh A. Current status of adverse drug reactions monitoring centres under pharmacovigilance programme of India. *Indian J Pharm Pract*. 2014;7:9-22.
7. Thota P, Vivekanandan K, Prakash J, Singh S, Singh GN. Weight gain in association with insulin use—an analysis of individual case safety reports an Indian database. *J Pharmacovigil*. 2014;2: 119.
8. Bergwal T, Noren GN, Lindquist M. vigiGrade: a tool to identify well-documented individual case reports and highlight systematic data quality issues. *Drug Saf*. 2013;37:65-77.
9. Edwards IR, Aronson JK. Adverse drug reactions: definitions, diagnosis, and management. *Lancet*. 2000;356:1255-1259.
10. Paul L, Robinson K. Capture and documentation of coded data on adverse drug reactions: an overview. *HIM J*. 2012;41:27-36.
11. Hunsel FV, Härmark L, Pal S, Olsson S, Grootheest KV. Experiences with adverse drug reaction reporting by patients. *Drug Saf*. 2012;35:45-60.
12. Lihite RJ, Lahkar M. An update on the pharmacovigilance programme of India. *Front Pharmacol*. 2015;6:194.
13. Indian Pharmacopoeia Commission. Ministry of Health and Family Welfare, Government of India. http://ipc.nic.in/showfile.asp?lid=398&EncHid=. Accessed September 4, 2015.