

An evaluation of trigger tool method for adverse drug reaction monitoring at a tertiary care teaching hospital

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Abstract

Objectives: The objective of this study is to evaluate the trigger tool method (TTM) in detection, monitoring, and reporting of adverse drug reactions (ADRs) at Civil Hospital Ahmedabad, India.

Materials and Methods: A prospective, single-center, observational cum intervention study was conducted in two phases in the Department of Medicine over 15 months. In phase I, preliminary trigger tool list (PTTL) comprising 55 triggers was evaluated by pharmacologist in terms of detection of ADR in 400 patients and then, modified trigger tool list (MTTL) was prepared. In Phase II, the TTM using MTTL was compared with the spontaneous method of ADR monitoring after educational interventions in resident doctors of the two units of medicine department.

Results: Of the 55 triggers in PTTL, 34 triggers were observed in 327 patients, of which 19 triggers lead to the detection of 66 ADRs. The rate of ADEs was 16.5%/100 patients. Positive predictive value (PPV) of each trigger ranged from 0% to 100%. PPV for drug trigger, laboratory trigger, and PT was 14.4%, 4.5%, and 23.3%, respectively. Overall, PPV of PTTL was 19.27%. Sensitivity and specificity were 100% and 21.66%, respectively. MTTL consists of these 19 triggers. In Phase II, resident doctors reported 16 ADRs, using spontaneous method and 23 ADRs using MTTL. The rate of ADEs per 100 patients was 1.63 and 2.13, respectively, with these methods. A total of 105 ADRs were reported during both phases.

Conclusion: TTM is an effective method of ADR reporting if it is utilized by a trained person. This method could be used as add-on method to spontaneous method to improve ADR reporting.

Keywords: Adverse drug reaction, adverse drug reaction monitoring, pharmacovigilance, trigger tool method

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INTRODUCTION

An adverse drug reaction (ADR), is “a response to a drug that is noxious and unintended that occurs at doses normally used in man for prophylaxis, diagnosis, or treatment of disease, or for the modification of physiological function.” Pharmacovigilance is “the science and activity relating to the detection, assessment, understanding, and prevention

of adverse effects or any other possible drug-related problems.”^[1] Epidemiological studies in India show that about 50% of all hospital admissions are associated with ADRs.^[2]

Several methods are used to monitor ADRs. These can broadly be categorized as: voluntary reporting, record

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review, triggers, direct observation, interviews, targeted reporting, cohort event monitoring, and electronic health record mining.^[3] The most popular method of ADRs reporting is spontaneous or voluntary reporting. However, under reporting, bias in reporting, and incomplete data are the major drawbacks of this method.^[4] These problems can be overcome by one of the active surveillance methods like the trigger tool method (TTM). A trigger is defined as an “occurrence, prompt or flag, found on review of the medical record that “triggers” further investigation to determine the presence or absence of an adverse event.”^[5] A trigger may be a laboratory trigger (LT) or a drug trigger (DT) or a patient trigger (PT).

In 1990s, the Institute for Healthcare Improvement (IHI) developed the IHI Global Trigger Tool to identify adverse events.^[6] This tool has been shown to be highly effective and efficient for detecting up to ten times more AEs than other methods of reporting.^[6] Positive predictive value (PPV), sensitivity, and specificity are parameters for the accuracy of trigger tool.^[5] Studies conducted worldwide show that the TTM improve ADR reporting in terms of both quality and quantity.^[7] However, TTM is a lesser evaluated method in India. Most studies conducted worldwide have used TTM retrospectively to detect ADR. This has several limitations such as sole dependence on documentation and the lack of details at the time of the assessment of causality and preventability. To overcome these problems, we used TTM prospectively, which allow real-time review of cases to detect ADR. The present study was, therefore, undertaken to evaluate the efficacy of trigger tools to detect ADRs at Civil Hospital Ahmedabad (CHA). It also aims to compare the conventional existing spontaneous reporting with the underused TTM.

MATERIALS AND METHODS

This prospective, continuous, single-center study was conducted in the Department of Medicine of a tertiary care teaching hospital in Gujarat in two phases over 15 months. Phase I (6 months) of the study was observational, whereas Phase II (9 months) was interventional [Figure 1]. Prior permissions to conduct the study were obtained from the Institutional Ethics Committee (Letter No: EC/203/2015) and Head of the Department of Medicine.

Phase I (evaluation of triggers-6 months) [Figure 1]
After a pilot study by the investigator, a preliminary trigger tool list (PTTL) was prepared based on IHI Global TTL,^[6] Abideen^[2] List which includes 55 triggers: 20 DTs, 28 LTs, and 7 PTs. A total of 400 patients were enrolled after calculating sample size using formula

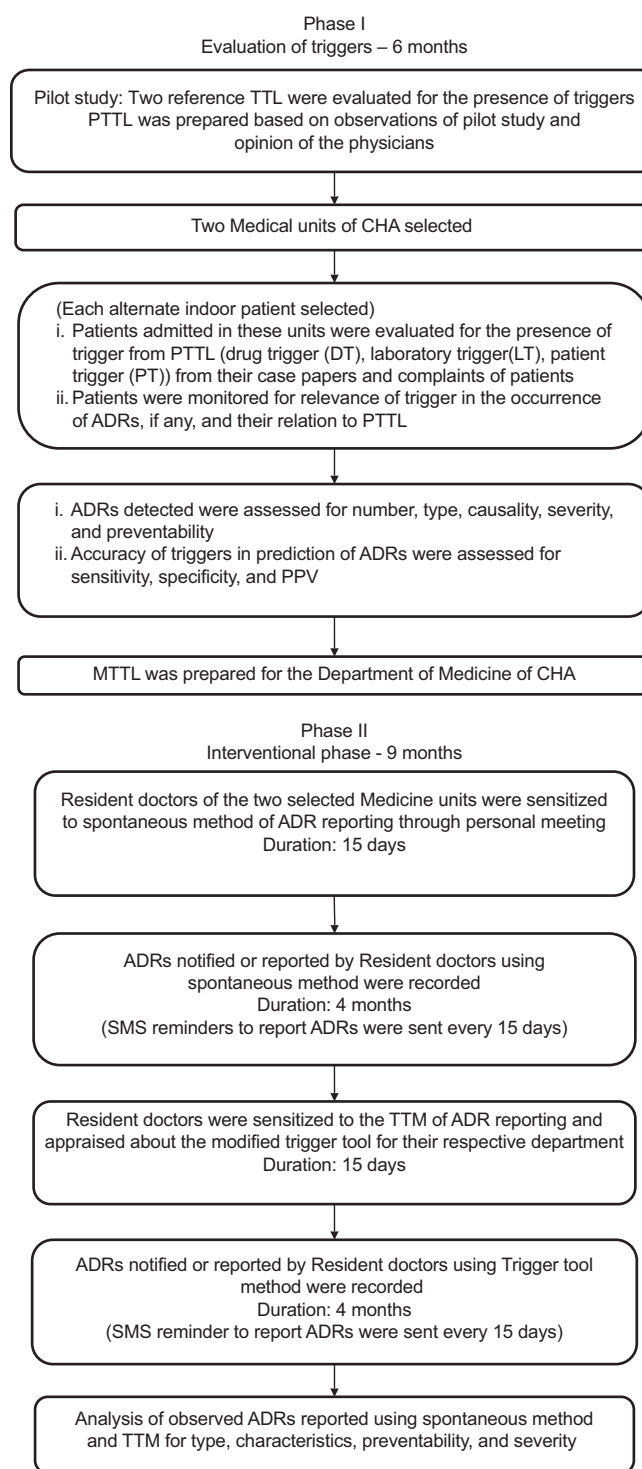


Figure 1: Study design and analysis: Phase I, Phase II

$n = 4PQ/L^2$ (n = sample size, P = prevalence, $Q = 1 - P$, L = allowable error). PTTL was tested in each alternate patient admitted in two selected Medicine units who consented to participate was included. Case papers of the patient, laboratory investigations, discharge form, and patients’ complaints were observed by the investigator and evaluated for the detection of triggers until the discharge

of the patient. The presence of one or more triggers and adverse event, if any, were recorded in pretested case record form. All detected triggers and adverse events were recorded and analyzed in terms of positive triggers (triggers related to ADRs) and negative triggers (triggers not related to ADRs). For accuracy of TT, the PPV, sensitivity, and specificity were calculated.

PPV was calculated as follows:

$$\text{PPV} = \frac{\text{Number of medical records in which the trigger indicated an ADE}}{\text{Number of medical records with triggers}} \times 100$$

Based on PPV of observed triggers a modified trigger tool list (MTTL) that was relevant and applicable to Medicine Department of CHA was prepared. The MTTL comprised 19 triggers (DT [10], LT [3], and PT [6]).

Phase II (interventional phase-9 months) [Figure 1]

Resident doctors of the selected medicine units were enrolled after consent to evaluate TTM and spontaneous method after an educational intervention. They were sensitized for 15 days to both methods through personal meetings and lectures. Then, they were observed for ADR reporting and notification over 4 months for each method. The need to report ADRs was reiterated through SMS reminders sent to them every 15 days during the study period. All ADRs reported or notified by resident doctors were collected in CDSCO ADR reporting form and assessed for causality, severity, and preventability using the standard Scales. Following the study, feedback was obtained from the resident doctors about their opinion regarding TTM and its usefulness in ADR reporting. All data are entered in Microsoft Excel 2007® and analyzed using appropriate statistical tests.

RESULTS

Phase I

A total of 1245 patients were admitted during the Phase I (6 months) of which 400 patients, who met with the inclusion criteria were included. Male: female ratio was 1.61:1 (males - 61.7% and females - 38.3%). The mean age of patients was 43.46 ± 18.08 years, and mean length of hospital stay was 4.75 ± 3.34 days.

Of 55 triggers (PTTL), a total of 34 triggers were found 1202 times in 327 patients. Among these, only 19 triggers detected 66 ADRs in 63 inpatients. Hence, the rate of ADE per 100 patients was 16.5. Neither a trigger nor an ADR was observed in 73 (18.25%) of patients.

DT (763 times; 63.47%) was the most commonly observed triggers followed by LT (327 times; 27.20%) and PT (112 times; 9.3%). One or more DT was observed 763 times in 298 patients; of which 43 patients had ADRs. Hence, PPV of DT was 14.43% (sensitivity 100% and specificity 22%). Similarly, LT were observed 327 times in 132 patients and 6 patients had ADRs. The PPV of LT was 4.5% (sensitivity 100% and specificity 36%). While PT was observed 112 times in 79 patients; of which 24 patients had ADRs. Hence, PPV of PT was 23.30% (sensitivity 100% and specificity 48%). The PTTL have high sensitivity (100%) and low specificity (21.66%) with PPV (overall) of 19.27%. The PPV for individual triggers ranged from 0% to 100%. The “use of thrombophob gel” has the highest PPV (100%), followed by rash (62.5%), sudden stoppage of the drug (54.05%), other complaints not related to disease (48.38%), pruritus (33.3%), and antidiarrheals (19.35%) [Table 1].

Among positive triggers, DT (10) was detected 47 times, whereas PT (6) and LT (3) were detected 27 times and 6 times, respectively. Hence, 19 triggers were observed 80 times which related to 66 ADRs. A minimum one to a maximum of nine triggers was observed in patients with ADRs. It is, therefore, apparent that more than one trigger was associated with a single ADR. It was further observed that patients in whom more than five triggers were present showed >30% “yield” in terms of detection of an ADR [Table 2]. The association of the ADRs with individual triggers is listed in Table 3.

All PT were observed in the study population. Twenty-one triggers (8 out of 20 DT and 13 out of 28 LT) were not observed in the study population. These were, therefore, deleted from the PTTL for preparation of MTTL made for the Department of Medicine, CHA. The triggers with PPV > 0% were included in the MTTL which comprise 19 triggers (DT = 10, LT = 3, and PT = 6) [Table 4].

Phase II

In Phase II, a total of 12 resident doctors participated: Male: Female ratio was 4.98:1. A total of 39 ADRs were reported by the resident doctors; 16 were reported using spontaneous method and 23 were reported by TTM using MTTL. Rate of AEs per 100 was 1.63 and 2.13 for spontaneous method and TTM, respectively. No statistically significant difference was observed between the numbers of ADRs reported by the two methods ($P = 0.51$). Triggers with higher PPV such as the use of thrombophob gel, rash, sudden stoppage of the drug, and other complaints lead to the detection of a greater number of ADRs than those with a lesser PPV. However, three triggers such as drowsiness,

Table 1: Positive predictive value of triggers evaluated during Phase I at a tertiary care hospital (n=400)

Trigger	Total triggers observed	Positive triggers (related to ADRs)	Negative triggers (not related to ADRs)	PPV (%)
DT	763	47	716	-
DT1 - Sudden stoppage of drug	37	20	17	54.054
DT2 - New drug administration	92	8	84	8.69
DT3 - Antihistamines	12	3	9	25
DT4 - Antiemetics	263	1	262	0.377
DT5 - Antidiarrheal	31	6	25	19.35
DT6 - Antacids	259	2	257	0.766
DT7 - Laxatives	18	1	17	5.55
DT8 - Vitamin K	13	0	13	0
DT14 - Steroids	2	0	2	0
DT15 - IV fluids started/dose increased	10	1	9	10
DT19 - Thrombophob gel	4	4	0	100
DT20 - Blood/blood product transfusion	18	1	17	5.55
LT	327	6	321	-
LT1 - PTT >100 seconds	2	0	2	0
LT4 - Abrupt drop in hemoglobin	16	2	14	12.5
LT5 - ESR increased	2	0	2	0
LT9 - ECG	63	0	63	0
LT11 - Hypocalcemia	9	0	9	0
LT13 - Hypokalemia	44	2	42	4.45
LT14 - Hyperkalemia	8	0	8	0
LT15 - Hyponatremia	50	0	50	0
LT16 - Hypnatremia	1	0	1	0
LT17 - Abnormal acid-base balance	27	0	27	0
LT18 - Hypoglycemia	3	0	3	0
LT19 - Hyperglycemia	2	0	2	0
LT20 - High cholesterol	6	0	6	0
LT23 - Abnormal LFT	56	0	56	0
LT24- Increased serum creatinine	38	2	36	5.26
PT	112	27	85	-
PT1 - Rash	8	5	3	62.5
PT2 - Pruritus	6	2	4	33.33
PT3 - Drowsiness/falls/lethargy	4	1	3	25
PT4 - Death	7	0	7	0
PT5 - Transfer/reference to other center	52	2	50	3.84
PT6 - Weight gain	4	2	2	50
PT7 - Other complaints	31	15	16	48.3

DT=Drug trigger, LT=Laboratory trigger, PT=Patient trigger, PPV=Positive predictive value, ADR=Adverse drug reactions, LFT=Liver function test, PTT=Partial thromboplastin time, ESR=Erythrocyte sedimentation rate, ECG=Electrocardiogram, IV=Intravenous

Table 2: Number of triggers observed per patient and their association with adverse drug reactions

Number of triggers detected	Number of patients (n=400), n (%)	Patients without adverse events (n=327), n (%)	Patients with adverse events (n=63), n (%)	Yield of total (%)	P
0	73 (18.25)	73 (18.25)	0 (0)	0	-
1	36 (9)	29 (7.25)	7 (1.75)	19.4	0.1697
2	79 (19.75)	75 (18.75)	4 (1)	5.06	0.0001*
3	51 (12.75)	45 (11.25)	6 (1.5)	11.75	0.0184
4	65 (16.25)	48 (12)	17 (4.25)	26.15	0.1262
5	38 (9.5)	30 (7.5)	8 (2)	21.05	0.1005
6	23 (5.75)	15 (3.75)	8 (2)	34.78	0.6827
7	13 (3.25)	9 (2.25)	4 (1)	30.76	1.00
8	14 (3.5)	8 (2)	6 (1.5)	42.85	1.37
9	8 (2)	5 (1.25)	3 (0.75)	37.5	0.6212

Statistical significance was determined by Chi-square test. $P < 0.05$ was considered statistically significant. * $P < 0.05$ as compared between patients without adverse events and patients with adverse events

use of laxatives, and IV fluids were not associated with any ADR.

In both phases, DT was most frequently observed, followed by PT and LT. However, no statistically significant difference

was observed between the number of positive triggers of two phases (P value for DT = 0.39, PT = 0.65, LT = 0.61).

The common organ system affected was gastrointestinal (36.28%) followed by skin and appendages disorder (13.3%),

Table 3: Positive triggers and related adverse drug reactions observed during Phase I

Trigger	ADRs	Number of ADRs detected	
DT			
DT1 - Sudden stoppage of drug	Diarrhea	4	
	Headache	3	
	Rash	3	
	Peeling of skin	1	
	Anemia	1	
	Loss of appetite	1	
	Increased serum keratinize	1	
	Hypokalemia	1	
	Muscle pain	1	
	Itching	1	
	Delirium	1	
	Cough	1	
	Vomiting	1	
	DT2 - New drug administration	Diarrhea	3
		Neuropathy	1
		Dry cough	2
		Hypokalemia	1
	DT3 - Antihistamines	Vomiting	1
		Rash	3
DT4 - Antiemetics	Vomiting	1	
DT5 - Antidiarrheal	Diarrhea	6	
DT6 - Antacids	Gastritis	2	
DT7 - Laxatives	Constipation	1	
DT15 - IV fluids started/dose increased	Hypoglycemia	1	
DT19 - Thrombophob gel	Thrombophlebitis	4	
DT20 - Blood/blood product transfusion	Anemia	1	
Total		47	
LT			
LT4 - Abrupt drop hemoglobin	Anemia	2	
LT13 - Hypokalemia	Hypokalemia	2	
LT24 - Increased serum keratinize	Increased serum creatinine	2	
Total		6	
PT			
PT1 - Rash	Rash	5	
PT2 - Pruritus	Pruritus	2	
PT3 - Drowsiness/falls/lethargy	Drowsiness	1	
PT5 - Transfer/reference to other centre	Rash	1	
	Pancreatitis	1	
PT6 - Weight gain	Weight gain	2	
PT7 - Other complaints	Somnolence	2	
	Headache	1	
	Dizziness	1	
	Vomiting	1	
	Myalgia	1	
	Loss of appetite	1	
	Metallic taste	1	
	Pedal edema	1	
	Dry cough	1	
	Edema on the face	1	
	Dizziness	1	
	Malaise	1	
	Increased bleeding tendency	1	
	Pancreatitis	1	
Total		27	

DT=Drug trigger, LT=Laboratory trigger, PT=Patient trigger, ADR=Adverse drug reactions, IV=Intravenous

Table 4: Modified trigger tool list for the Department of Medicine, Civil Hospital Ahmedabad

DT	LT	PT
Stoppage of drug	Increased serum creatinine	Rash
Antihistamines	Abrupt drop hemoglobin	Pruritus
Antiemetic	Hypokalemia	Patient fall/oversedation/lethargy
Antidiarrheal		Weight gain
Laxatives		Transfer to other health-care level
Transfusion of blood and blood product		Other complaints not related to disease
IV fluid started		
Thrombophob gel		
New drug administration		
Antacids		

DT=Drug trigger, LT=Laboratory trigger, PT=Patient trigger, IV=Intravenous

injection site disorder (11.4%), and neurological disorder (8.5%). A significantly higher number of ADRs of neurological disorder were reported by the spontaneous method as compared to the TTM ($P = 0.001$). No statistically significant difference was observed between other ADRs reported by the two methods.

The common causal drug groups which contributed to the ADRs were antibiotics (20.95%), antiretrovirals (15.23%), antitubercular drugs (7.6%), and NSAIDs (7.6%). ADRs occurring due to NSAIDs were better detected by TTM than by the spontaneous method ($P = 0.0006$). No statistically significant difference was observed between other causal drug groups with respect to the method of ADR reporting.

In majority of ADRs a causal association with the suspect drug was “possible” as assessed by the WHO-UMC Scale (61.91%) and by Naranjo’s Scale (55.24%). There was no significant difference in the causal association between the suspected drug and ADR reported by either method of reporting.

One serious ADR reported during Phase I, which required prolonged hospitalization. The severity assessment of ADRs by Hartwig and Siegel Scale showed that 62 ADRs were moderate and 43 were mild in severity. Moderately severe ADRs were better detected and reported by TTM as compared to the spontaneous method ($P = 0.0001$). Preventability of ADRs as evaluated by modified Schumock and Thornton criteria showed that 27 ADRs were probably preventable and 78 ADRs were not preventable.

All resident doctors responded for feedback (response rate 100%). All resident doctors were aware of pharmacovigilance and ADR reporting (100%). Majority of resident doctors (11, 91.6%) opined that the detection of ADRs was easier with TTM. Seven residents (58.33%)

agreed that TTM decreases the time to detect ADRs, whereas five (41.6%) were uncertain. Majority (10, 83.33%) opined that TTM improves the accuracy of reporting ADRs. Nine resident doctors (75%) were uncertain about the appropriateness of MTTL for the Department of Medicine.

DISCUSSION

In the current study, only 19 triggers (80 times) were related to one or more ADRs. Minimum one to maximum nine triggers was observed in a single patient. DT (58.75%) was most frequently associated with ADRs followed by PT (33.75%) and LT (7.5%). A prospective study conducted in 220 patients of the Internal Medicine Department at a tertiary care hospital of Karnataka, India, used 83 triggers in 40 patients; medication trigger (42, 50.6%) contributed most to detect ADRs followed by clinical trigger (16, 19.2%) and LT (5, 6.0%).^[7] A prospective study conducted by Naessens *et al.* observed eighteen triggers 3361 times in all cases; of which, 1465 (43.6%) were identified in 307 (27.0%) cases with an adverse event.^[8] Furthermore, a retrospective study conducted in Malaysia by Sam *et al.* observed nine triggers 45 times in 38 patients; 29 ADEs were detected using these triggers.^[9] In all the above studies, DTs were more frequently detected than PTs and LTs.

It was further observed that patients in whom more than five triggers were present showed >30% “yield” in terms of detection of an ADR in compared to Naessens *et al.* (50% “yield”).^[8] This suggests that the likelihood of detection of ADRs increases with the number of triggers per case.

PPV is the most commonly used parameter to assess the accuracy of trigger tool along with sensitivity and specificity. In the current study, the TT had a sensitivity of 100% and specificity of 21.66%. Matlow *et al.*^[10] found high sensitivity (85%) and low specificity (44%) of the TT. Karpov *et al.* observed the sensitivity of the trigger tools to be between 2.6% and 15.8% and specificity varied from 99.3% to 100%.^[11] Above findings indicate difference in sensitivity and specificity of TT used in different health-care setting.

In the current study, the overall PPV of PTTL was 19.27% as compared to Rozenfeld *et al.* (14.4%),^[12] Haffner *et al.* (18.6%),^[13] and Takata *et al.* (16.8%).^[14] In the current study, trigger with higher PPV were use of thrombophob gel (100%), sudden stoppage of drug (54.05%), weight gain (50%), other complains not related to disease (48.1%), pruritus (33.33%), antihistamines (25%),

antidiarrheal (19.35%), etc., An observational study conducted by Yerramilli *et al.*^[15] found that the triggers which have higher PPV were antihistamines (65%) followed by 25% dextrose (17%) and INR >6 (33%), whereas Rozenfeld *et al.* found maximum PPV was rash (100%) followed by blood sugar < 50 mg/dL (33.3%), the use of digoxin (33.3%), coagulants (16.7%), and antiemetics (12%). Hence, the range of observed PPV was 0%–100%.^[12] Kennerly *et al.* using TTM observed PPV of triggers to be between 0% and 100% with an overall PPV of 17.1%.^[16] Above findings reflects that PPV for predicting adverse events can be different for the same trigger in different clinical settings because the performance of the trigger may vary over time and is dependent on the existing diagnostic and therapeutic practices in the given health-care setting. Certain triggers occurring with a relatively lower frequency were more efficient in identifying ADE.

The final MTTL comprises 19 triggers. Certain triggers were not observed in the study population, which does not indicate the insignificance of the trigger. Trigger tools with a limited number of triggers reduce chances of false-positive triggers with less burden on the reviewer. TTM using lesser number of triggers, with higher PPV and comprising triggers which have clinical relevance are more effective.

Using TTM in Phase I, the rate of detection of ADEs was 16.5/100 patients which is comparable to other studies such as Brenner *et al.*^[17] (17.6 ADEs per 100 patients), Sam *et al.*^[9] (17 ADEs per 100 patients), and Rozenfeld *et al.*^[12] (26.6 ADEs per 100 patients).

During Phase II, there was no significant difference between spontaneous method (1.63) and TTM (2.13) in terms of rate of the AEs per 100 patients. Contradictory results were observed by other studies conducted Takata *et al.*,^[14] Kilbridge *et al.*,^[18] and Schildmeijer *et al.*^[19] where TTM was found more effective than spontaneous method. This may be explained by the fact that a separately trained reviewer was appointed to use TTM in these quoted studies, whereas in our study, TTM was used by resident doctors during Phase II. It is interesting to note that the improvement in the detection of ADR with TTM that was observed in Phase I, was not evident during Phase II in which a rate of 2.13 ADE per 100 patients, which was significantly less than the rate of ADE detected and reported during Phase I (16.5/100 patients) ($P < 0.001$). This finding can be explained by reasons like different judgments of reviewers in both phases. In Phase I, it was the investigator (a pharmacologist), whereas in Phase II, it was the resident doctor. Several other reasons have been

cited for this, including the lack of continuous on-going training, perceived lack of time by prescribers, patient burden, etc., which can affect the manual review of case record which is a more difficult task for treating doctors, especially if it is done in real time or prospectively.

TTM can be used as an add-on tool to existing methods like spontaneous method for the health-care professionals for better detection of ADRs in the pharmacovigilance program. However, further research is required to explore the feasibility and acceptability of TTM.

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Conflicts of interest

There are no conflicts of interest.

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