Original Article

Onsite serious adverse events reporting: Seven-year experience of the institutional ethics committee of a tertiary care hospital

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Abstract

Background: Over the years, Indian regulations have undergone numerous amendments, including stringent reporting deadlines, relatedness requirements, and compensation obligations for serious adverse event (SAE). A historic change, new drugs and trial rules-2019, was proposed on March 19, 2019. The purpose of the study was to ascertain whether various stakeholders were reporting in accordance with the evolving SAE criteria.

Materials and Methods: Data were retrieved after the Ethics Committee's approval between August 2014 and December 2021. Data gathered before March 19, 2019, were categorized as "BEFORE" data, while the remaining data were categorized as "AFTER." Utilizing causality, on-site SAE reporting, and the ethics committee review procedure, we evaluated the compliance. The data were evaluated using descriptive statistics, and the Chi-square or Mann–Whitney tests were used to compare the "BEFORE" and "AFTER" groups.

Results: A total of 77 SAEs were reported in 26 clinical trials, where most clinical trials were phase III. Endocrine projects made up 9/26 (34.61%). In the cardiology studies, the greatest SAE distribution was 21 SAEs/89 participants (23.59%) with approximately 48% of these being vascular. The "AFTER" group noticed a decrease in the total number and length of SAE subcommittee meetings. In the "AFTER" group, there was a significantly higher median number of agenda items/meetings (8 [4.5–10.75]) ($P < 0.0001$). The median interval between the onset of SAE and the first reporting date, however, was just 1 day (interquartile range: 1–5 days). In nondeath SAEs, there was no significant difference in the compensation paid. In the "AFTER" group, there were no discrepancies in reporting SAE.

Conclusion: There is acceptable adherence to SAE reporting criteria.

Keywords: Central Licensing Authority, Drugs Controller General of India, New Drugs and Clinical Trials Rules 2019, SUGAM portal

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INTRODUCTION

Clinical trials (CTs) are an integral element of the drug development process that produce proof of a drug's therapeutic advantages, efficacy, and safety with the aim of bringing a novel treatment to market. The National Institutes of Health revised the definition of "CTs" in

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2014, defining it as a "research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes."[1] Similar to this, the New Drugs and CT Rules 2019 (NDCTR-2019) in India provided new drug definitions with a research portfolio defining the subtleties of clinical research, the operation of ethics committees (ECs), and serious adverse event (SAE) reporting for all stakeholders.[2] However, performing a CT has a price and has its own pitfalls. The investigator, sponsor, EC, and regulators are required by the incidence of SAE to guarantee the safety of every participant. SAE is defined as any untoward medical occurrence, which results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect.[3] The investigator has an ethical obligation to make sure that all trial-related injuries and SAEs are properly collected and reported to trial stakeholders to confirm the drug's safety.[4] The investigator, sponsor, and EC are required to notify the Central Licensing Authority (CLA) of any SAEs of deaths and injuries within 24 h after their occurrence in accordance with the Drugs and Cosmetics Rules GSR 63 (E); February 1, 2013. In the event that a report is not submitted within the allotted time frame, the investigator notifies the CLA of the delay in reporting with the SAE report. After due analysis, it is mandatory for the investigator to submit the report to the CLA, EC, and the head of the institution of the trial site within 14 days.[5] It is the duty of the sponsor and EC to opine to the CLA and expert committee regarding the relatedness of the SAE to the CT and the amount of compensation to be paid to the participant within 30 days. The CLA will have 105 days to submit any suggestions to the expert committee regarding compensation and 150 days for the receipt of the final order from the CLA to the sponsor.[6]

After the Government of India released the NDCTR-2019 on March 19, 2019, a paradigm shift in reporting guidelines was noted. A new set of regulations was introduced after several modifications for better conduct of CT. The SAE reporting modifications, however, were minimal. According to the NDCTR-2019, investigators are required to send an initial report of all the SAEs (death/SAEs other than death) to the CLA, the sponsor, or its agent, and the EC within 24 h after the occurrence. After the investigator and sponsor become aware of the occurrence of SAE, they have 14 days to send a thorough analysis to the EC and CLA. Within 30 days of receiving the SAE report, the EC will send the reports on the causation of the SAE and the financial compensation that must be paid by either the sponsor or its representative to the CLA. Similar to this, free medical management will be provided if a trial participant is injured while participating in a CT for as long as necessary or until it can be established that the injury is unrelated to the trial, whichever comes first. The expert group designated by the CLA will next conduct a thorough investigation to determine the reason for the SAE. Further suggestions on the quantum of compensation will be put forward within 60 days. After receiving the CLA's order, the sponsor has 30 days to provide the remuneration to the study participant.[7,8] Previously, the Drugs Controller General of India (DCGI) received SAE reports from offline, physical files. On the other hand, the NDCTR-2019 offered a hassle-free electronic submission to the CLA. All CT stakeholders are required by a notice published on February 25, 2021, to submit SAE reports online through the SUGAM portal. Time and transaction costs have decreased with the introduction of e-submission.[9,10] The NDCTR-2019 has addressed the needless time frame delays.

Regulatory authorities work round the clock aiming to enhance and standardize the reporting of SAEs. However, determining how well the trial stakeholders adhere to the reporting deadlines has been made extremely difficult by the changing guidelines. Before and after the law's change, Tripathi *et al.* conducted a comparable study that documented the degree of compliance and adherence to the deadlines for SAE reporting by the investigators to the EC. Yet, the scope of the study was limited to the investigators' compliance in responding to EC.[11]

Hence, we designed a study to compare the SAE's reporting requirements before and after the adoption of the NDCTR-2019. We evaluated the adherence and compliance criteria in terms of the timing, the quantity of EC inquiries, the letters sent, the responses to EC letters, the filing of deviations, the actions done, and the compensation paid. This study will shed light on the drawbacks of CT enterprise SAE reporting and provide recommendations for future CT organizations.

MATERIALS AND METHODS

This study examined SAE reports that were reported to the Institutional EC (IEC) in a retrospective, observational manner. An expedited approval was granted by the IEC of Seth Gordhandas Sunderdas Medical College and the King Edward Memorial Hospital (EC/OA-35/2020). The research team followed the standard operating procedures for document recovery, and a thorough analysis was completed in the institute's Office of IEC. A confidentiality

agreement with the IEC was required to be signed by the study team to protect the privacy of the sponsor, participants, and investigators. The documents, including the SAE reports, correspondence from the IEC, agendas and minutes from meetings of the SAE subcommittee and the full board, as well as correspondence between the EC and the investigator, sponsor, and DCGI office between August 2014 and December 2021, were examined for each trial that was submitted. Only reports received by the IEC that were sponsored by pharmaceutical companies were included by the authors, and only those reports' relatedness to the SAE's cause was accurately recorded. The NDCTR guidelines went into effect on March 19, 2019; hence, a prespecified study period of 2014–2021 was chosen. Every piece of information gathered was evaluated "BEFORE" or "AFTER" the NDCTR regulations. The trials considered to be "BEFORE" were those that were submitted to the EC before March 19, 2019. Trials submitted after March 19, 2019, were regarded as being "AFTER." We assessed the following factors to gauge how closely different stakeholders were adhering to their guidelines.

Indicators of on-site serious adverse event reports

- Number of on-site SAE reports received per project
- Number of on-site SAE reports received per therapeutic area
- Type of SAE reports based on SAE term classification
- Number of reports changed the SAE term
- Number of initial and follow-up SAE
- Number of close-out reports per project.

Indicators of causality

- Assessment of causality by EC, sponsor, and principal investigator (PI)
- Degree of agreement among PI and sponsor.

Indicators of the institutional ethics committee review process

- Number of meetings: SAE subcommittee and full board
- Duration of meetings
- Number of reports reviewed per meeting
- Difference in timelines between onset and reporting date
- Action taken by the IEC
- Timelines followed by the DCGI.

Microsoft Excel 365 was used to record the information received for each SAE, and descriptive analysis of the demographic data was performed. Using Fisher's exact test/Chi-square test, the number of studies reporting SAEs and the delay in SAE reporting to EC were compared in the BEFORE and AFTER groups. Parameters including the number of queries per project and the duration of time for EC's response between the two study periods were compared using the Mann–Whitney test. $P < 0.05$ was deemed statistically significant.

RESULTS

The data were gathered between August 2014 and December 2021 (88 months), with the "BEFORE" group being 4 years, 6 months, and 25 days and the "AFTER" group being 2 years, 8 months, and 4 days.

Indicators of on-site serious adverse event reports

Only 163 (6.9%) of the 2361 research submitted to the EC were CTs for drugs. The IEC received 77 SAEs from 26 CTs, with 24/26 (92.3%) being phase III trials. Only 1/26 (3.8%) people were in phases II and IV, respectively. Figure 1 shows the therapeutic areas of the included trials.

The median number of reports per project was 3 (interquartile range: 1–11). 77 SAEs were reported in 70 patients, 61% of whom were men and 39% of whom were women. The mean age of the patients experiencing SAE was 54.32 ± 17.96 years.

The frequency of SAEs reported to the total sample size authorized at the site in that therapeutic area was used to analyze the distribution of SAEs. Cardiology had the most SAEs, 21/89 (23.59%), followed by hematology, 3/14 (21.42%), and endocrinology, 37/197 (18.78%). Clinical pharmacology studies with vaccines revealed the lowest SAE distribution, at just 7/840 (0.83%). Figure 2 depicts the detailed on-site SAE reports per therapeutic area. In Figure 3, type of SAE based on SAE term classification has been illustrated.

Ethical review process indicators are mentioned in Table 1.

Figure 4 depicts the indicators of causality by different stakeholders (investigator/sponsor/EC).

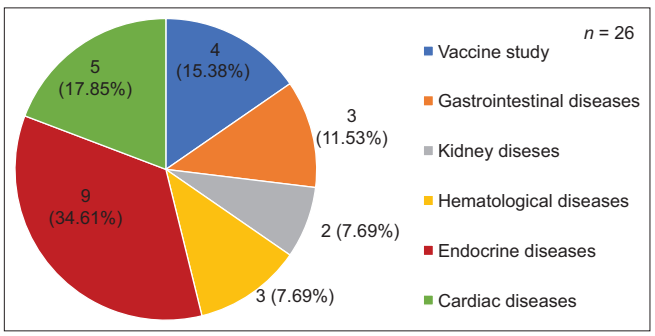

Figure 1: Number of projects per therapeutic area

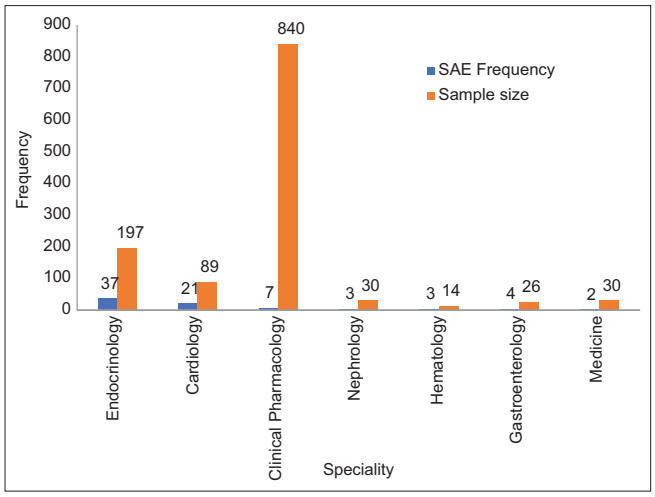

Figure 2: Number on-site serious adverse event reports per therapeutic area. SAE = Serious adverse event

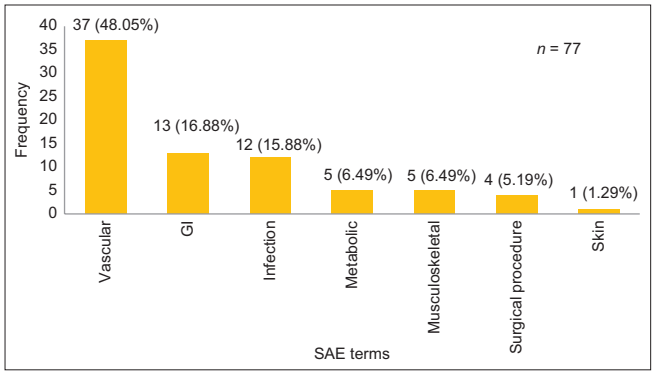

Figure 3: Type of serious adverse event (SAE) reports based on SAE term classification. GI = Gastrointestinal, SAE = Serious adverse event

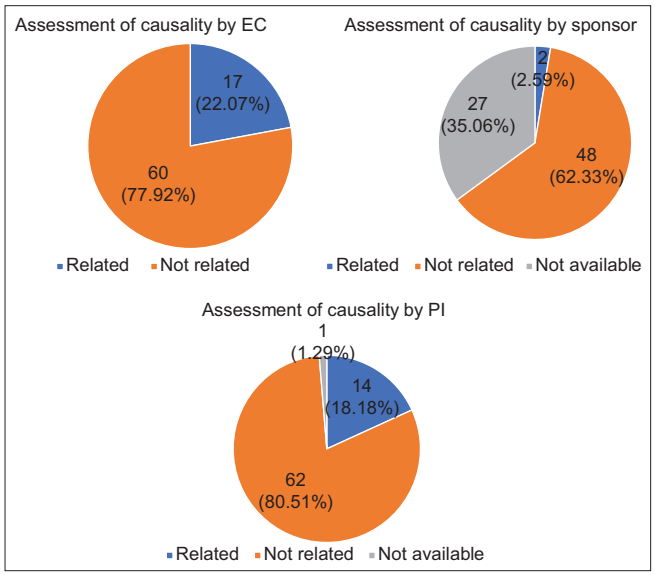

Figure 4: Causality assessment of serious adverse events by various stakeholders ($n = 77$), EC = Ethics committee, PI = Principal investigator

A precisely matched agreement was seen in 50/77 (64%) trials, according to an evaluation of the causality agreement between the PI and the sponsor. 48/77 (62.33%) trials indicated agreement of unrelatedness and 2/77 (2.59%) trials demonstrated relatedness across the 50 matched causality experiments. 27/77 (35%) trials showed disagreement between the sponsor and PI. Out of the 27 unmatched causalities, disagreement was observed in five SAE reviews between PI and sponsor; one in the "BEFORE" group and four in the "AFTER" group; nevertheless, this disagreement was not statistically significant when compared with the Chi-square test. Two reports each from the PI and sponsor showed a change in causality from the initial reporting to the follow-up report (from nonrelated to related association).

Table 1: Indicators of on-site serious adverse event report

Indicators	Before, *n* (%)	After, *n* (%)	Total
Initial reports	51 (66.23)	26 (33.76)	77
Follow-up	51 (66.23)	26 (33.76)	77
Closeout	12 (75)	4 (25)	16
Deaths as SAE	3 (60)	2 (40)	5
Nondeath as SAE	46 (63.88)	26 (36.11)	72

SAE = Serious adverse event

Indicators of the ethical review process

Table 2 lists the indicators of the EC evaluation procedure. Out of the 26 clinical trials, 17 trials (51 SAE reports) were in the "BEFORE" group. Table 2 contains a list of the additional EC review indicators.

The EC has reported to the DCGI office; the review process and the timelines are mentioned in Table 3.

DISCUSSION

Due to its quick completion and lower cost to the multinational pharmaceutical sector, India is already establishing itself as a desirable location for the conduct of CT.[12] It serves as a hub for CT due to the wide population with a variety of traits, easily accessible supplies, and infrastructure. The demand for strict reporting criteria has increased as a result of this expanding trend.[13]

In 2005, amendments were made to Schedule Y to bring Indian norms on par with international guidelines. The SAE reporting timelines for sponsors and investigators were mentioned. The necessary paperwork for reporting an SAE and the rules for postmarketing surveillance, like Periodic Safety Update Reports, are listed.[13,14] With the implementation of many SAE reporting requirements and the reimbursement for these SAE, 2013 was a watershed year.[11] With several amendments and major revisions, the Indian government has announced the NDCTR-2019 to replace Part XA and Schedule Y of the Drugs and Cosmetics Rules-1945, which offers benefits, strengthens, and expedites SAE reporting.[15] Due to our

Table 2: Indicators of the ethical review process

Indicators	Before	After	Total
Period	4 years, 6 months, and 25 days	2 years, 8 months, and 4 days	88 months
Number of projects	17	9	26
Number of on-site SAE reports received	51	26	77
Number of SAE subcommittee meetings	183 (all offline)	50 (35 offline; 15 online)	233
Number of agenda items/meeting, median (IQR)	3 (2–6)	8 (4.5–10.75)*	5 (2–10)
Duration of subcommittee meetings, mean±SD (min)	30±5	20±5	31.87±6.95
Full board meetings (reports/meetings)	54 (2)	30 (1)	84 (1.04)
Median time duration between onset of SAE and date of reporting of the initial report of on-site SAE	Timely (delay in 2 reporting)	Timely# (delay in 1 reporting)	1 day (IQR: 1–5 days)
Median time duration between onset of SAE and date of reporting of follow-up report of on-site SAE, median (IQR)	Timely	Timely	14 (4–18)
Compensation paid in nondeath SAEs, median (IQR)	6835 (2412–12,355)	8627 (2276–12,060)	7289 (2276–12,355)
Number of letters sent by the EC to investigators	102 letters/51 SAEs	63 letters/26 SAEs	165 letters/77 SAEs
Number of queries sent by the EC to investigators, median (IQR)	Four queries/letter: 1 (0–5)	Three queries/letters: 1 (0–5)	Four queries/letters: 1 (0–5)
Number of query replies sent by the investigator to the EC	101 letters/51 SAEs	62 letters/26 SAEs	163 letters/77 SAEs
Deviations in SAE initial reporting by investigators	3	No deviations	3/77 SAEs
Deviations in replying to queries of the EC	1	1	2/77 SAEs
IEC action	Warned all four investigators	Warned one investigator	Warned all five investigators

*$P<0.0001$ statistically significant; Mann–Whitney *U*-test, #$P<0.001$ significant; Chi-square test. SAE=Serious adverse event, IQR=Interquartile range, IEC=Institutional ethics committee, EC=Ethics committee, SD=Standard deviation

Table 3: Indicators of the ethical review process from the regulators

Indicators	Total	Before	After
Letters received from the DCGI office to EC	16 letters/77 SAEs Two related and one not related. 13 letters related to compliance with guidelines	Three letters	13 letters (SUGAM portal reporting not done by PI)
Median time duration between the IEC letter and DCGI response (days)	399 (IQR: 124–622)	399 (IQR: 124–622)	Within 30 days of the IEC reporting on email and hard copy submission

IQR=Interquartile range, IEC=Institutional ethics committee, EC=Ethics committee, PI=Principal investigator, SAEs=Serious adverse events, DCGI=Drugs Controller General of India

decision to choose the duration "BEFORE" and "AFTER" the NDCTR-2019 recommendations, the two groups' durations are not equal. The study's primary objective was to determine how closely stakeholders adhered to the rules during the two time periods.

In this 7-year retrospective study, a meager 77 SAEs from 26 projects were filed. The drop from 17 to 9 proposals submitted to the EC was apparent. Another intriguing finding was a 50% decrease in the SAE reporting, following the introduction of NDCTR 2019, attributed to the fewer research being reported in the "AFTER" group. The strict NDCTR-2019 regulations on the compensations that must be paid in the event of an SAE may also be to blame for the decrease in frequency. It entails license cancellation, a CT conduct prohibition for the future, blacklisting, and penalization of the study center and team.[16] The underreporting of SAE might be due to the fear of enormous compensation payments in the short stipulated time.

Endocrine therapy was the focus of most phase III trials. Cardiology research and vaccination studies were among others. The possibility of running into an SAE is substantially higher in phase III trials because they involve a lot of subjects.[17] 77 SAEs (five deaths and 72 nondeaths) were reported in a total of 70 patients with a male preponderance and mean age of 54.32 ± 17.96 years. Cardiology reported the most on-site SAEs, followed by hematology with over 48% vascular-related SAE. The vulnerability of cardiovascular patients to an SAE could be due to advanced age, polypharmacy, and the impact of heart disease on drug metabolism.[18]

The main duties of the EC are to regulate CT and guarantee the rights, welfare, and safety of test subjects.[19] After opining on the relatedness of each reported SAE, the EC evaluates all reported SAEs and recommends either free treatment or compensation for any trial-related deaths or injuries.[20] In addition, there is a discrepancy in the way ECs work in India, with some of them debating SAE in a full board meeting. However, at our institute a distinct SAE subcommittee has been established within the EC which assists in analyzing all SAEs submitted and then informs the members of whole board of EC.[21] Reviewing SAE reports on-site should be completed quickly.

We noticed a reduction in the number of SAE subcommittee meetings (50 online "AFTER" vs. 183 offline "BEFORE") and a decrease in the total meeting time with a mean duration of 20 ± 5 min "AFTER" versus 30 ± 5 min "BEFORE." Compared to 54 meetings "BEFORE," there were only 30 full board meetings. Furthermore, three meetings each month were organized to analyze the 77 SAE reports generated on-site. Shortly after the NDCTR-2019, the COVID-19 pandemic was struck, and the meetings were held online. The SAE subcommittee's activities may have decreased due to the difficulties the members have had adjusting to the electronic review process due to a variety of technical issues, such as network connectivity, communication gaps, audio-visual interruptions, fear of file sharing on an e-platform, a lack of face-to-face interaction, and difficulty interacting with the researchers. Reviewing the evidence that can influence the causality analysis, decision-making is a laborious procedure.[22] Due to their experience in the field, hiring a medical scientist – preferably a pharmacologist – benefits causality analysis. All through the year, the EC receives SAE data in bits and pieces. Hence, a panel with a pharmacologist, clinician, and adequate training of EC members is recommended to analyze the SAE causality and decide the quantum of compensation.[7,8]

In the "AFTER" group, we noticed a marked increase in the number of agenda items discussed at each meeting. Initial reporting (two) "BEFORE" and (one) "AFTER" periods was delayed. These were the lapses made by the investigator. However, the EC warned and censured these sites in writing. Timely follow-up reporting of SAEs was seen. Only 16 SAE close-out reports could be retrieved and evaluated because either the SAEs were unresolved or they were still in progress.

Disagreement was found in the causality assessment five SAE reporting between the PI and sponsor, who thought the two were "unrelated," whereas the PI and EC disagreed. It is important to address this serious concern. When various circumstances need to be considered, the clinician's knowledge and clinical judgment serve as a pillar in determining causation.[23] For a trial sponsor, SAE will be adopted and the causality assessment will be performed by the separate pharmacovigilance team.[24] The best approach is using the global introspective technique coupled with other causality measures, such as the Naranjo Scale or the WHO-Uppsala Monitoring Center Scale. The disparity in causality may also result from the fact that only "related" SAEs in India are eligible for financial compensation, which devalues causality.[7,25] However, the DCGI makes the final decision. Due to the challenges participants faced with finances, employment, transportation, and hospitalization during the COVID-19 pandemic, as well as the value they contributed to the research, a higher compensation was availed in the "AFTER" group than in the "BEFORE" group.[26]

There was a difference in the number of letters received between the groups (3 vs. 13 letters: "AFTER"). These 13 letters from the PI mostly informed DCGI of the PI's failure to report SAEs online using the SUGAM portal. Most sites encountered difficulties uploading the SAE through the SUGAM portal and instead continued to submit their reports by email or hard copy. The CDSCO has laid down a user-friendly manual for online submissions through SUGAM.[10] However, suggestions can be made for all stakeholders to receive the required training.

The median time between the IEC letter and DCGI answer was 399 days as opposed to 30 days in the "AFTER" group underlining the flexibility of the timetables before NDCTR-2019. The DCGI and e-platforms have dedicated staff, which has shortened the response lag time.[7]

Limitations

1. It was a retrospective analytic study
2. The data cannot be generalized to tertiary care centre where regulatory studies are not conducted
3. There was no rhyme or reason behind the period choice. Therefore, it is impossible to rule out the inherent investigator bias.

CONCLUSION

The current study assessed how well different stakeholders were following the NDCTR-2019 recommendations. There were no significant delays in reporting, demonstrating satisfactory adherence to the rules. The NDCTR-2019's introduction has been demonstrated to improve SAE reporting. For increased generalizability, we advise a study with many IECs from India.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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