Original Article

A retrospective audit to analyze protocol deviations that occurred in regulatory clinical trials at a tertiary referral center in India

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Abstract

Context: Protocol deviations (PDs) are not uncommon in clinical trials (CTs) and understanding their nature can help mitigate their occurrence.

Aims: To audit PDs in archived regulatory CTs conducted at a single research department over a 25-year period.

Subjects and Methods: We included archived regulatory CTs and excluded ongoing studies and academic studies. Data were extracted from trial master files and PD forms filed with the Institutional Ethics Committee. PDs were categorized by type, category, and whether corrective and preventive actions (CAPAs) were taken.

Statistical Analysis: Both descriptive and inferential statistics were applied to the data. Chi-square tests compared PD frequencies between pandemic and nonpandemic periods and content analysis was used for qualitative categorization.

Results: A total of 21 regulatory CTs yielded 526 PDs, of which 85.2% were minor and 14.8% were major, respectively. The majority (42%) related to follow-up visits beyond the allowed window, and 37% to sample collection, processing, and storage. Only 0.8% were consent-related. There was a significant increase in PDs during the coronavirus disease 2019 (COVID-19) pandemic ($P < 0.00001$), with 85% of PDs in six trials attributed to pandemic-related disruptions. The most frequent CAPA was re-counselling participants (39%).

Conclusions: Most PDs were minor and manageable, but the COVID-19 pandemic led to a significant rise in deviations.

Keywords: Clinical research, pharma-sponsored, protocol violations

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Received: 27-05-25, **Revised:** 15-11-25, **Accepted:** 10-12-25, **Published:** 25-02-26.

INTRODUCTION

Protocol deviations (PDs) in Institutional Ethics Committee (IEC) and regulator approved protocols are known to occur. They can be minor, inconsequential divergences (e.g., missing a visit and administrative errors) or more serious affecting data quality and participant safety (for e.g., enrolling an ineligible participant).[1,2]

Access this article online	
Quick Response Code:	Website: www.picronline.org
	DOI: 10.4103/picr.picr_159_25

How to cite this article: Parida R, Chaudhari VL, Hinglaspurkar SS, Argade AS, Jagushte S, Sawant N, *et al*. A retrospective audit to analyze protocol deviations that occurred in regulatory clinical trials at a tertiary referral center in India. Perspect Clin Res 0;0:0.

Evaluation of these PDs can understand areas where improvement is needed and this formed the primary objective of the study. The secondary objective was to compare PDs that occurred during the coronavirus disease 2019 (COVID-19) pandemic with those that occurred in a nonpandemic setting.

SUBJECTS AND METHODS

Ethics

We obtained IEC approval (with a consent waiver) and registered our study (CTRI/2024/07/069818).

The institute, study design, and eligibility criteria

Our department is housed in a 2200 bedded tertiary referral center and conducts all phases of clinical trials (CTs). We conducted a retrospective audit and included all archived regulatory CTs. Academic trials and ongoing regulatory studies were excluded.

Major and minor protocol deviations

We classified the PDs as major and minor and also evaluated the corrective and preventive actions (CAPAs) taken A major PD was defined as one which deviated significantly from the IEC approved protocol and impacted participants rights and safety and data integrity (for example use of the wrong version of informed consent form (ICF), missing signature on the ICF, any other consent related issues or any investigation product (IP) related issue or ineligible participant enrolment). We defined a minor PD one which was considered nonsignificant or one that could not be controlled (some examples-missed visit by the patient, visits slightly outside the window period, delay in blood collection by a few minutes). We further sub-classified the PDs as related to-follow-up, sample collection/processing/storage, documentation, IP administration/storage, consent-related, and patient selection. We also had a category of *PDs not required* but reported as a PD (lost to follow-up or consent withdrawal after enrolment) as these were not in line with the protocol. We did not use the term protocol violations for the study.

Corrective and preventive action categories

The following categories were used-for classification-retraining of the study team, re-counseling participant, participant recalled to study site, safety related (for example: Administration of IP [next dose] adjusted, Safety assessment of relatives who consumed IP, Possible safety data captured via telephonic call, Patient withdrawn from study, IP randomization sheet adjusted by sponsor, data and safety monitoring board held), correction in document, Temperature Excursion, and CAPA not possible. Each category was subsequently coded independently by four authors and a consensus reached.

Information gathered and outcome measures

Phase of the CT, total number of regulatory studies from 1998 to date, total number of PDs, whether major or minor, category of PD, and the CAPA taken.

Qualitative analysis

Content analysis[3] was done using the categories mentioned in the previous section.

Quality checks

Four authors independently evaluated the data with one senior author conducting quality checks. Any disputes were resolved through the consensus.

Statistical analysis

Both descriptive and inferential statistics were applied. Quantitative data were expressed as mean standard deviation (SD) and categorical data as frequency (percentage) and 95% confidence intervals were calculated. Normality was assessed using the Shapiro–Wilk test. The comparison between the occurrence of PDs due to COVID-19 and without COVID-19 and in various CTs phases was done using the Chi-squared test. Similarly, we used the Chi-square test to compare the differences in PDs between early phase trials (Phase I and Phase II) and later phase trials (Phase II/II and Phase IV) All statistical analyses were done using the SPSS software version 29, IBM Corporation, Armonk, New York, USA and the *P* value was set at < 0.05.

RESULTS

Demographics

We reviewed 21 trials with 526 PDs. Ten of 21 trials were Phase III followed by Phase I, II, and II/III trials (3/21 each). There were 2/21 Phase IV trials. There were 78/526 (14.8%) major PDs and 448/526 (85.2%) minor PDs.

Comparison of protocol deviations based on phase of study

The proportion of major *versus* minor PDs differed significantly by study phase ($P < 0.0001$): Phase I had only minor deviations, while Phase II had the highest proportion of major deviations (43.3%) [Table 1]. Mean (±SD) major and minor deviations per study were 3.71 ± 9.13 and 21.33 ± 39.09, respectively.

Comparison of occurrence of protocol deviations during coronavirus disease 2019 and prior coronavirus disease 2019

A total of six regulatory trials were ongoing during the COVID-19 pandemic, of which three regulatory trials were initiated before the COVID-19 pandemic. A total

of n = 242 PDs occurred in these six CTs. Of which, n = 205/242 (85%) occurred due to the COVID-19 pandemic-related lockdown [travel restrictions] and fear of contracting SARS-CoV2 infection. There was a statistically significant rise in the occurrence of PDs during the COVID-19 pandemic as compared to prior COVID-19 pandemic (χ^2 [1, n = 526] =390.12, $P \leq 0.00001$).

Content analysis for protocol deviations during the coronavirus disease 2019 pandemic time period [Table 2a]

Most 205 PDs (155/205, 75.6%) were due to follow-up beyond the protocol allowed window and sample collection/processing/storage (40/205; 19.5%). About 4.9% were related to IP administration/storage.

Content analysis for protocol deviations during the nonpandemic time period [Table 2b]

Most 321 PDs (154/321, 48%) were due to sample collection/processing/storage and follow-up beyond the protocol allowed window (65/321; 20.2%). About 15% and 12.8% were related to documentation and IP administration/storage. Consent-related PDs accounted for 1.2% (4 cases), and only one PD was due to wrong patient selection.

Content analysis for corrective and preventive action

A total of seven categories were created - re-counseling participant (n = 204), retraining of the study team (n = 65), participant recalled to study site (n = 45), safety (n = 27), correction in document (n = 20), temperature excursion (n = 27), and corrective action reporting (n = 115). These categories were further delineated using several codes [total 26 codes, Table 3]. Of total n = 526 PDs majority of the 204/526 (39%) corrective actions involved re-counseling participant followed by one quarter 138/526 (26%) were the PDs where the CAPA was either not possible or not mentioned or mentioned inappropriate (13/526, 2.4%). Whereas, approximately 12% CAPAs involved retraining of the study team. For n = 45/526 (9%) PDs the participants were recalled to the study site to correct the PD. Similarly, for n = 27/526 (5%) PDs, the safety of the participant and data integrity were compromised each and later on corrected and prevented.

Table 1: Comparison of major and minor protocol deviations per the phase of the study

Number of studies (n=21)	Phase	Major PD (n=78), n (%)	Minor PD (n=448) n (%)	Total
3	I	0	41 (100)	41
3	II	13 (43.33)	17 (56.67)	30
3	II/III	3 (1.61)	183 (98.39)	186
10	III	57 (23.36)	187 (76.64)	244
2	IV	5 (20)	20 (80)	25

P<0.0001, χ^2=64.099, df=4. PD=Protocol deviation

DISCUSSION

In the present retrospective audit, we evaluated n = 526 PDs that occurred in a total of 21 regulatory CTs during last 15 years and found a majority of the PDs (85%) to be minor in nature. There was a significant rise in PD reporting during the COVID-19 pandemic compared to nonpandemic period. The most common PD seen was participant follow-up beyond the protocol allowed window (42%, including both time frames – pandemic and nonpandemic) and the most common CAPA linked to this PD was re-counseling trial participants (39%).

The predominance of minor PDs (85.2%) over major PDs (14.8%) suggests that while deviations were not uncommon, most were not critical. The presence of nearly 15% major PDs underscores the importance of stringent monitoring systems and quality checks by the various stakeholders. In a retrospective study (January 2011–August 2014) of 447 PDs conducted by Jalgaonkar *et al*.[4] that evaluated PDs that were reported to the IEC, 73% major PDs. The 447 PDs from 73/1387 studies included regulatory, government-funded, academic, and thesis-based studies. The majority were related to study procedures (68%), followed by safety, informed consent, and eligibility issues. This difference is likely because of the IEC seeing PDs from studies all over the institute and we seeing PDs only from studies conducted in our department.

Table 2a: Content analysis of protocol deviations during the coronavirus disease 2019 pandemic (n=205): Time frame: March 2020–May 2022

Category	Sub-category	Coding	n	Frequency (%)
Follow up beyond the allowed window (n=155)	COVID-19 pandemic	Unable to travel to reach study site	155	75.6
Sample collection, processing and storage (n=40)	Sample collection	Not collected due to lockdown	22	19.5
		Sample not collected as patient discharged before EOS visit and unable to return due to pandemic lockdown	6	
		Sample not collected on time due to lockdown	2	
	Sample analysis	Sample not analysed due to reagent shortage from cancelled international flights during the pandemic	10	
IP administration or storage (n=10)	IP dose skipping	IP dose skipping as per PI discretion or not administered at trial site due to fear of contracting SARS-CoV2 infection	10	4.9

COVID-19=Coronavirus disease 2019, PI=Principal investigator, IP=Investigation product, EOS=End of stay

Table 2b: Content analysis of protocol deviations during the noncoronavirus disease 2019 (n=321): Time frame: April 2013–August 2023 (excluding March 2020–May 2022)

Category	Sub-category	Coding	*n*	Frequency (%)
Follow up beyond the allowed window (*n*=65)	Participant related	Personal reasons	7	20.2
		Participant away from study site	8	
		Developed medical event	3	
		Mobile phone lost/not recharged	3	
		Forgot about the visit	1	
		Early visit (visited the site before the actual visit)	4	
	Study team member related	Home visit not conducted by study team member	15	
		Picked up during monitoring	2	
	Unknown reason	Reason not mentioned	22	
Sample collection, processing and storage (*n*=154)	Sample collection	Not collected due to loss to follow-up after migration out of the city	1	48
		Participant refused to give sample	4	
		Unable to collect the exact sample volume	2	
		PK sample not collected at specified timelines	39	
	Sample processing	Blood sample centrifuged immediately instead of after 60 min	22	
		Tube kept at room temperature for <2 h instead of 2 h	1	
	Sample storage	Temperature excursion in the deep freezer	24	
	Sample analysis	Not analysed due to clotting/hemolysis	9	
		Sample could be analysed due to leak	2	
		Urine ketone body estimation missed by the laboratory	50	
Documentation (*n*=48)	Failure to record	Readings/procedures within timeline (e.g., 24-h ECG, ECG triplets with 1-min gap, 72-h temperature)	21	15
		Data entry in electronic data capture software in specified timelines	11	
		Laboratory reports in CRF	1	
		Correct duties in duty delegation log	1	
		Principal signature on study document	1	
		Designated person's signature on CRF	9	
		Consent narrative	2	
	Failure to report	SAE initial report within timeline	2	
IP administration or storage (*n*=41)	IP administered	At wrong timelines	19	12.8
		In wrong condition	8	
		To wrong participant	1	
		By wrong person (not designated)	2	
		With wrong dose calculation	1	
	IP sharing	By participant to relative	2	
	Concomitant medication administered	Which was prohibited/a rescue medication	2	
	IP storage	Temperature excursion	5	
	IP accountability	Missing IP vials	1	
Consent related (*n*=4)	Version	Wrong ICF version used	1	1.2
	Documentation	Signature of participant missed	1	
	Wrong age calculation	Instead of consent from LAR, adolescent participant's consent was taken (assent missed)	1	
	Procedure performed before consent	ECG done prior consent	1	
Patient selection (*n*=1)	Eligibility criteria missed	Exclusion criteria missed	1	0.3
Not required (*n*=8)	Consent withdrawal	Did not wish to continue in the study	2	2.5
	Lost to follow up	Migrated, did not receive telephonic calls, visit the study site even after the scheduled visit	6	

CRF=Case record form, PK=Pharmacokinetic, ECG=Electrocardiogram, SAE=Serious adverse event, IP=Investigation product, ICF=Informed consent form, LAR=Legally authorized representative

Our analysis revealed that 85% of PDs in the six trials conducted during the pandemic were directly linked to COVID-19-related disruptions, such as lockdowns and travel restrictions. The statistically significant rise in PDs during the pandemic ($P < 0.001$) highlights the challenges faced by both investigator teams and the participants during this difficult period. This finding aligns with the predicted increase in protocol violations/PDs during the pandemic period compared to the prepandemic period, as outlined by various ethical guidelines[5-7] and other global reports,[8,9] emphasizing the need for decentralized trials (for example-liaising with family practitioners, online training for subcutaneous injections, courier delivery of IPs) so that participant care (that is an ethical imperative) is not impacted.

The content analysis showed the majority of PDs occurring due to follow-up visits beyond the allowed window (42%) and issues with samples (collection, processing, and storage). These findings align those of Jalgaonkar *et al*.[4] The low occurrence consent related PDs (0.8%) and

Table 3: Content analysis of corrective and preventive actions

Category	Coding	Frequency, *n* (%)
Re-counselling participant (*n*=204; 39%)	1.1. Importance of adhering to the study visits	18 (8.8)
	1.2. To visit the study site whenever possible	180 (88.2)
	1.3. To receive vaccine at nearby hospital	4 (2.0)
	1.4. Not to share IP with relatives	2 (1.0)
Retraining of the study team (*n*=65; 12%)	2.1. Protocol	54 (83.1)
	2.2. Duty delegation	8 (12.3)
	2.3. SAE timelines	2 (3.1)
	2.4. ICF documentation	1 (1.5)
Participant recalled to study site (*n*=45; 9%)	3.1. To perform lab investigations	42 (93.3)
	3.2. To re-consent	2 (4.4)
	3.3. To sign on ICF which was missed at one place	1 (2.2)
Safety (*n*=27; 5%)	4.1. Administration of IP (next dose) adjusted	19 (70.4)
	4.2. Safety assessment of relatives who consumed IP	2 (7.4)
	4.3. Possible safety data captured via telephonic call	2 (7.4)
	4.4. Patient withdrawn from study	2 (7.4)
	4.5. IP randomization sheet adjusted by sponsor	1 (3.7)
	4.6. DSMB held	1 (3.7)
Correction in document (*n*=20; 4%)	5.1. Correction in duty delegation log	9 (45.0)
	5.2. Appointing new member in study	7 (35.0)
	5.3. Consent narrative recording	2 (10.0)
	5.4. SAE reporting immediately when recognized	2 (10.0)
Temperature excursion (*n*=27; 5%)	6.1. IP storage- engineer called, review of calibration certificate, power back up set, permission to use IP is obtained from sponsor	3 (11.1)
	6.2. Sample storage - engineer called, review of calibration certificate, power back up set, back up data logger installed, temperature stabilizer installed, transfer of sample to back up deep freezer, regular defrosting, timer purchased	24 (88.9)
Corrective action (*n*=138; 26%)	7.1. Not possible	103 (74.6)
	7.2. Not mentioned	22 (15.9)
	7.3. Not appropriate	13 (9.4)

IP=Investigation product, ICF=Informed consent form, SAE=Serious adverse event, DSMB=Data and safety monitoring board

participant selection PDs (0.2%) suggests a high regulatory and compliance bar of the site.

Re-counseling participants were the most common corrective action (39%) indicating the need for more effective clear communication with participants, especially early on in the study. However, the fact that CAPA was either not possible (for PDs that were beyond the control of the investigator/study team), not mentioned, or inappropriate in 26% of PDs suggests gaps in the implementation of corrective actions themselves. Our recommendations for other PIs thus would be to have a quality manager in the academic setting who oversee these trials real time to mitigate some of the PDs. This QC manager would be someone over and above the sponsor's monitor. For ethics committees, we suggest increased frequency of monitoring and at multiple time points during the course of the study, especially if the study has a long duration.

The strength of the study lies in it being both quantitative and qualitative in nature of a well-known research center and also spanning the COVID pandemic. It is however limited by the nature of the studies given to the center by the sponsor and being a single center study only and also some subjectivity in the classification of major and minor PDs. We also did not classify PDs based on impact as suggested previously by Ghooi *et al*.[2]

In summary, ongoing training of CT teams, implementation of stronger CAPA processes, and early and effective communication with participants hold the key to minimizing PDs. While PDs may not be entirely avoidable, quality systems, and monitoring by all stakeholders may mitigate major PDs.

Acknowledgment

We acknowledge the dean of our institution for giving us the permission to carry out the study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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