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# Characterizing Adverse Event Methods Reported in ClinicalTrials.gov and Publications

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## Introduction

- Clinical trials provide data for the safety profiles of studied interventions.
  - Understanding how adverse events (AEs) are specified, collected, and assessed (AE methods) is essential to accurately interpret safety profiles.
- Prior work compared reporting of AEs in publications and ClinicalTrials.gov, including:
  - Completeness and consistency
  - Differences in reporting AE methods for systematic collection
- This cross-sectional analysis explored reporting of AE methods on ClinicalTrials.gov.
  - Database of >500,000 clinical studies
  - Provides structured format for trialists to report aggregate results information and AE methods

## Aim

- To examine the extent of AE methods reporting on ClinicalTrials.gov
- To assess how reporting on ClinicalTrials.gov complemented corresponding publications

## Methods

- Searched ClinicalTrials.gov on 8/1/2024 for:
  - Trials of drug and biological products
  - Primary Completion Dates: 1/18/2017 to 8/1/2021 (allowed 3 years for results posting & publication)
- Of 9,659 retrieved records, obtained convenience sample of 40 trials with:
  - summary results posted on ClinicalTrials.gov
  - corresponding primary results articles in PubMed
- Reviewed and extracted text for five ClinicalTrials.gov AE method data elements:
  1. Collection period (time frame)
  2. Collection approach (i.e., systematic or not)
  3. Vocabulary source for AE terms (e.g., MedDRA, CTCAE)
  4. Analysis population description (e.g., participants administered intervention at least once)
  5. Whether participants withdrew due to harms
- Each set of results independently reviewed by two authors with discrepancies resolved by consensus.

## Results

- Characteristics of the 40 trials examined in this analysis include (Table 1):
  - Median size: 250.5 participants (IQR, 68-524).
  - Primarily industry-sponsored: 32 trials (80.0%)
  - Studied US approved drugs/biologics: 33 trials (82.5%)
  - Of 35 trials (87.5%) with multiple study arms:
    - Randomized: 32 trials(91.4%)
    - Masked: 24 trials (68.6%)
- **Availability:**
  - Three of five AE methods were reported for all sampled trials in ClinicalTrials.gov only, publications only, or both; two exceptions with missing information (reported in neither):
    - Analysis population description: 8 trials (20.0%)
    - Vocabulary source: 5 trials (12.5%)
- **Completeness:**
  - 31 trials (77.5%) reported information about 5 AE methods in at least one source.
- **Scope/Coverage:**
  - Four of five AE methods were reported in both sources for at least half of all sampled trials; one exception with fewer than half trials:
    - Collection Approach: 4 trials (10.0%)
  - Three of five AE methods reported in both sources (ClinicalTrials.gov and publications) showed inconsistencies among half of trials; two exceptions with different rates of inconsistencies:
    - Withdrawal for Harm: 20 trials (57.1%)
    - Analysis Population Description: 6 trials (22.2%)
  - Three of five AE methods were reported only in ClinicalTrials.gov for one-third or more of all sampled trials:
    - Collection Approach: 36 trials (90.0%)*
    - Vocabulary Source: 14 trials (35.0%)
    - Collection Period: 12 trials (30.0%)*

*Required data elements on ClinicalTrials.gov

**Table 1. Characteristics of 40 Sampled Trials**

| | N (%) |
|---|---|
| **Study Phase** | |
| Phase 2 | 15 (37.5) |
| Phase 3 | 21 (52.5) |
| Phase 4 | 4 (10.0) |
| **Intervention Type** | |
| Drug | 36 (90.0) |
| Biological | 2 (5.0) |
| Drug and Biological | 2 (5.0) |
| **Study location** | |
| U.S. only | 12 (30.0) |
| Non-U.S. | 5 (12.5) |
| U.S. and non-U.S. | 22 (55.0) |
| No location data provided | 1 (2.5) |
| **Primary study sponsor**§ | |
| Industry | 32 (80.0) |
| Non-industry | 8 (20.0) |

§The primary organization or individual who initiates and oversees the study. “Non-industry” includes university, hospital, research organizations, and federal agencies.

**Table 2: Availability and consistency of AE methods data elements in drug or biologic trials registered in ClinicalTrials.gov and matching publication**

| AE Method Element | Availability by Source No. (%) | | | | Overall Availability No. (%) | |
|---|---|---|---|---|---|---|
| | CTG Only | Pub Only | Both | Neither | On CTG | In Pub |
| **Collection Period*** (when AEs collected) | 12 (30.0) | 0 (0) | 28 (70.0)<br>14 (50.0) Consistent<br>14 (50.0) Inconsistent | 0 (0) | 40 (100) | 28 (70.0) |
| **Collection Approach*** (whether AEs collected systematically or non-systematically) | 36† (90.0) | 0 (0) | 4 (10.0)<br>2 (50.0) Consistent<br>2 (50.0) Inconsistent | 0 (0) | 40† (100) | 4 (10.0) |
| **Vocabulary Source** (how AE terms were standardized) | 14 (35.0) | 1 (2.5) | 20 (50.0)<br>10 (50.0) Consistent<br>10 (50.0) Inconsistent | 5 (12.5) | 34 (85.0) | 21 (52.5) |
| **Analysis Population Description‡** (from whom AEs were collected) | 1 (2.5) | 4 (10.0) | 27 (67.5)<br>21 (77.8) Consistent<br>6 (22.2) Inconsistent | 8 (20.0) | 28 (70.0) | 31 (77.5) |
| **Withdrawal for Harm‡** (whether participants withdrew because of AEs) | 2 (5.0) | 3 (7.5) | 35 (87.5)<br>15 (42.9) Consistent<br>20 (57.1) Inconsistent | 0 (0) | 37 (92.5) | 38 (95.0) |

**Abbreviations:** AE, adverse event; CTG, ClinicalTrials.gov; Pub, Publication.
†Three trial records that did not list any observed AEs also did not report the AE collection approach.
‡Extraction of information from ClinicalTrials.gov was not limited to the AE information module but potentially included information reported in the ClinicalTrials.gov participant flow and outcome measures modules.

## Conclusion

- Some AE methods were reported only on ClinicalTrials.gov, only in publications, or in neither source.
- Even when available, AE methods were often inconsistent between sources, possibly due to variations in the time frames used for AE reporting.
- Complete AE methods reporting is needed for accurate safety profiles of study interventions and unbiased risk-benefit assessments.
- Limitations include the exclusion of supplementary appendices and study protocols that may provide additional methodological details on AE methods.
- Future research may include:
  - Reviewing publicly available study protocols for AE methods information.
  - Comparing the quality of AE methods reporting by source.

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