

Enrollment cuts and primary-outcome changes, not completion-date delays, predict the termination of industry phase 2–3 drug trials: a landmark analysis of ClinicalTrials.gov version histories

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Abstract

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Background. Sponsors update their ClinicalTrials.gov records throughout a trial, and the registry keeps every version. Feasibility and portfolio teams commonly read repeated postponements of the completion date as a warning sign. Whether any registry change predicts that a trial will be terminated rather than completed has not been tested on the version history itself.

Methods. From all industry-sponsored interventional phase 2, 2/3 and 3 drug trials on ClinicalTrials.gov that started in 2014–2021 and had reached COMPLETED or TERMINATED status ($n = 13,605$), a simple random sample of 4,000 was drawn (seed 2026) and the full version history of 3,985 was read (October 2026). In a pre-specified landmark design, three signals were computed only from versions dated on or before 12, 24 and 36 months after the registered start, and strictly before any final-status version: the number of postponements of the primary completion date by at least one month; a reduction of the estimated enrollment by at least 20%; and a change of a primary outcome measure (switched, added or removed) after the start. Trials still active at the landmark were followed to their final status. Risk ratios (RR) with 95% confidence intervals compare termination rates with and without each signal.

Results. At the 24-month landmark, 2,292 trials were still active and 471 (20.5%) were later terminated. An enrollment cut (9.7% of trials) carried a termination rate of 33.8% against 19.1% (RR 1.77, 95% CI 1.44–2.17); a primary-outcome change (12.2%) 27.1% against 19.6% (RR 1.38, 1.12–1.71). Completion-date postponements, although present in 61% of trials, did not predict termination: one or more postponements RR 1.02 (0.86–1.20), two or more 1.06 (0.89–1.26), three or more 1.04 (0.82–1.34). The same pattern held at 12 and 36 months. A count of the signals showed a monotone gradient: 18.3% termination with none, 22.4% with one, 27.6% with two and 40.0% with all three. The association was strongest in phase 3 (any signal, RR 1.51, 1.11–2.06).

Conclusions. In the registry's own history, lowering the enrollment target and changing a primary outcome are early markers of later termination, while delaying the completion date is not. Registry version histories can be read automatically for this purpose; the delay signal that practitioners commonly watch is the one with no predictive value.

Introduction

About one in five industry phase 2–3 drug trials registered on ClinicalTrials.gov ends as TERMINATED rather than COMPLETED, most often for reasons other than the data: poor accrual, business decisions, or changes in the sponsor's priorities [1, 2]. Insufficient enrollment alone accounts for a large share of terminations [1]. For sponsors planning competing or follow-on trials, for contract research organisations preparing proposals, and for investors, an early indication that a running trial is in trouble has obvious value, and the registry record is the only public, structured source that is updated while the trial runs.

ClinicalTrials.gov retains every version of a record, and the version history has been used to study changes to registered outcomes [3–6] and, through the R package cthist, to describe how registry entries evolve [7]. Two recent studies, one of them reading the version history directly, found substantive and often undisclosed changes to primary outcomes in the large majority of trials examined [5, 6]. What has not been tested is whether registry changes observed *during* a trial predict its fate. In practice, feasibility teams treat repeated postponements of the primary completion date as the warning sign [8]; the registry also records when the estimated enrollment is lowered and when primary outcome measures are altered. This study asks which of these signals, if any, predicts termination, using a landmark design that uses only information available at the time.

Methods

Design and pre-specification

The design, signals, landmarks and analysis were written into the analysis script before any version history was read (the script's docstring is the protocol; the repository commit history dates it). No analysis was added after the results were seen except the descriptive sensitivity analysis of three or more postponements, which follows the pre-specified pattern.

Cohort and sample

The source cohort was every interventional phase 2, 2/3 or 3 drug trial on ClinicalTrials.gov with lead sponsor class INDUSTRY, a registered start date in 2014–2021, and a final overall status of COMPLETED or TERMINATED as of 11 October 2026 (API v2; $n = 13,605$). WITHDRAWN and SUSPENDED trials were excluded from the cohort. A simple random sample of 4,000 trials was drawn with a fixed seed. Version histories were read on 18 October 2026 through the registry's own history endpoints (the ones the public site's "Record History" tab uses), through a headless Chromium browser, at four concurrent requests; 3,985 histories were read (one request failed, fourteen were not reached in the time allotted). Up to 60 versions per trial were read in chronological order, stopping at the first version with a final status; 171 trials (4.3%) had more than 60 versions.

Signals

From each version the following fields were kept: overall status, estimated or actual enrollment and its type, start date, primary and study completion dates and their type, primary outcome measures, collaborators, and number of sites. Between consecutive versions three signals were derived.

Completion-date postponement: the primary completion date moved later by at least one month while still marked as estimated; the count of such postponements is the slip count. *Enrollment cut*: the estimated enrollment was lowered by 20% or more between two versions both marked estimated.

Primary-outcome change: after the registered start date plus a 30-day grace period, a primary outcome

measure was replaced (less than 60% word overlap with every measure in the previous version), added or removed. The rules are those of Phaseline's protocol watch and are published with the code.

Landmark analysis

Landmarks were set at 12, 24 and 36 months after the registered start date (the 28th of the month). At each landmark a trial was at risk if no version dated on or before the landmark carried a final status (COMPLETED, TERMINATED, WITHDRAWN or SUSPENDED). Signals were computed only from versions dated on or before the landmark and strictly before the first final-status version, so that a change posted together with the termination could not count as a predictor. The outcome was the trial's final status, TERMINATED versus COMPLETED. For each signal the termination rate with and without the signal is reported with a risk ratio and a 95% confidence interval (log method). A signal count (two or more postponements, enrollment cut, outcome change; 0–3) and a stratification by phase were pre-specified. As a secondary outcome, termination for enrollment reasons was defined from the sponsor's stated reason (rule-based categories; AI-assisted labels for reasons the rules could not place, assigned before this study).

Ethics and data

Only public registry data on trials were used; no individual-level or investigator data were read. Ethics approval was not required. The analysis code, the version data of the sample and the results tables are deposited with the preprint (see Data availability).

Results

Of the 3,985 trials, 2,244 were phase 2, 111 phase 2/3 and 1,630 phase 3; 790 (19.8%) were terminated. Among terminated trials the stated reason was categorised as business or strategic in 296 (37%), efficacy or futility in 204 (26%), enrollment in 152 (19%), safety in 46 (6%), external in 31 (4%), regulatory or other in 23 (3%) and unstated in 38 (5%). The median registry record had 10 versions (interquartile range 5–21.5); the median estimated enrollment was 120. By the 24-month landmark 61% of the trials still active had postponed their completion date at least once, 9.7% had cut their enrollment and 12.2% had changed a primary outcome measure.

Table 1

Termination by registry signal observed before the landmark. Rate with signal vs without; risk ratio (95% CI).

Signal	12 months (n = 3,390; 20.2% terminated)	24 months (n = 2,292; 20.5%)	36 months (n = 1,511; 19.5%)
≥ 1 completion-date postponement	21.6 vs 19.4%; 1.11 (0.97–1.27)	20.7 vs 20.3%; 1.02 (0.86–1.20)	20.6 vs 16.4%; 1.26 (0.99–1.62)
≥ 2 postponements	21.5 vs 20.0%; 1.07 (0.88–1.31)	21.4 vs 20.2%; 1.06 (0.89–1.26)	19.5 vs 19.4%; 1.01 (0.82–1.24)
Enrollment cut ≥ 20%	37.2 vs 19.4%; 1.92 (1.55–2.38)	33.8 vs 19.1%; 1.77 (1.44–2.17)	30.7 vs 17.8%; 1.72 (1.35–2.20)
Primary outcome changed	23.8 vs 20.0%; 1.19 (0.90–1.57)	27.1 vs 19.6%; 1.38 (1.12–1.71)	23.6 vs 18.4%; 1.28 (1.01–1.62)
Any of: ≥ 2 postponements, cut, outcome change	24.4 vs 19.2%; 1.27 (1.09–1.49)	23.9 vs 18.3%; 1.30 (1.11–1.53)	21.3 vs 17.1%; 1.24 (1.00–1.53)

Postponing the completion date did not predict termination at any landmark, and the absence of an effect did not depend on the threshold: at 24 months the termination rate was 20.5% among all trials at risk, 20.7% with one or more postponements, 21.4% with two or more, 21.3% with three or more and 25.6% with four or more (n = 117). An enrollment cut roughly doubled the termination rate at every landmark. A change of a primary outcome measure was associated with termination from 24 months on.

Table 2

Termination by the number of signals (≥ 2 postponements, enrollment cut, primary-outcome change) observed before the 24-month landmark.

Signals	Trials	Terminated	Rate
0	1,375	252	18.3%
1	711	159	22.4%
2	181	50	27.6%
3	25	10	40.0%

By phase (any signal, 24 months): phase 2, 26.1% vs 22.9% (RR 1.14, 0.94–1.38); phase 3, 18.9% vs 12.5% (RR 1.51, 1.11–2.06); phase 2/3, too few trials (n = 74). For the secondary outcome, termination for enrollment reasons, any signal at 12 months carried RR 1.53 (1.04–2.25; 5.2% vs 3.4%); at 24 and 36 months the estimates pointed the same way with wider intervals (1.46, 0.93–2.29; 1.18, 0.66–2.12).

Discussion

Three findings stand out. First, the signal practitioners watch most – the postponed completion date – carries no information about termination in this cohort, at any threshold or landmark. Six in ten industry trials postpone their completion date within two years of starting, and those that do are completed as often as those that do not. A postponement is the registry's record of a plan being revised; it is not the record of a plan failing. Second, lowering the enrollment target is a strong and stable predictor: trials that cut their estimated enrollment by a fifth or more are terminated roughly twice as often, and the association is as strong at 12 months as at 36. A sponsor that reduces the target has, in effect, already written down the trial. Third, changing a primary outcome measure during the trial is associated with later termination, modestly but consistently from the second year, which adds a prognostic dimension to the transparency concern that earlier work has documented [3–6].

The signals are additive. A trial with all three carries a 40% chance of termination against 18% with none – a difference large enough to matter in feasibility assessments of competing trials, in due diligence, and in the planning of follow-on studies, and obtainable from a public source that is updated while the trial runs. The registry's version history is not exposed through the documented API and is unfamiliar to most readers of the site; the methods here show that it can be read automatically and that doing so yields information the current record does not contain.

Limitations

The cohort consists of finished trials, so trials still running from the later start years are under-represented, and very long trials are under-represented in every year; the landmark design limits but does not remove this. Sponsors differ in how often they update records, and an update-shy sponsor contributes fewer signals of every kind; the null result for postponements therefore cannot be explained by under-reporting unless it is specific to dates. TERMINATED is the registry's status, assigned by the sponsor, and does not distinguish a trial stopped for futility from one stopped for a business reason; the secondary analysis of enrollment-related terminations relies on sponsor-stated reasons and rule-based categorisation. No adjustment was made for therapeutic area, sponsor size or enrollment target, all of which are associated with termination and may be associated with the signals; the stratification by phase suggests the associations are not an artefact of phase mix, but a multivariable analysis is the natural next step. Histories were capped at 60 versions, which affects 4% of trials and only their later landmarks. Finally, the sample is one random draw from the cohort; the full cohort of 13,605 can be read with the same code.

Conclusion

In ClinicalTrials.gov's version history, an enrollment cut and a change of primary outcome are early markers of later termination, while postponing the completion date is not. Tools that monitor registry changes should weight them accordingly.

Declarations

Data availability

The analysis script (study_slips.py, with the signal rules in protocol.py and the browser fetch in regfetch.py), the version data of the 3,985 sampled trials and the results tables are deposited on Zenodo: doi:10.5281/zenodo.23457680. Registry data are public domain (U.S. National Library of Medicine).

Use of a large language model

The analysis code (study_slips.py, protocol.py, regfetch.py) and the first draft of this manuscript were produced with the assistance of a large language model (Claude, Anthropic), working under the author's direction. The author specified the design, reviewed and tested all code against the registry records, verified every figure in the results against the deposited output files, and edited the text. The model took no part in the extraction rules, the statistical calculations or the interpretation, and is not an author.

Competing interests

The author builds and operates Phaseline (usephaseline.com), a trial-intelligence service that includes a registry-history feature based on the rules described here. No funding was received for this work.

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Figures

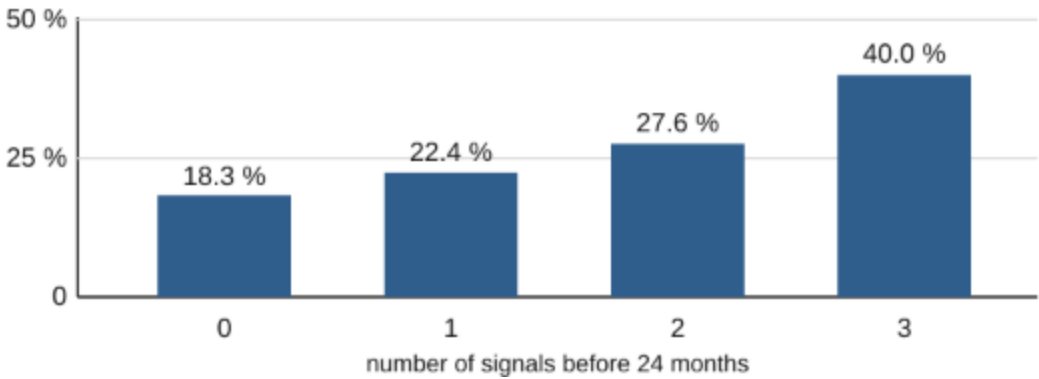


Figure 1

Share of trials later terminated, by the number of registry signals (two or more completion-date postponements, enrollment cut of 20 % or more, primary-outcome change) observed before the 24-month landmark; n = 1,375 / 711 / 181 / 25.