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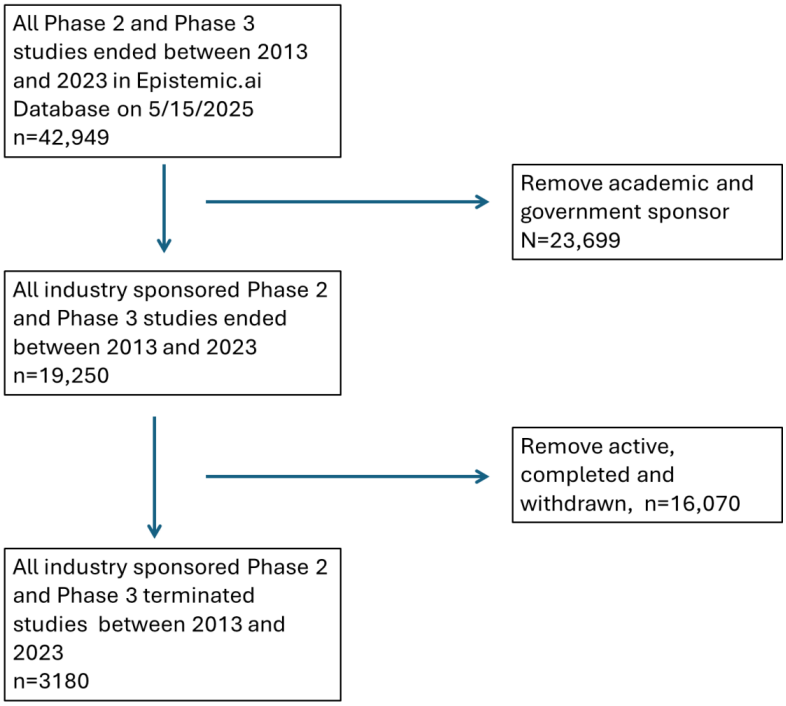
Supplementary information

Analysis of phase II and phase III clinical trial terminations from 2013 to 2023

In the format provided by the authors and unedited

Data and analysis

The data were extracted from the Epistemic AI database on 15 May 2025. The data is derived from publicly available data sources such as ClinicalTrials.gov, press releases, company presentations and other news sources. We extracted all phase II and phase III studies for the years 2013 to 2023. We removed academic- and government-sponsored trials, then removed active, completed and withdrawn trials, and finally removed trials for which no reason for termination was given. This resulted in 3,180 trials for analysis (see the flow chart below).



From the extracted data, we manually read and assessed the stated reason for termination for each trial independently on 3 separate occasions. Where there was agreement, the reason was assigned, and where there was discrepancy, we looked at the press release or trial information to assign a reason. In addition, we codified a program with keywords to automatically assign a reason. Where the manual and automated analysis agreed, we used the reason, and where they disagreed (87 out of 3,180), we went back to the press releases of publications for further analysis. In cases where there were 2 or more termination reasons given (and there were only 97 out of 3,180), we focused on reasons that can be addressed with changes in procedures, better science, or better planning. The order of assignment was efficacy>safety>operational>strategy>business>enrollment.

We focused on terminated trials for several reasons:

- The status of a trial as 'terminated' is clearly defined in Clinical.Trials.gov
- The 2016 mandate from the FDA stating that starting in 2017 sponsors must provide a reason for termination, whereas it is not required to report completed trials as failures or provide a reason.
- The sponsor is so sure that a terminated trial is not likely to generate meaningful data that they end it early.

By contrast, completed but failed trials are not consistently defined, and the outcomes are not always clear, with many trials just finishing with no results published. Failures are also harder to define. For example, failure in a phase III trial may often be considered as failure to progress to regulatory submission, but could

also be considered as failure to gain regulatory approval, failure to beat the standard of care, failure to gain further investment for business reasons or failure to attract a marketing partner.

Consequently, we consider terminated trials to be a particularly useful source of insights for reducing the likelihood of expending resources on unproductive clinical trials, especially when termination is due to factors that may be more under control of sponsors, such as strategic/business choices or operational issues, compared with the uncertainty around efficacy or safety. That is not to say that insights cannot be gained from completed trials; indeed, in some cases, the longer duration and deeper analysis possible may lead to additional insights.

Comparisons with previous analyses

The increase in clinical trial terminations that we identified in our analysis is in sharp contrast to a reported decrease in trial terminations over a similar time period[1]. The reason for the difference may be in the data used for the analysis. Our analysis relied on industry-sponsored reported termination using the primary completion date and the primary source of ClinicalTrials.gov, whereas Fultinaviciute and Maragkou relied on the difference between the expected and reported end date and a different trial source[1]. Their analysis would include completed and terminated trials, in contrast to our analysis relying on reported terminations only.

The proportion of terminations due to efficacy reasons, 24%, is below the efficacy failure rate of ~50% previously reported a decade ago for phase II and phase III trials[2]. This is because this study examined only terminated trials, whereas publications examining failures, on the other hand, included a combination of terminated and completed trials. When examining terminated trials only, efficacy terminations from 7% to 21% have been reported[1,3,4,5].

Enrollment terminations accounted for 18% of all terminated trials. This is similar to previous reports[5,6,7], but in sharp contrast to one study that reported that half of trial terminations were due to enrollment issues[3,4]. We believe there are several reasons for this discrepancy. First, our focus was on industry-sponsored trials. If we included trials sponsored by government, academic institutions or hospitals, the percentage of enrollment terminations is closer to, but still less than, half. Secondly, we excluded phase I trials in our analysis. These trials have been reported to fail to meet their recruitment goals 80% of the time and would increase the percentage of enrollment terminations if included.

References

1. Fultinaviciute, U. Maragkou, I. Trial termination analysis unveils a silver lining for patient recruitment. https://www.clinicaltrialsarena.com/features/clinical-trial-terminations/ (2022)
2. Harrison, R. K. Phase II and phase III failures: 2013-2015. *Nat Rev Drug Discov.* **15**, 817-818 (2016).
3. Williams RJ, T. T., DiPiazza K, Zarin DA. Terminated trials in the ClinicalTrials.gov results database: evaluation of availability of primary outcome data and reasons for termination. *PLoS ONE* **2015**, *10* (5), e0127242.
4. GlobalData. *Pharmaceutical Technology Enrolment Issues are the Top Factor in Clinical Trial Terminations.* https://www.pharmaceutical-technology.com/analyst-comment/reasons-for-clinical-trial-termination/ (2018).
5. Liebman, R. *Why Do Sponsors Terminate Clinical Trials…and at What Cost?* https://go.syneoshealth.com/l/63102/2024-03-19/4skmdv/63102/1710862129E57ZIOjF/Why_Do_Sponsors_Terminate_Clinical_Trials_and_at_What_Cost_Syneos_Healt.pdf (2022).
6. Pak, T. R., Rodriguez, M. D. & Roth, F. P. Why clinical trials are terminated. *bioRxiv* 021543. DOI: 10.1101/021543 (2015).
7. Wong, A. R. et al. . Barriers to participation in therapeutic clinical trials as perceived by community oncologists. *JCO Oncol. Pract.* **16** , e849-e858 (2020).