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Participant Attrition and Its Reasons in 34,070 Completed U.S. Clinical Trials, 2008 to 2025

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Abstract
Background: Federal efforts launched in 2026 to restore U.S. leadership in clinical research focus on trial start-up and recruitment. How many participants leave U.S. trials after enrolling, and why, has not been measured nationally.
Objectives: To quantify participant non-completion in U.S. trials, its reasons, its trial-level determinants, differences between randomized arms, and its relation to site rurality.
Methods: Cross-sectional analysis of all completed interventional trials with posted results, conducted only at U.S. sites, with primary completion from 2008 to 2025 (ClinicalTrials.gov, retrieved 25 October 2026). Reasons were classified, separating retention-sensitive loss from clinical and administrative discontinuation. Sites were linked to Rural-Urban Commuting Area codes. Fractional logit regression estimated adjusted odds ratios (aOR).
Results: Across 34,070 trials, 15.8% of 13.8 million participants did not complete; the median trial lost 9.1%. Retention-sensitive causes explained 50.3% of documented losses. Loss rose with duration (aOR 3.23, more than 48 versus 6 months or less) and site count, and did not improve over 18 years. In 20.6% of two-arm randomized trials, arm losses differed by at least 10 percentage points. Only 6.5% of geocoded trials used any nonmetropolitan site, yet rural participation was not associated with higher loss.
Conclusion: One in six U.S. trial participants does not finish, half of documented losses are retention-sensitive, and the rate has been flat since 2008. Retention should be measured and funded as part of national clinical trial policy.

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1. Introduction

1.1. Why Retention Matters

Clinical trials are the evidentiary foundation for regulatory approval, clinical guidelines, and coverage decisions. Their value depends not only on how many participants are enrolled but on how many remain until the outcomes are measured. Participants who start a trial and do not complete it reduce statistical power, and when the reasons for leaving are related to treatment or prognosis, they introduce bias that randomization cannot correct [1, 2]. Plausible assumptions about the outcomes of participants lost to follow-up are enough to overturn the conclusions of a meaningful share of trials published in leading journals [2], and in more than half of a large sample of trials the number of participants lost to follow-up exceeded the number of events whose reclassification would have erased statistical significance [3]. Expert panels have therefore identified the prevention of missing data, rather than its statistical repair, as the first line of defense [4, 5]. Missing outcome data nonetheless remain common: a review

of trials in four major general medical journals found missing data in 95% of trials, with a median of 9% of participants affected [6].

Loss that differs between randomized arms is a particular concern. Differential dropout does not always bias the estimated treatment effect, and equal dropout does not guarantee its absence, but when the reasons for leaving differ by arm the comparability created by randomization is at risk [7]. Regulators now ask sponsors to define estimands that state how events such as treatment discontinuation are handled, which places the conduct of follow-up at the center of trial interpretation [8].

1.2. The Policy Context

National policy has recently turned to the competitiveness of American clinical research. In June 2026 the U.S. Department of Health and Human Services (HHS) launched Operation TrialBlazer, a department-wide effort to restore U.S. leadership in clinical research that cited China surpassing the United States in registered trials in 2024 and in Phase 1 trials as early as 2021 [9]. Its components include an expedited Investigational New Drug pilot, updated guidance on confirmatory evidence, and a Phase 1 contact center [9]. In September 2026 HHS and the Advanced Research Projects Agency for Health announced SURPASS and companion projects to speed trial design, activate research-naive sites, and support patient-contributed real-world data [10]. The HHS Office of Inspector General has sought comment on whether sponsors may provide remuneration to trial participants [11]. In parallel, the Food and Drug Administration has issued final guidance on trials with decentralized elements [12], and the Centers for Medicare & Medicaid Services has awarded $50 billion over five years to transform rural health care in all 50 states, with technology and workforce among its aims [13]. These efforts address how quickly trials start, how readily they enroll, and where care is delivered. None of the announced components addresses whether enrolled participants stay.

1.3. What Is Known

The evidence on retention is fragmented. Reviews of publicly funded trials in the United Kingdom report median retention near 89% [14], and pediatric trials in major journals report a median of 92% [15]. A recent analysis of 10,252 Phase III trials with results on ClinicalTrials.gov reported a median drop-out rate of 11% but examined sample size rather than reasons or design correlates [16]. Individual participant data from 90 pharmacological trials showed that attrition affected 16.9% of participants, most often through adverse events and voluntary withdrawal [17], and machine learning work on respiratory trials identified trial duration as a leading driver of dropout [18]. Protocols have grown more demanding, with more procedures and visits per participant [19], and some populations, including participants in psychotherapy, substance use, and digital health studies, show particularly high dropout [20-22]. Systematic reviews of retention strategies find few interventions supported by high-certainty evidence and very few aimed at bringing participants back to trial sites [23], work in longitudinal cohorts suggests that reducing participant burden matters more than adding reminders [24], and evidence on whether decentralized methods improve retention remains insufficient [25]. Rural patients can be well represented in cooperative group trials [26], but whether rural trial sites retain participants as well as metropolitan sites has not been examined at national scale.

To the author's knowledge, no study has quantified attrition, its reasons, its trial-level determinants, between-arm differences, and its geography across the full U.S. trial enterprise, spanning all phases, sponsors, intervention types, and nearly two decades.

1.4. The Registry Opportunity and Objectives

The Food and Drug Administration Amendments Act of 2007 and its 2016 Final Rule require results reporting for applicable clinical trials, including a participant flow that records how many participants started and completed each period in each group and, when given, the reasons they did not complete [27-30]. This creates a national, standardized record of participant loss. The objectives of this study were to use that record to (1) measure the magnitude of non-completion in completed U.S. trials; (2) separate retention-sensitive loss from clinical and administrative discontinuation; (3) identify trial characteristics independently associated with loss; (4) quantify differences in loss between randomized arms and between experimental and inactive control arms; (5) assess whether trials using nonmetropolitan sites lose more participants; and (6) determine whether loss has changed since results reporting began.

2. Materials and Methods

2.1. Study Design and Data Source

This was a cross-sectional, registry-based study reported in accordance with the STROBE guideline for observational studies where applicable [31]. All interventional studies with posted results and at least one U.S. location were retrieved through the ClinicalTrials.gov API, version 2.0 [32], on 25 October 2026 (registry data timestamp 23 October 2026). The query returned 56,772 records. For each record we extracted identification, status, sponsor, design, eligibility, location (including postal codes), arm, intervention, Medical Subject Headings (MeSH) condition data, baseline characteristics, and the full participant flow module. A second retrieval of arm, baseline, and location data was made the same day with the same query and returned the same 56,772 records.

2.2. Eligibility

Trials were included if their overall status was completed, every listed location was in the United States, the primary completion date fell between 1 January 2008 and 31 December 2025, the units analyzed were participants, and the participant flow reported numeric counts with at least one participant started and no more completers than starters. Restricting to completed trials separates attrition from early termination, and restricting to U.S.-only trials ensures that the observed losses arose within the U.S. research system. Multinational trials and terminated trials were examined in sensitivity analyses.

2.3. Outcomes

ClinicalTrials.gov defines the STARTED milestone of the first period as the number of participants assigned to each group, and COMPLETED as the number at the end of a period; NOT COMPLETED is calculated automatically as the difference [30]. The primary outcome, the non-completion proportion, was the number of participants who started the first period minus the number who completed the final

period, divided by the number who started, summed across groups. When a trial reports reasons for non-completion, the registry requires the reasons to account for all participants not completed [30].

2.4. Classification of Reasons

Reported reasons were classified into 13 categories using a prespecified, ordered set of text rules applied to 55,707 reason entries carrying 11,739 distinct labels (Supplementary Table S2). The registry offers eight standard reasons plus Other [30], but investigators may enter free text. Categories were grouped as retention-sensitive (lost to follow-up; withdrawal by participant; missed assessments or non-response), clinical or protocol-driven (adverse event; death; lack of efficacy or progression; physician or investigator decision; pregnancy; protocol deviation or noncompliance), administrative (sponsor or study decision; ongoing or transitioned to an extension; eligibility or analysis exclusion), and unclassified. The secondary outcome, documented retention-sensitive loss, was the number of participants in retention-sensitive categories divided by the number started. Because reasons are optional, this measure is a lower bound, so it was also analyzed in the subset of trials whose reasons accounted for 95% to 105% of non-completers (full-coverage trials).

2.5. Trial Characteristics

Covariates were phase (grouped as early phase 1 or phase 1; phase 1/2 or 2; phase 2/3 or 3; phase 4; not applicable), lead sponsor class (industry; National Institutes of Health; other U.S. federal; academic or other), primary purpose, intervention type (assigned hierarchically as behavioral, device, biological, drug, procedure, dietary supplement, or other), allocation, masking, acceptance of healthy volunteers, inclusion of adults aged 65 years or older, inclusion of children, trial duration from start to primary completion, number of U.S. sites, number of participants started, period of primary completion, and Census region of sites. Therapeutic areas were assigned from MeSH condition terms and their ancestors to ten non-exclusive top-level headings, and condition-specific estimates were produced for every MeSH condition term attached to at least 150 trials.

2.6. Site Rurality

Each U.S. site's five-digit postal code was linked to the 2020 Rural-Urban Commuting Area (RUCA) codes of the U.S. Department of Agriculture Economic Research Service [33], obtained from a published research package whose file checksum was verified against the package archive [34]. Sites with primary RUCA codes 4 to 10 (micropolitan, small town, and rural areas) were classified as nonmetropolitan. A trial was classified as including a nonmetropolitan site if any of its sites met this definition. Because the share of trials with any nonmetropolitan site rises mechanically with the number of sites, rurality was analyzed with adjustment for site count, within single-site trials, and, among multisite trials, as the proportion of a trial's sites that were nonmetropolitan.

2.7. Participant Composition

From the baseline characteristics module, the share of female participants and the mean participant age in the overall (total) group were extracted when reported. Sex composition was examined because federal policy since the NIH Revitalization Act of 1993 has required the inclusion of women in NIH-funded clinical research [35]. The region of enrollment, when reported, was used to identify trials listing only U.S. sites that nonetheless reported enrolling participants outside the United States.

2.8. Arm-Level Analyses

Started and completed counts were extracted for each participant flow group. Groups were matched to registered arm types (experimental, active comparator, placebo comparator, sham comparator, no intervention, other) by exact or containing title match, with a keyword rule (for example, placebo, sham, usual care, wait list, control) used only when no registered arm matched. Crossover trials were excluded because their groups represent treatment sequences (2,823 trials). Among parallel-group randomized trials with exactly two groups, the absolute between-arm difference in non-completion was computed in percentage points. Among trials with one experimental arm and one placebo, sham, or no-intervention arm, non-completion and reason-specific losses were compared between arms within trials with the Wilcoxon signed-rank test, and the analysis was repeated using only registry-matched arms.

2.9. Statistical Analysis

Non-completion was summarized at the trial level as median, interquartile range (IQR), and mean, with a bootstrap 95% confidence interval (CI; 2,000 resamples) for the median, and at the participant level as the pooled proportion. Differences across categories were tested with the Kruskal-Wallis test. Adjusted associations were estimated with fractional logit regression, a generalized linear model with binomial variance and logit link suited to proportions bounded by 0 and 1 [36], with heteroskedasticity-robust standard errors; each trial contributed equally. Results are reported as adjusted odds ratios (aOR) with 95% CIs, and as adjusted predicted means obtained by setting every trial to each duration category and averaging predictions. The same model was fitted for documented retention-sensitive loss. Rurality, participant sex, and participant age were each added to the base model in the subsets with available data. Monotonic trends with duration and calendar year were assessed with Spearman correlation. Two-sided P values below.05 were considered statistically significant.

2.10. Sensitivity Analyses

The primary estimates were repeated (1) including terminated trials, (2) including multinational trials with U.S. sites, (3) restricted to trials with a single participant flow period, (4) restricted to trials with at least 20 participants started, (5) excluding the largest 1% of trials, (6) restricted to the Final Rule era (primary completion 2017 to 2025), and (7) excluding trials that reported enrolling participants outside the United States. The regression was refitted with participant-weighted observations, with weights capped at the 99th percentile of trial size. Multinational and U.S.-only trials were compared with a fractional logit model adjusted for phase, sponsor, number of sites, trial size, duration, randomization, and masking, overall and among phase 2/3 or 3 trials.

2.11. Validation and Reproducibility

Five checks were performed. First, the extraction code was tested against constructed records with known answers. Second, a random sample of 200 included trials was re-

downloaded one record at a time and the started and completed counts were recomputed with separately written code. Third, for single-period trials reporting a NOT COMPLETED milestone, the registry value was compared with the computed difference. Fourth, arm-level started and completed counts were summed and compared with trial totals. Fifth, the full pipeline was rerun from the raw download, and a second independent download of the same query was rebuilt and compared record by record. Analyses used Python 3.13 with pandas 3.0, statsmodels 0.15, and SciPy 1.18. All code and the analytic datasets are available as described under Data Availability.

2.12. Ethical Considerations

The study used publicly available, aggregate, de-identified registry data and involved no interaction with human participants or access to identifiable private information. It therefore did not constitute human subjects research and did not require institutional review board review.

3. Results

3.1. Included Trials

Of 56,772 interventional studies with results and a U.S. site, 11,253 were not completed and 9,492 included non-U.S. sites (Figure 1). After further exclusions for completion date (835), non-participant units (855), missing or zero counts (47), and internal inconsistency (220), 34,070 trials were analyzed. Their median size was 51 participants started (IQR 25 to 124); 26.0% were industry-sponsored, 3.8% NIH-sponsored, 61.7% randomized, and 65.8% conducted at a single site (Table 1), similar to the 66% single-center share reported for trials registered from 2007 to 2010 [37]. The trials used 222,876 site listings.

3.2. Magnitude of Non-Completion

Across the cohort, 13,789,644 participants started a trial and 2,180,484 did not complete it, a pooled non-completion proportion of 15.8% (17.4% after excluding the largest 1% of trials). The median trial lost 9.1% of its participants (95% CI 8.8 to 9.1%; IQR 0.0 to 22.8%; mean 16.7%). The distribution was strongly right-skewed (Figure 2): one quarter of trials (25.9%) retained every participant, while 47.8% lost 10% or more, 29.1% lost 20% or more, and 17.9% lost 30% or more. In 567 trials (1.7%) no participant was recorded as completing, typically because completion was defined by a treatment milestone that few participants reached.

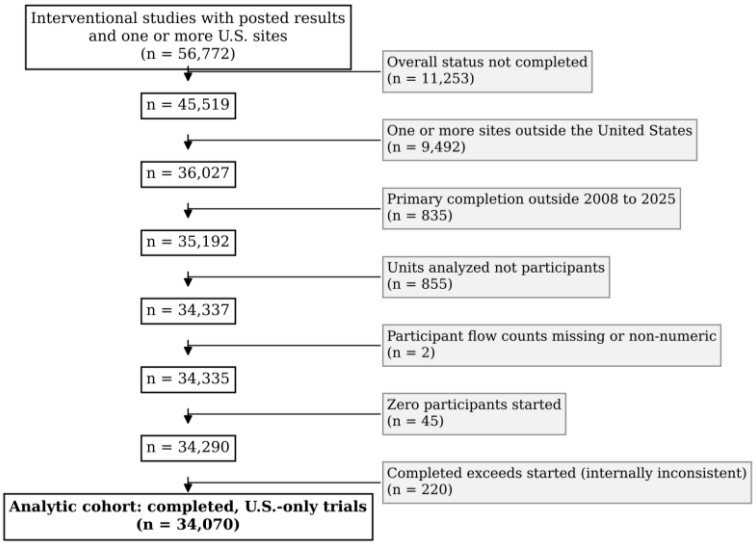


Fig 1: Selection of trials. Source: ClinicalTrials.gov API, version 2.0, retrieved 25 October 2026.

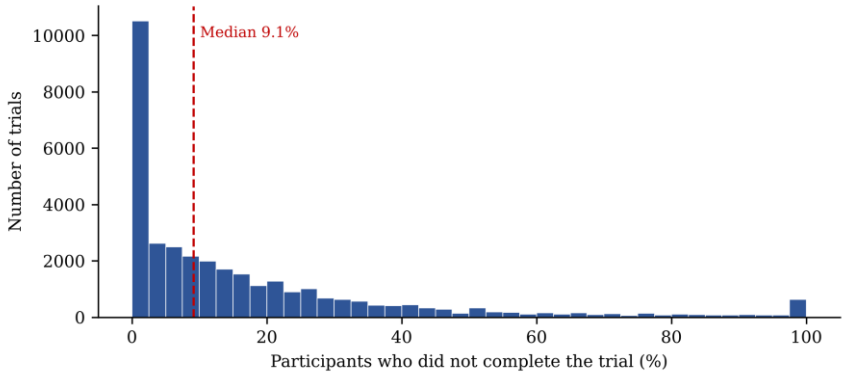


Fig 2: Distribution of participant non-completion across 34,070 completed U.S.-only trials. The dashed line marks the median.

3.3. Reasons for Non-Completion

Of 25,254 trials with at least one non-completer, 17,891 (70.8%) reported at least one reason, and in 16,957 the reported reasons accounted for all non-completers. Only 64.8% of reason entries used the eight standard registry labels; the remainder were free text. In full-coverage trials, retention-sensitive causes accounted on average for 50.3% of non-completion per trial: withdrawal by participant 28.2%

and loss to follow-up 21.3% (Table 2, Figure 3). Adverse events accounted for 10.3%, lack of efficacy or progression 5.2%, and death 4.8%; 15.2% could not be classified. In these trials the median participant-level retention-sensitive loss was 5.3% (IQR 0.8 to 12.5%). Across the whole cohort, 40.8% of trials documented at least one retention-sensitive loss and 23.3% documented at least one participant lost to follow-up.

Table 1: Characteristics of included trials and participant non-completion

Characteristic	Trials, n (%)	Non-completion, median % (IQR)	Non-completion, mean %	Retention-sensitive loss, mean %
All trials	34,070 (100)	9.1 (0.0 to 22.8)	16.7	4.9
Phase; P <.001				
Early phase 1 or phase 1	2,561 (7.5)	6.5 (0.0 to 20.0)	16.8	3.9
Phase 1/2 or 2	10,364 (30.4)	9.5 (0.0 to 25.8)	20.3	4.3
Phase 2/3 or 3	3,379 (9.9)	10.9 (3.3 to 24.0)	17.5	5.2
Phase 4	3,860 (11.3)	8.2 (0.0 to 20.5)	14.1	4.6
Not applicable	13,906 (40.8)	8.7 (0.0 to 21.6)	14.5	5.6
Lead sponsor; P <.001				
Industry	8,865 (26.0)	9.3 (2.4 to 23.0)	18.4	4.8
NIH	1,283 (3.8)	10.5 (2.0 to 30.0)	23.0	4.3
Other U.S. federal	1,364 (4.0)	14.8 (5.0 to 27.3)	18.8	7.4
Academic or other	22,558 (66.2)	8.3 (0.0 to 22.2)	15.5	4.8
Intervention type; P <.001				
Drug	17,323 (50.8)	9.1 (0.0 to 23.3)	17.7	4.3
Device	6,003 (17.6)	6.1 (0.0 to 17.8)	12.6	4.0
Behavioral	5,463 (16.0)	14.0 (4.5 to 26.7)	18.4	8.1
Biological	2,415 (7.1)	8.0 (1.1 to 25.0)	20.2	4.1
Other	2,133 (6.3)	6.4 (0.0 to 19.4)	13.0	5.2
Procedure	404 (1.2)	5.0 (0.0 to 17.1)	11.3	4.3
Dietary supplement	329 (1.0)	8.7 (1.6 to 20.0)	14.0	4.3
Allocation; P <.001				
Randomized	21,035 (61.7)	9.3 (1.7 to 21.4)	15.2	5.2
Not randomized	13,035 (38.3)	8.1 (0.0 to 25.7)	19.0	4.4
Masking; P <.001				
Open label or not reported	19,148 (56.2)	8.3 (0.0 to 25.0)	18.2	4.8
Masked	14,922 (43.8)	9.4 (2.1 to 21.1)	14.7	5.1
Population; P <.001				
Patients only	25,237 (74.1)	9.8 (0.3 to 24.2)	17.9	4.9
Accepts healthy volunteers	8,833 (25.9)	6.8 (0.0 to 19.0)	13.3	5.0
Older adults; P =.004				
Includes adults 65+	26,480 (77.7)	9.1 (0.0 to 23.3)	17.2	4.9
Excludes adults 65+	7,590 (22.3)	8.5 (0.0 to 21.4)	14.8	5.2
Trial duration; P <.001				
6 months or less	3,769 (11.1)	2.9 (0.0 to 9.3)	7.7	2.4
>6 to 12 months	4,471 (13.1)	6.4 (0.0 to 16.3)	12.0	4.2
>12 to 24 months	7,495 (22.0)	9.3 (0.0 to 22.0)	16.0	5.1
>24 to 48 months	10,120 (29.7)	11.5 (1.6 to 26.3)	19.2	5.8
More than 48 months	8,215 (24.1)	12.1 (1.2 to 29.2)	20.8	5.2
U.S. sites; P <.001				
1 site	22,413 (65.8)	7.7 (0.0 to 20.7)	14.5	4.7
2 to 9 sites	7,516 (22.1)	9.8 (1.4 to 24.4)	18.6	5.0
10 to 49 sites	3,358 (9.9)	13.9 (5.3 to 30.5)	23.7	6.0
50 or more sites	783 (2.3)	18.4 (7.8 to 44.3)	30.6	6.5
Participants started; P <.001				
Fewer than 20	5,859 (17.2)	6.2 (0.0 to 22.2)	15.8	4.6
20 to 49	10,524 (30.9)	8.2 (0.0 to 21.2)	15.9	4.5
50 to 99	7,156 (21.0)	9.8 (1.9 to 23.0)	17.6	4.8
100 to 299	6,705 (19.7)	10.4 (2.5 to 24.0)	17.0	5.4
300 or more	3,826 (11.2)	10.6 (2.6 to 24.4)	17.8	5.9
Census region of sites; P <.001				
Multiple regions	8,688 (25.5)	12.1 (3.6 to 28.1)	22.1	5.4
South	8,427 (24.7)	8.0 (0.0 to 21.8)	15.4	4.7
Northeast	6,888 (20.2)	9.1 (0.0 to 23.1)	16.0	5.2
Midwest	5,333 (15.7)	7.1 (0.0 to 19.7)	13.7	4.7
West	4,734 (13.9)	6.8 (0.0 to 19.4)	13.3	4.3
Primary completion period; P <.001				
2008 to 2012	7,961 (23.4)	9.1 (0.0 to 23.6)	17.3	4.6
2013 to 2016	7,330 (21.5)	8.6 (0.0 to 22.2)	16.5	4.4
2017 to 2020	8,564 (25.1)	8.3 (0.0 to 21.4)	16.1	4.8

Characteristic	Trials, n (%)	Non-completion, median % (IQR)	Non-completion, mean %	Retention-sensitive loss, mean %
2021 to 2025	10,215 (30.0)	9.6 (0.0 to 23.4)	16.8	5.6
Therapeutic area (selected, not mutually exclusive)				
Neoplasms	6,580 (19.3)	8.8 (0.0 to 32.6)	23.6	3.9
Cardiovascular diseases	3,095 (9.1)	8.3 (0.0 to 20.8)	15.5	4.1
Mental disorders	4,740 (13.9)	16.2 (5.6 to 30.7)	20.7	7.8
Substance-related disorders	1,359 (4.0)	20.2 (6.9 to 36.1)	23.8	9.4
Nervous system diseases	4,548 (13.3)	10.0 (1.0 to 23.2)	16.4	5.3
Infections	2,544 (7.5)	7.0 (0.5 to 19.4)	14.4	4.9

IQR, interquartile range. P values from Kruskal-Wallis tests of non-completion across levels. Retention-sensitive loss is documented loss to follow-up, withdrawal by participant, or missed assessments as a percentage of participants started (a lower bound). Additional characteristics are in Supplementary Table S1.

Table 2: Reported reasons for participant non-completion

Reason category	Group	Trials reporting, n (% of cohort)	Mean share per trial, full-coverage trials, %	Mean share per trial, all trials with reasons, %
Withdrawal by participant	Retention-sensitive	11,060 (32.5)	28.2	28.0
Lost to follow-up	Retention-sensitive	7,933 (23.3)	21.3	21.3
Missed assessments or non-response	Retention-sensitive	308 (0.9)	0.8	0.8
Adverse event	Clinical or protocol	5,508 (16.2)	10.3	10.4
Lack of efficacy or progression	Clinical or protocol	2,473 (7.3)	5.2	5.3
Death	Clinical or protocol	2,994 (8.8)	4.8	4.8
Protocol deviation or noncompliance	Clinical or protocol	3,099 (9.1)	4.7	4.6
Physician or investigator decision	Clinical or protocol	3,048 (8.9)	4.6	4.5
Pregnancy	Clinical or protocol	386 (1.1)	0.3	0.3
Eligibility or analysis exclusion	Administrative	1,707 (5.0)	3.8	3.9
Sponsor or study decision	Administrative	582 (1.7)	0.6	0.7
Ongoing or transitioned	Administrative	85 (0.2)	0.1	0.1
Other or unspecified	Unclassified	6,600 (19.4)	15.2	15.2

Full-coverage trials (n = 16,957) are those whose reported reasons accounted for 95% to 105% of non-completers; all trials with reasons, n = 17,891. Shares are averaged across trials so that each trial counts equally.

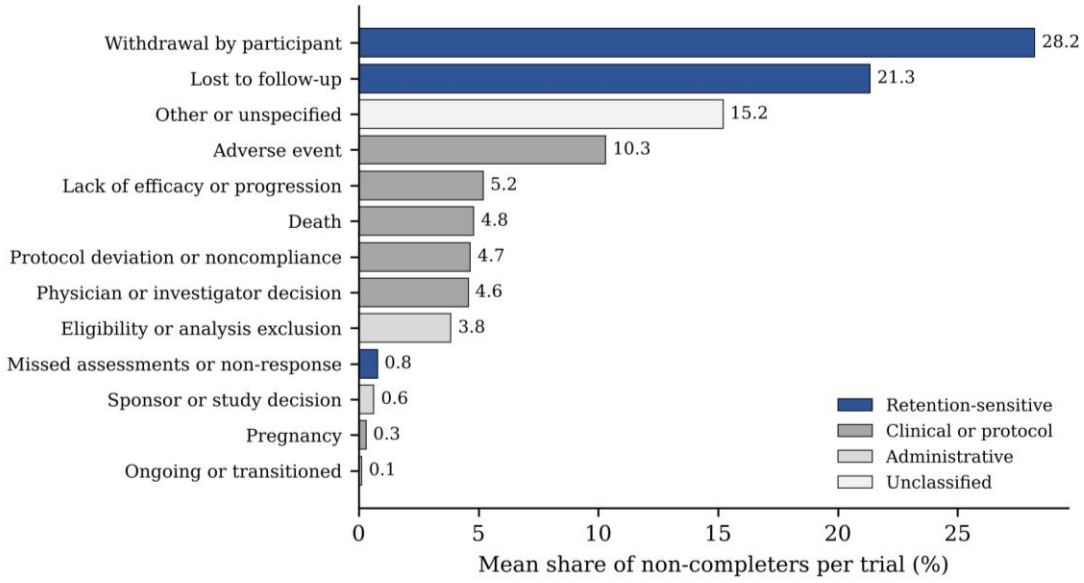


Fig 3: Mean share of non-completers attributed to each reason category per trial, among 16,957 full-coverage trials.

3.4. Trial Characteristics Associated with Non-Completion

After adjustment (Table 3, Figure 4), non-completion was higher in trials of behavioral interventions than drug trials (aOR 1.32; 95% CI 1.25 to 1.41) and in trials addressing mental disorders (aOR 1.37; 95% CI 1.30 to 1.44), substance-related disorders (aOR 1.36; 95% CI 1.26 to 1.47), and neoplasms (aOR 1.36; 95% CI 1.29 to 1.44). For neoplasms the excess reflected clinical discontinuation: documented retention-sensitive loss was lower than in other trials (aOR 0.80; 95% CI 0.74 to 0.87), whereas for mental and substance-related disorders both outcomes were elevated. Device trials lost fewer participants than drug trials (aOR 0.83; 95% CI 0.78 to 0.88). Non-randomized (aOR 1.15; 95%

CI 1.10 to 1.21) and open-label trials (aOR 1.18; 95% CI 1.13 to 1.23) lost more participants. Compared with industry-sponsored trials, academic (aOR 0.61; 95% CI 0.58 to 0.65), NIH (aOR 0.76; 95% CI 0.69 to 0.85), and other federal trials (aOR 0.71; 95% CI 0.65 to 0.78) had lower adjusted non-completion. Non-completion rose steadily with the number of U.S. sites, reaching its highest level in trials with 50 or more sites compared with a single site (aOR 2.04; 95% CI 1.82 to 2.28). Inclusion of adults aged 65 years or older was not associated with higher loss (aOR 0.96; 95% CI 0.92 to 1.00).

Table 3: Adjusted associations with participant non-completion and documented retention-sensitive loss

Characteristic	Non-completion, aOR (95% CI)	Retention-sensitive loss, aOR (95% CI)
Trial duration (ref: 6 months or less)		
>6 to 12 months	1.63 (1.51 to 1.77)	1.72 (1.53 to 1.93)
>12 to 24 months	2.38 (2.21 to 2.58)	2.17 (1.95 to 2.43)
>24 to 48 months	3.02 (2.79 to 3.27)	2.67 (2.39 to 2.99)
More than 48 months	3.23 (2.96 to 3.52)	2.77 (2.45 to 3.13)
U.S. sites (ref: 1 site)		
2 to 9 sites	1.16 (1.11 to 1.21)	1.11 (1.05 to 1.18)
10 to 49 sites	1.53 (1.44 to 1.64)	1.47 (1.36 to 1.59)
50 or more sites	2.04 (1.82 to 2.28)	1.66 (1.45 to 1.89)
Intervention (ref: drug)		
Behavioral	1.32 (1.25 to 1.41)	1.76 (1.62 to 1.92)
Biological	0.96 (0.89 to 1.03)	0.92 (0.84 to 1.01)
Device	0.83 (0.78 to 0.88)	0.93 (0.85 to 1.02)
Procedure	0.71 (0.61 to 0.84)	1.06 (0.80 to 1.39)
Dietary supplement	1.10 (0.95 to 1.29)	1.03 (0.83 to 1.28)
Lead sponsor (ref: industry)		
Academic or other	0.61 (0.58 to 0.65)	0.69 (0.64 to 0.74)
NIH	0.76 (0.69 to 0.85)	0.73 (0.64 to 0.84)
Other U.S. federal	0.71 (0.65 to 0.78)	0.79 (0.70 to 0.90)
Phase (ref: phase 2/3 or 3)		
Early phase 1 or phase 1	1.18 (1.08 to 1.29)	0.89 (0.80 to 1.00)
Phase 1/2 or 2	1.10 (1.03 to 1.16)	0.93 (0.85 to 1.01)
Phase 4	1.02 (0.95 to 1.09)	1.04 (0.94 to 1.14)
Not applicable	1.07 (1.00 to 1.15)	1.07 (0.97 to 1.17)
Design and population		
Not randomized	1.15 (1.10 to 1.21)	0.96 (0.89 to 1.02)
Open label or masking not reported	1.18 (1.13 to 1.23)	1.10 (1.03 to 1.17)
Accepts healthy volunteers	1.00 (0.96 to 1.04)	1.06 (1.00 to 1.13)
Includes adults 65+	0.96 (0.92 to 1.00)	0.90 (0.84 to 0.96)
Includes children	0.88 (0.84 to 0.92)	0.86 (0.80 to 0.92)
Primary completion period (ref: 2008 to 2012)		
2013 to 2016	0.95 (0.91 to 1.00)	0.94 (0.88 to 1.00)
2017 to 2020	0.97 (0.92 to 1.02)	1.01 (0.94 to 1.08)
2021 to 2025	1.03 (0.99 to 1.08)	1.08 (1.01 to 1.16)
Therapeutic area (ref: area absent)		
Neoplasms	1.36 (1.29 to 1.44)	0.80 (0.74 to 0.87)
Mental disorders	1.37 (1.30 to 1.44)	1.33 (1.24 to 1.43)
Substance-related disorders	1.36 (1.26 to 1.47)	1.40 (1.24 to 1.57)
Cardiovascular diseases	0.93 (0.88 to 0.99)	0.82 (0.75 to 0.89)
Nutritional and metabolic diseases	1.05 (0.99 to 1.10)	1.12 (1.04 to 1.20)
Musculoskeletal diseases	1.07 (0.99 to 1.16)	1.19 (1.07 to 1.32)

aOR, adjusted odds ratio; CI, confidence interval. Fractional logit models (n = 34,070 trials) with robust standard errors, mutually adjusted for all characteristics shown plus primary purpose, trial size, and four further therapeutic areas. Full models are in Supplementary Table S3.

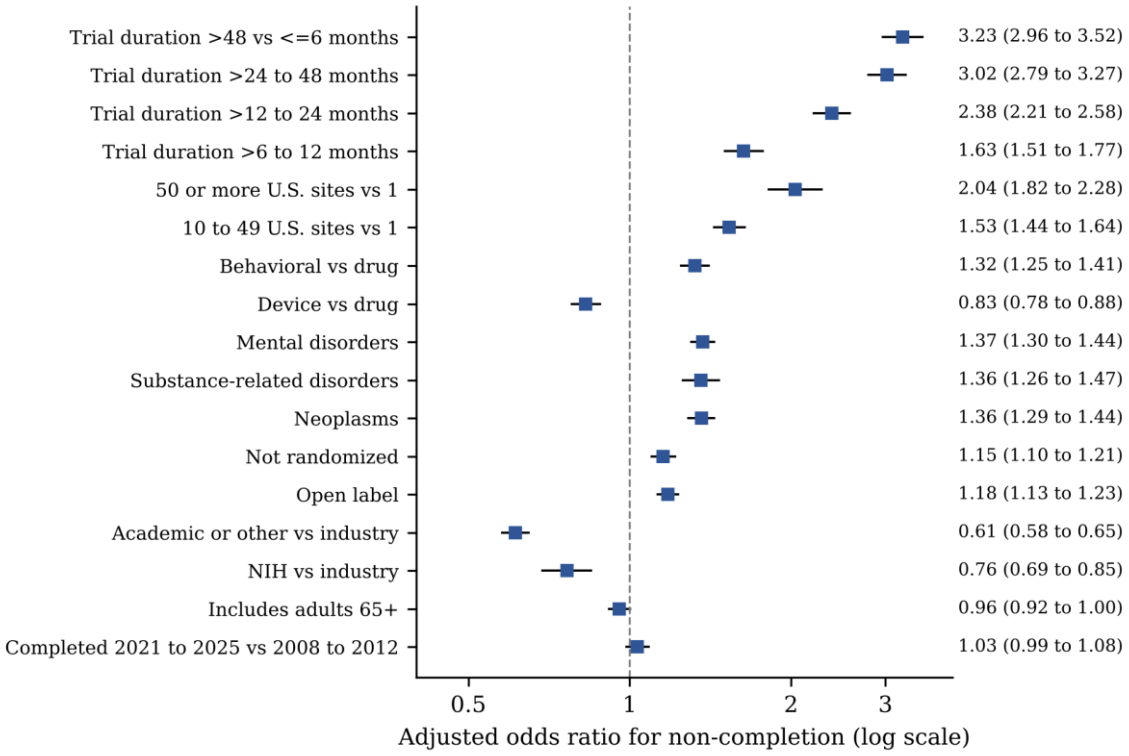


Fig 4: Selected adjusted odds ratios for participant non-completion from the fractional logit model in Table 3, with 95% confidence intervals.

3.5. Trial Duration and Intervention Type

Non-completion increased monotonically with trial duration (Spearman ρ = 0.18, P <.001; Figure 5). The adjusted predicted mean rose from 7.6% in trials lasting 6 months or less to 16.2% at 12 to 24 months and 20.6% beyond 48 months (aOR 3.23; 95% CI 2.96 to 3.52). Documented retention-sensitive loss followed the same gradient, from 2.3% to 6.0% (aOR 2.77; 95% CI 2.45 to 3.13). The gradient was present within every intervention type (Figure 6); the highest mean losses occurred in biological-product trials lasting more than 48 months and in long behavioral and drug trials. Table 4 converts these observations into planning allowances: to retain the intended number of completers, a trial lasting more than 48 months that plans for the average experience would need to enroll 26% more participants than its completer target, and 41% more to be protected at the 75th percentile.

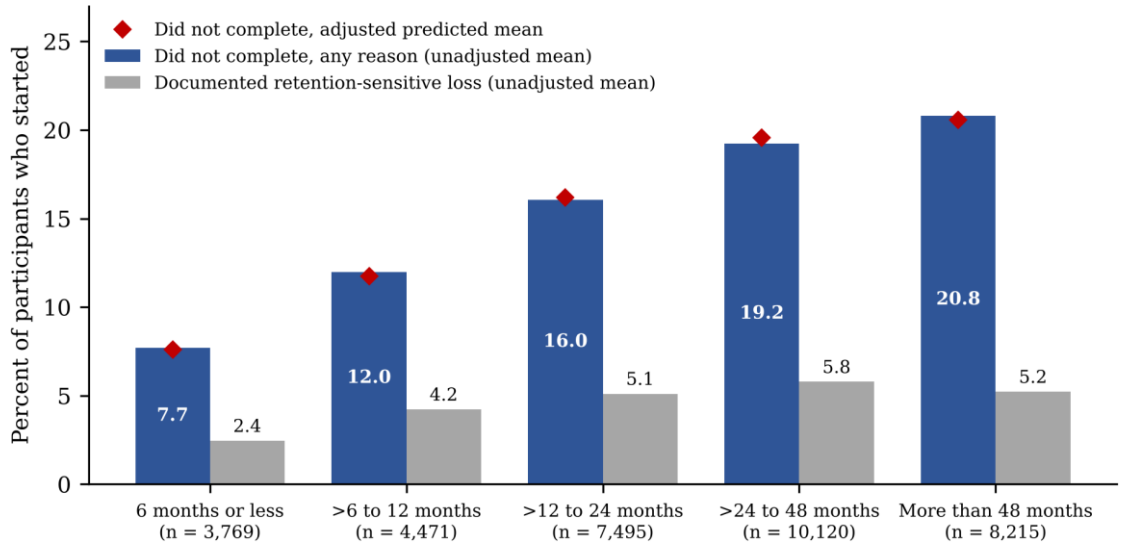


Fig 5: Participant non-completion and documented retention-sensitive loss by trial duration. Bars show unadjusted means; diamonds show adjusted predicted means from the fractional logit model in Table 3.

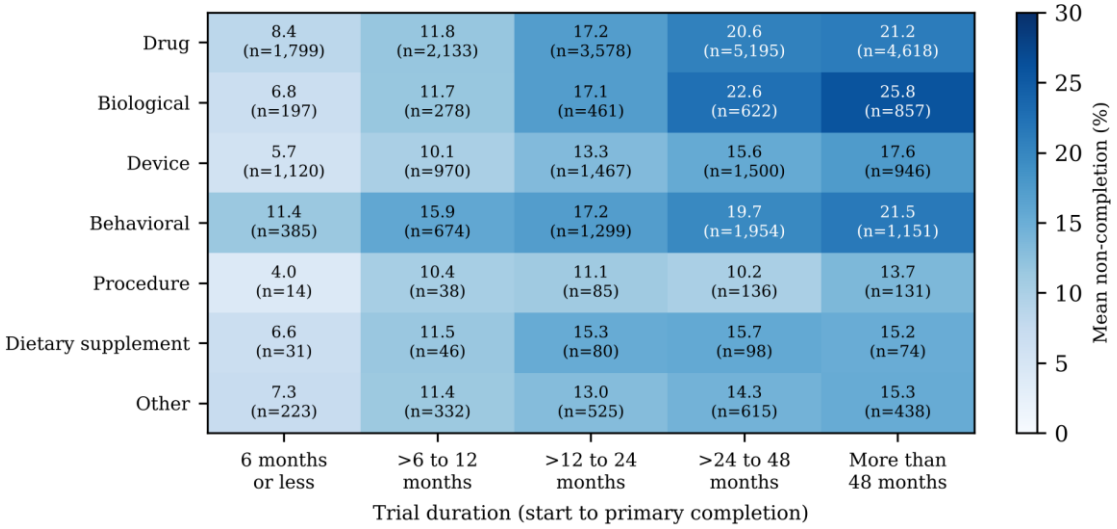


Fig 6: Mean participant non-completion (%) by intervention type and trial duration. Numbers in parentheses are trials per cell.

Table 4: Empirical non-completion and enrollment allowances by trial duration

Trial duration	Trials	Mean non-completion, %	75th percentile, %	Enrollment factor (mean)	Enrollment factor (75th percentile)
6 months or less	3,769	7.7	9.3	1.08	1.10
>6 to 12 months	4,471	12.0	16.3	1.14	1.19
>12 to 24 months	7,495	16.0	22.0	1.19	1.28
>24 to 48 months	10,120	19.2	26.3	1.24	1.36
More than 48 months	8,215	20.8	29.2	1.26	1.41

Enrollment factor = 1 / (1 - non-completion), the multiplier applied to a target number of completers to obtain the number of participants to enroll. Values are descriptive benchmarks from completed U.S.-only trials and should be combined with design-specific evidence.

3.6. Conditions with the Highest Retention-Sensitive Loss

Among 78 MeSH condition terms attached to at least 150 trials, documented retention-sensitive loss was highest for tobacco use disorder (10.8% of participants started), smoking cessation (10.7%), smoking (10.2%), and stress disorders, post-traumatic (9.9%) (Table 5), and lowest for precursor cell lymphoblastic leukemia-lymphoma, dry eye syndromes, and leukemia. Total non-completion was highest in advanced cancers such as non-small-cell lung carcinoma (mean 36.9%), where losses were dominated by clinical discontinuation rather than retention-sensitive causes. The complete list is in Supplementary Table S4.

Table 5: Conditions with the highest documented retention-sensitive loss (MeSH terms in 150 or more trials)

Condition (MeSH term)	Trials	Non-completion, median % (IQR)	Non-completion, mean %	Retention-sensitive loss, mean %
Tobacco Use Disorder	300	21.5 (7.9 to 34.6)	22.8	10.8
Smoking Cessation	322	17.4 (5.1 to 34.4)	22.1	10.7
Smoking	251	16.4 (4.3 to 30.6)	20.4	10.2
Stress Disorders, Post-Traumatic	407	22.8 (10.4 to 34.0)	24.3	9.9
Substance-Related Disorders	319	18.8 (6.1 to 35.3)	23.1	9.7
Bipolar Disorder	223	25.0 (10.0 to 41.7)	28.7	9.7
Opioid-Related Disorders	258	20.0 (5.0 to 40.6)	26.1	9.4
Sleep Initiation and Maintenance Disorders	190	13.0 (6.7 to 29.8)	19.1	8.6
Alcoholism	321	19.0 (8.3 to 31.9)	21.0	8.4
Acquired Immunodeficiency Syndrome	232	15.6 (4.9 to 26.8)	19.3	8.1
Schizophrenia	377	18.9 (7.9 to 30.6)	21.4	7.9
Attention Deficit Disorder with Hyperactivity	237	15.6 (6.1 to 27.7)	19.6	7.6
Psychotic Disorders	230	19.8 (9.3 to 31.9)	22.8	7.6
Dementia	215	14.8 (5.0 to 30.4)	19.6	7.6
Depression	792	15.1 (5.9 to 27.3)	19.6	7.5

Conditions are not mutually exclusive. Retention-sensitive loss is a lower bound because reasons are optional.

3.7. Differences in Loss Between Randomized Arms

Among 18,212 parallel-group randomized trials, 12,637 had exactly two groups. The median absolute between-arm difference in non-completion was 2.9 percentage points (IQR 0.0 to 8.3; mean 6.1), and arm losses differed by 5 or more percentage points in 38.3% of trials, by 10 or more in 20.6%, and by 20 or more in 6.9% (Table 6, Figure 7A). Large differences (10 or more points) became more common as trials lengthened, from 12.8% of trials lasting 6 months or less to 21.5% of those lasting more than 48 months, and were most frequent in dietary supplement (25.4%) and behavioral trials (24.3%). Masked and open-label trials differed little (20.4% versus 21.1%).

In 4,097 trials comparing one experimental arm with one placebo, sham, or no-intervention arm, the experimental arm lost more participants in 42.0% of trials and the inactive arm in 34.4% (mean non-completion 15.5% versus 14.7%; P <.001). The reasons differed in a clinically coherent pattern (Figure 7B): losses attributed to adverse events were higher in experimental arms (mean 0.90% versus 0.55% of arm participants; P <.001), losses attributed to lack of efficacy were higher in inactive arms (0.28% versus 0.44%; P =.015), withdrawal by participant was slightly higher in experimental arms (2.49% versus 2.25%; P =.001), and loss to follow-up did not differ (3.06% versus 3.05%; P =.699). Results were unchanged when only registry-matched arms were used (3,955 trials; P <.001).

Table 6: Absolute between-arm differences in non-completion in two-arm parallel-group randomized trials

Group	Trials	Difference, median percentage points (IQR)	Difference of 5 points or more, %	Difference of 10 points or more, %
All two-arm parallel randomized trials	12,637	2.9 (0.0 to 8.3)	38.3	20.6
Trial duration				
6 months or less	864	1.5 (0.0 to 5.4)	27.9	12.8
>6 to 12 months	1,592	2.2 (0.0 to 7.1)	32.3	17.5
>12 to 24 months	3,010	3.1 (0.0 to 8.3)	39.3	20.8
>24 to 48 months	4,322	3.3 (0.1 to 9.0)	40.1	22.6
More than 48 months	2,849	3.4 (0.3 to 8.8)	40.8	21.5
Intervention type				
Drug	5,898	2.8 (0.0 to 8.0)	37.0	19.8
Biological	559	2.2 (0.1 to 7.4)	35.6	17.9
Device	1,981	2.5 (0.0 to 8.0)	35.6	20.0
Behavioral	2,975	4.1 (0.8 to 9.7)	44.6	24.3
Dietary supplement	134	4.6 (1.2 to 10.0)	47.0	25.4
Procedure	206	1.9 (0.0 to 5.6)	27.2	18.0
Other	884	2.2 (0.0 to 7.1)	34.5	16.4
Masking				
Masked	8,533	3.0 (0.0 to 8.3)	37.9	20.4
Open label or not reported	4,104	2.9 (0.0 to 8.3)	38.9	21.1

Difference is the absolute difference between the two arms in the percentage of participants started who did not complete.

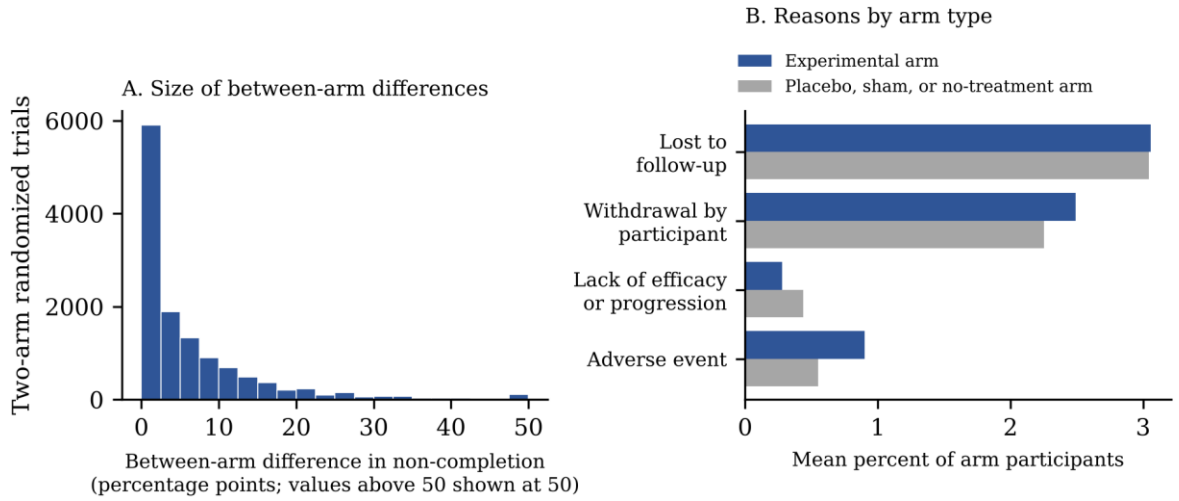


Fig 7: (A) Distribution of absolute between-arm differences in non-completion among 12,637 two-arm parallel-group randomized trials. (B) Mean percentage of arm participants lost for selected reasons, experimental versus placebo, sham, or no-intervention arms, within 4,097 trials.

3.8. Rural Sites

Postal codes linked to RUCA codes for 208,829 of 222,876 site listings and for at least one site in 33,253 trials (97.6%; hereafter geocoded trials). Only 7.2% of linked site listings were nonmetropolitan, compared with 13.6% of the U.S. population living in nonmetropolitan counties [38]. Just 2,168 of these trials (6.5%) included any nonmetropolitan site and 273 (0.8%) were conducted only at nonmetropolitan sites. Rural reach depended almost entirely on scale: 1.1% of single-site trials, 5.3% of trials with 2 to 9 sites, 29.5% with 10 to 49 sites, and 84.5% with 50 or more sites included a nonmetropolitan site (Table 7).

Unadjusted non-completion was higher in trials with a nonmetropolitan site (median 12.2% versus 8.7%), but this difference reflected their larger size and site count. After adjustment, including a nonmetropolitan site was not associated with higher non-completion (aOR 0.94; 95% CI 0.87 to 1.01) and was associated with modestly lower documented retention-sensitive loss (aOR 0.89; 95% CI 0.81 to 0.98). Among single-site trials, the 252 nonmetropolitan trials lost a median of 6.2% of participants versus 7.7% in 21,822 metropolitan trials (aOR 0.89; 95% CI 0.73 to 1.08). Among 11,179 multisite trials, each 10-percentage-point increase in the share of nonmetropolitan sites was not associated with non-completion (aOR 1.03; 95% CI 0.99 to 1.07).

Table 7: Rurality of trial sites and its association with participant non-completion

Measure	Value
Site listings linked to RUCA codes	208,829 of 222,876
Nonmetropolitan share of linked site listings	7.2%
U.S. population in nonmetropolitan counties [38]	13.6%
Geocoded trials with any nonmetropolitan site	2,168 (6.5%)
Geocoded trials with only nonmetropolitan sites	273 (0.8%)
Any nonmetropolitan site, by number of U.S. sites	
1 site	1.1%
2 to 9 sites	5.3%
10 to 49 sites	29.5%
50 or more sites	84.5%
Non-completion, median (IQR)	
Any nonmetropolitan site	12.2% (3.8 to 28.9)
Metropolitan sites only	8.7% (0.0 to 22.3)
Adjusted association, any nonmetropolitan site	
Non-completion	aOR 0.94; 95% CI 0.87 to 1.01
Retention-sensitive loss	aOR 0.89; 95% CI 0.81 to 0.98
Non-completion, single-site trials	aOR 0.89; 95% CI 0.73 to 1.08
Non-completion per 10% nonmetropolitan sites, multisite trials	aOR 1.03; 95% CI 0.99 to 1.07

Nonmetropolitan sites are those with primary Rural-Urban Commuting Area codes 4 to 10. Adjusted models include all covariates in Table 3 (number of U.S. sites included except for the single-site model). The population benchmark is from USDA Economic Research Service, Rural America at a Glance, 2025 edition.

3.9. Participant Age and Sex

The share of female participants was reported for 32,613 trials (median 50.0%) and was not associated with non-completion (aOR 1.00; 95% CI 0.99 to 1.00 per 10 percentage points). Mean participant age was reported for 23,376 trials (median of trial means 49 years). Older trial populations had slightly lower non-completion (aOR 0.98; 95% CI 0.97 to 1.00 per 10 years) and clearly lower documented retention-sensitive loss (aOR 0.90; 95% CI 0.88 to 0.93 per 10 years). Mean retention-sensitive loss was 5.7% in trials whose participants averaged 18 to 39 years and 6.3% at 40 to 49 years, compared with 4.3% at 60 to 69 years and 4.9% at 70 years or older.

3.10. Trends over Time

Despite growth in results reporting, non-completion did not change across primary completion years 2008 to 2025 (Spearman ρ = 0.001, P = 0.81; Figure 8). Period medians varied by no more than 1.3 percentage points without a consistent direction. Adjusted odds for trials completing in 2021 to 2025 were similar to those completing in 2008 to 2012 (aOR 1.03; 95% CI 0.99 to 1.08). Documented retention-sensitive loss was modestly higher in 2021 to 2025 (aOR 1.08; 95% CI 1.01 to 1.16), which may reflect more complete reporting of reasons as well as true change.

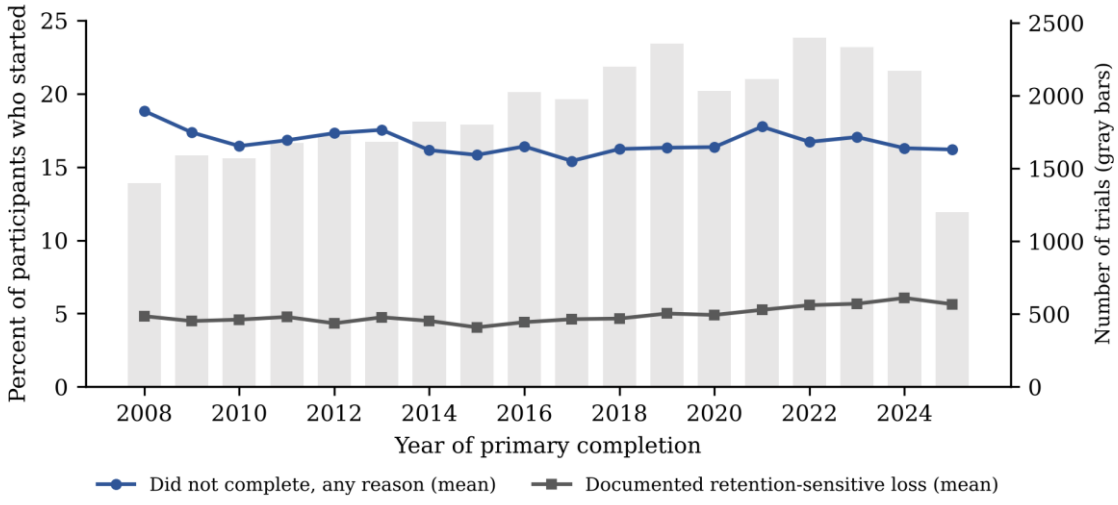


Fig 8: Mean participant non-completion and documented retention-sensitive loss by year of primary completion, 2008 to 2025. Gray bars show the number of trials per year; counts for 2025 are incomplete because results may be posted up to 12 months after primary completion.

3.11. U.S.-only Versus Multinational Trials

Among 43,158 completed trials with any U.S. site, the 9,088 multinational trials had higher unadjusted non-completion than U.S.-only trials (median 18.2% versus 9.1%), reflecting their larger, longer, and later-phase designs. After adjustment, multinational trials retained a higher odds of non-completion overall (aOR 1.21; 95% CI 1.15 to 1.27), but among 7,798 phase 2/3 or 3 trials, which are most often run multinationally, the difference disappeared (aOR 1.03; 95% CI 0.95 to 1.12). U.S.-only conduct was therefore not associated with worse retention.

3.12. Sensitivity Analyses and Validation

Median non-completion ranged from 8.0% to 10.7% across sensitivity analyses (Table 8). Of 22,159 trials reporting a region of enrollment, 429 listed participants enrolled outside the United States despite U.S.-only site listings; excluding them left the median unchanged (9.1%). In the participant-weighted model, the duration gradient (aOR 2.53; 95% CI 1.94 to 3.30), the excess for behavioral interventions (aOR 1.54; 95% CI 1.33 to 1.79), and the excess for 50 or more sites (aOR 1.51; 95% CI 1.27 to 1.80) persisted. In validation, started and completed counts recomputed from 200 individually re-downloaded trials matched the pipeline in 200 of 200 trials (100.0%); the registry NOT COMPLETED value matched the computed difference in 30,106 of 30,108 single-period trials (99.99%); arm-level counts summed to trial totals in all but two trials; and two independent downloads and a full rerun produced identical results.

Table 8: Sensitivity analyses

Analysis	Trials	Non-completion, median % (IQR)	Mean, %	Pooled across participants, %
Primary cohort	34,070	9.1 (0.0 to 22.8)	16.7	15.8
Completed and terminated trials	41,634	9.7 (0.0 to 26.4)	20.1	16.0
Terminated trials only	7,564	18.5 (0.0 to 66.7)	35.3	19.8
Any U.S. site, including multinational	43,158	10.7 (2.0 to 26.0)	19.9	19.3
Multinational trials with U.S. sites only	9,088	18.2 (7.9 to 47.1)	32.2	27.4
Single participant-flow period only	30,109	8.0 (0.0 to 20.6)	15.1	17.6
At least 20 participants started	28,211	9.4 (1.7 to 23.0)	16.9	15.8
Excluding largest 1% of trials	33,729	9.1 (0.0 to 22.8)	16.7	17.4
Primary completion 2017 to 2025 (Final Rule era)	18,779	9.1 (0.0 to 22.6)	16.5	14.9
Excluding trials reporting non-U.S. enrollment	33,641	9.1 (0.0 to 22.8)	16.7	15.4

4. Discussion

4.1. Principal Findings

This analysis of 34,070 completed trials conducted entirely in the United States shows that participant loss after enrollment is common, substantial, and unchanged over 18 years. About one in six participants who started a trial did not complete it, nearly half of trials lost at least 10% of their participants, and about one in six trials lost 30% or more. Where reasons were fully reported, on average half of each trial's non-completion arose from participants withdrawing or being lost to follow-up, causes that are, at least in part, within the control of trial design and conduct. Adverse events, the most common reason in individual participant data from pharmacological trials [17], accounted for about a tenth. Loss rose steeply with trial duration and with the number of sites, concentrated in behavioral, mental health, and substance use research, and differed between randomized arms by 10 percentage points or more in one in five two-arm trials. Fewer than 1 in 15 trials reached a nonmetropolitan site, yet trials that did were no worse at keeping participants.

4.2. Comparison with Prior Evidence

These estimates are consistent with, and extend, earlier work. The median of 9.1% in U.S.-only trials sits close to the median of 9% missing outcome data in leading journals [6] and to the 11% median retention gap in publicly funded U.K. trials [14]. The higher median among phase 2/3 or 3 trials with U.S. sites (15.0%) than in a global Phase III analysis (11%) [16] likely reflects differences in inclusion, since that analysis did not restrict by status or geography. The participant-level estimate of 15.8% closely matches the 16.9% observed in individual participant data from 90 pharmacological trials [17]. The smaller share attributed to adverse events here (about 10% versus 43.5%) is expected, because this cohort includes behavioral, device, and other non-drug trials and because retention-sensitive categories are reported explicitly. The elevated losses in behavioral, mental health, and substance use trials mirror dropout rates of about 20% in psychotherapy [20] and 30% in psychosocial substance use treatment [21]. The lower retention-sensitive loss in older trial populations is consistent with pediatric and adult evidence that retention varies with participant age and with the burden of follow-up [15, 24].

4.3. Differential Attrition and the Credibility of Trial Evidence

The arm-level results add a dimension that trial-level summaries miss. A between-arm difference of 10 percentage points or more occurred in about one in five two-arm randomized trials and became more frequent as trials lengthened. Differential dropout does not always bias a treatment effect, but it signals that the arms may no longer be comparable and requires analyses that make the missing data assumptions explicit [5, 7]. The direction of reason-specific losses was coherent: experimental arms lost more participants to adverse events, while placebo, sham, and no-intervention arms lost more to lack of efficacy, consistent with nocebo-related and expectation-related discontinuation reported in placebo arms [39]. Loss to follow-up, by contrast, was balanced between arms. Because results are fragile when the number of lost participants exceeds the number of events needed to change a conclusion [3], routine reporting of arm-specific, reason-specific losses would let readers and regulators judge whether attrition threatens a trial's inference.

4.4. Retention and the National Clinical Research Agenda

Three findings carry particular weight for current policy. First, the duration gradient is steep and persists after adjustment: trials lasting more than four years lose nearly three times as many participants as trials lasting six months or less. This matches evidence that duration is a leading driver of dropout [18] and implies that the trials most important for long-term safety and durable effectiveness are the most exposed, a concern heightened by the growth in protocol burden per participant [19]. Second, non-completion rises with the number of sites. Federal plans to expand domestic capacity by activating research-naive sites [10] could increase retention risk unless site activation includes retention infrastructure such as tracing protocols, flexible visit options, and participant support. Third, attrition has not improved since results reporting began, even as trial volume grew. Retention research has produced few strategies supported by high-certainty evidence, and almost none aimed at bringing participants back to sites [23], so a flat national trend is unsurprising.

The rural findings point to an opportunity rather than a risk. Only 7.2% of trial site listings were nonmetropolitan, roughly half the nonmetropolitan share of the U.S. population [38], and rural reach came almost entirely from large multisite trials. Yet trials with nonmetropolitan sites retained participants at least as well as metropolitan trials after adjustment, and single-site rural trials were no worse. This is consistent with evidence that rural patients enrolled in cooperative group trials are comparable to urban patients [26], and suggests that the binding constraint on rural participation is access rather than retention. The Rural Health Transformation Program's investments in rural technology and workforce [13], combined with FDA guidance permitting decentralized trial elements [12], could extend trial access to rural communities without compromising follow-up, although the evidence that decentralized methods themselves improve retention remains limited [25].

The comparison with multinational trials is also relevant to the national debate. Among late-phase trials, U.S.-only conduct was not associated with higher loss than multinational conduct. Bringing trials back to the United States therefore need not degrade retention, provided the domestic system invests in keeping participants once they are enrolled. Operation TrialBlazer and SURPASS seek faster start-up, fewer required participants, and broader enrollment [9, 10]. A participant recruited quickly and then lost adds cost, delay, and potential bias, and missing outcome data complicate the estimands that regulators now expect trials to define [5, 8]. The HHS Office of Inspector General's 2026 request for comment on participant remuneration [11] and the emphasis on reducing participant burden in the cohort literature [24] point toward practical levers.

4.5. Implications for Trial Design, Conduct, and Reporting

Table 9 translates the findings into priorities for sponsors, investigators, regulators, and funders. Four are most actionable. Treat documented retention-sensitive loss as a reportable quality measure alongside enrollment. Require structured reasons for every non-completer, since 29.2% of trials with non-completers reported no reason and, on average, 15.2% of each trial's documented losses could not be classified. Use empirical allowances such as those in Table 4, stratified by duration and design, in sample size planning. And fund retention infrastructure as part of site activation, particularly for long, multisite, behavioral, and mental health trials.

Table 9: Evidence-based retention priorities derived from this study

Trial type or population	Key finding in this study	Priority actions
Long trials (more than 24 months)	Mean non-completion 19% to 21%; adjusted odds about 3 times those of trials of 6 months or less	Plan enrollment with empirical allowances (Table 4); schedule regular low-burden contact between visits; collect updated contact information at every visit
Multisite trials, especially 50 or more sites	Adjusted odds of non-completion 2.0 times single-site trials	Standardize tracing and re-engagement protocols across sites; monitor site-level retention centrally; include retention support in site activation
Behavioral, mental health, and substance use trials	Highest retention-sensitive loss; behavioral aOR 1.76 for retention-sensitive loss	Reduce participant burden; offer flexible and remote follow-up; use peer or community partners for tracing
Randomized trials with inactive controls	Arm losses differ by 10 points or more in 1 in 5 two-arm trials; lack-of-efficacy losses higher in control arms	Report arm-specific, reason-specific losses; prespecify estimands and sensitivity analyses for differential dropout
Younger adult populations	Retention-sensitive loss falls about 10% (relative odds) per decade of mean age	Use digital and text-based contact; minimize travel and time costs
Rural participants	Fewer than 1 in 15 trials reach a nonmetropolitan site; retention is not worse when they do	Extend trials to rural sites and decentralized elements to widen access
All trials	29% of trials with losses report no reason; 15% of each trial's documented losses unclassifiable, on average	Report a reason for every non-completer using standard categories; treat retention as a quality metric

4.6. Future Research

Three lines of work follow. First, participant-level time-to-event analyses could show when in follow-up losses occur and whether the early peak described in pharmacological trials [17] holds across behavioral and device trials. Second, trials embedding randomized evaluations of retention strategies, especially those that reduce burden or bring participants back to sites, are needed to build the high-certainty evidence that is currently missing [23]. Third, linking site-level performance and community characteristics to retention would allow site activation programs to target support where it is most needed.

4.7. Strengths and Limitations

This is, to the author's knowledge, the largest analysis of participant non-completion restricted to trials conducted entirely in the United States, spanning all phases, sponsors, and intervention types, with reasons classified, arm-level differences measured, site rurality linked, and design correlates estimated jointly. The data are public, the extraction was validated independently, and the analysis is fully reproducible.

Several limitations apply. Participant flow data are reported by sponsors and investigators and are not independently audited [29, 40]. Only trials that posted results are included, and results reporting is incomplete, particularly outside industry [41, 42], so the cohort may under-represent trials with poor conduct. Completion is defined by each trial's own milestones, so non-completion includes protocol-specified discontinuation, for example on disease progression, which is why retention-sensitive loss was analyzed separately. Reasons are optional and partly free text; the classification rules were prespecified and tested, but some misclassification is likely, investigators may record a withdrawal prompted by side effects as withdrawal by participant, and the retention-sensitive measure is a lower bound. Trial duration was measured from start to primary completion, which combines enrollment and follow-up time rather than individual participant follow-up. Arm types were matched to participant flow groups by title, and a minority were classified by keyword. Rurality was assigned from site postal codes listed in the registry, which identify the institution rather than where participants live, and site lists may include sites that enrolled no participants. Baseline age and sex were not reported for all trials. The analysis is observational and cannot establish causation.

5. Conclusion

Across 34,070 completed U.S. clinical trials and nearly 14 million participants, about one in six participants who started did not finish, half of documented losses were retention-sensitive, and the rate has not improved since 2008. Losses are concentrated in long, multisite, behavioral, and mental health trials, differ materially between randomized arms in one in five two-arm trials, and are not worse at the few rural sites that participate. As the United States invests in making trials faster to start, easier to join, and more accessible to rural communities, keeping participants enrolled through follow-up deserves equal attention, measurement, and investment.

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Conflicts of Interest

The author declares no conflicts of interest.

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Data Availability

The trial-level and arm-level analytic datasets, reason classification rules, and complete analysis code are provided as supplementary files and will be deposited in a public repository upon acceptance.

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