nature reviews drug discovery

https://doi.org/10.1038/d41573-024-00183-4

Supplementary information

Benchmarking recruitment rates for phase III trials

In the format provided by the authors and unedited

Data sources and analysis methods

Clinical trials data were extracted on 10 August 2023 from ClinicalTrials.gov, which serves as the key source of data on clinical development and is used by nearly all third-party subscription services, as well as academic researchers. Furthermore, when trial sponsors update an entry, the data is reviewed for thoroughness by the US NIH. Completed trials with study results have fields for updated actual enrolment, actual start date (date of the first patient intervention), actual primary completion date (date of the last patient intervention for the primary outcome) and site locations.

Over 2,100 trials resulted when filtered for: industry-sponsored, started after 1 January 2011, last updated after 1 January 2015, completed, with study results, primary purpose for treatment, interventional and parallel intervention. The start date was chosen bearing in mind that drug development typically takes 7–9 years, and so going back 12+ years aims to ensure that a full horizon is captured given the potential for longer durations and factors such as the impact of the COVID pandemic on clinical trial timelines. Since updates vary, the 2015 date ensures that all trials have been updated by the company in the past 7–8 years.

We excluded non-parallel interventions such as crossover interventions to avoid potential double counting of the enrolees.

We then used formulas to annotate the following characteristics:

- Calculated duration (months between the dates in the "Actual Start Date" and "Primary Completion Date" fields)
- Enrolled patients are listed in trial records as Enrollment (Estimated) or Enrollment (Actual)
- Total number of sites (listed in "Locations")
- The top 20 pharmaceutical companies in 2019/2020 by revenues. These companies were: AbbVie, Amgen, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, CSL, Eli Lilly and Company, Gilead, GlaxoSmithKline, Hoffmann-La Roche, Janssen, Merck Sharp & Dohme LLC, Novartis, Novo Nordisk, Pfizer, Sanofi, Takeda and Teva
- Oncology indications (using the "Conditions Listed" field)
- Masking types: single (investigator only), double (participant and investigator), triple (participant, investigator and either care provider or outcomes assessor) and quadruple (participant, investigator, care provider and outcomes assessor)
- Number of sites in the USA

Recruitment rates in patients per site per month (ppsm) were calculated as the total number of enrolees divided by the duration divided by the total number of clinical sites.

We segmented to enrolees between 100–2,000 patients and trials with at least 5 sites. Supplementary Table 1 shows the respective number of trials analysed per segment:

Supplementary Table 1 | **Number of trials analysed**

Segment	Sample size
All trials	2,140
Enrollment: 100–500	1,253
Enrollment: 501–1,000	665
Enrollment: 1,001–1,500	163
Enrollment: 1,501–2000	59
Masking: single	48
Masking: double	571
Masking: triple	298
Masking: quadruple	798
Oncology	260
Non-oncology	1,880
Top 20 pharma companies	875
All other companies	1,265

Subgroup analysis

The vast majority of trials enrolled 100–1,000 participants, with masking greater than single (that is, double, triple and quadruple). We grouped the two categories and show the difference between oncology and non-oncology indications, further segmented by top 20 pharma companies compared with all others in Supplementary Table 2. Additionally, we also segmented the sites based on US locations, as the US is traditionally where these trials are conducted.

In this subgroup, top 20 pharma companies generally have similar enrolment targets to other companies (457 versus 410 participants), and similar trial durations (26.1 months versus 23.6 months). However, on average, top 20 pharma companies conduct trials at more sites (89 versus 62), with less dependency on US sites (26.4% versus 52.7%) and slower recruitment rates (0.66 ppsm versus 1.01 ppsm) than other companies. These similarities (enrolment targets, duration) and differences (more sites, less dependency on US sites and slower recruitment rates) also hold true for 20 pharma companies conducting oncology and non-oncology trials.

For top-20 pharma companies, recruitment rates being slower than all other companies may seem counter-intuitive, given their financial and operational reach. However, trials sponsored by top-20 pharma companies involve more sites on average, which will tend to decrease the rate measured in ppsm given that the number of sites is a divisor, even if the overall enrolment target is met more quickly owing to the larger number of sites. Also, a smaller percentage of the sites opened are in the US, owing to two main reasons: to ensure target enrolment rates are met by increasing the site pool, and to reduce operational costs on a per site basis, as sites outside the US generally have lower human and operational capital expenditures. Additionally, due to their financial reach, top-20 pharma companies may also recruit trial participants outside the US to engage patient demographics that better match the disease indication and promote diversity in patients enrolled.

Comparing oncology and non-oncology trials as cohorts shows that on average oncology trials take over a year longer than non-oncology trials (36.8 months versus 22.9 months), have nearly twice the number of sites (119 versus. 66), with half the number of sites in the US (22.5% versus 44.8%).

Supplementary Table 2 | **Subgroup analysis**

Enrollment: 100–1,000 Masking: double– quadruple	**Number of trials**	**Average enrollment**	**Average duration (months)**	**Average number of sites**	**Average percentage of US sites**	**Average recruitment rate (ppsm)**
Total	1,875	429	24.6	73	42%	0.87
Top 20 companies	764	457	26.1	89	26.4%	0.66
All other companies	1,111	410	23.6	62	52.7%	1.01
Oncology only	234	461	36.8	119	22.5%	0.80
Top 20 companies	132	485	35.9	135	17.7%	0.62
All other companies	102	429	38.1	98	28.9%	1.02
Non-oncology	1,641	425	22.9	66	44.8%	0.88
Top 20 companies	632	451	24.1	79	28.3%	0.67
All other companies	1,009	408	22.2	58	55.1%	1.01

Ppsm, patients per site per month.

Limitations

In trial operations, all sites are not 'opened' at the start; openings are rolling or staggered based on operational needs. Therefore, each site listed was not necessarily opened, which can only be gleaned from a sponsor or CRO's proprietary data. Furthermore, not all enrolled patients listed in "Enrollment size" may have been included as part of the primary completion date. This is also proprietary data. The actual completion date and/or results posted dates can better serve to get the true trial duration, with ClinicalTrials.gov being limited by data provided by sponsor across each metric listed.

Hence, recruitment rates provided in this analysis should serve as a starting point for analysing trial types, with factors that may increase or decrease the metric based on various criteria like indication, type of company, and past history of sponsor or CRO conducting specific trials.

Impact of COVID-19

Comparing primary completion dates for 2020/2021 to the years prior indicates a 10–15% drop in recruitment rates, which has increased marginally for those completed by 2022 (data not shown).