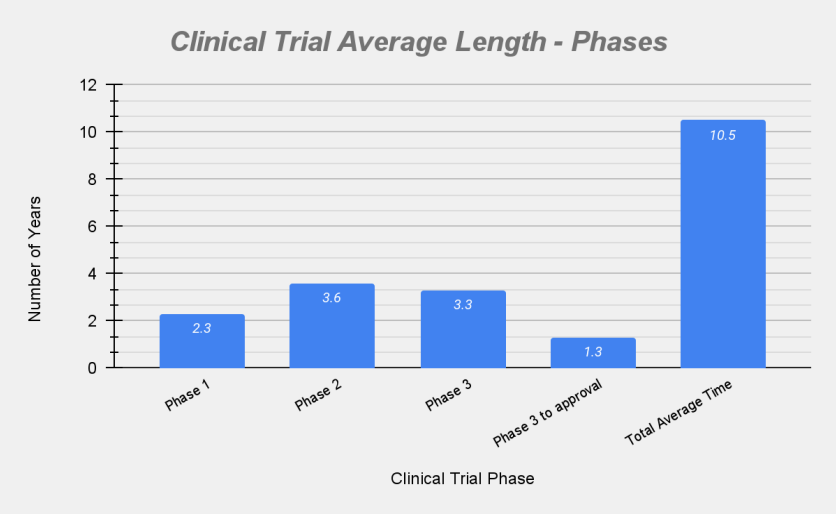
Evaluating Clinical Trial Times in the U.S. Pharmaceutical Industry

The research & development process is the driving force of American pharma. The industry remains the most R&D intensive in the U.S. and is also the main spender in comparison with other pharmaceutical industries in the world.[1] On average, R&D spending on pharmaceuticals is 6 times the amount spent on R&D in other manufacturing industries. The emphasis on R&D in the industry continues to increase with many years in the past decade setting new records for the number of drugs in development and drug approvals. The number of drugs in development has almost doubled from 3,200 in 2012 to 6,100 in 2022. Over the same period R&D spending also increased from $170 billion to $250 billion (inflation adjusted).[2] It also costs $2.6 billion on average to develop a new drug based on research by the Tufts Center for the Study of Drug Development with about 80% of these new drugs developed by the private sector. Despite the volume of activity in the industry, only 5% of 7,000 rare diseases have treatments available.[3] This has increased the focus on increasing the productivity of the industry especially in terms of the length and success rates of clinical trial cycles.

Numerous studies have shown a range of 10 to 15 years from Phase 1 start to FDA approval for the development of drugs across various types of clinical trials. A number of drugs do not complete the clinical trial process given the 12% approval rate across all drugs candidates that start the Phase 1 trial process.[4] Phase 1 to Phase 3 trials take different lengths of time as noted below with the longest phase (3.6 years) during Phase 2 according to data collected by the Biotechnology Innovation Organization (BIO) on trials from January 2011 to November 2020. Phase 2 also accounts for the largest drop off point in the cycle with only 28.9% of Phase 2 drug candidates progressing on from this phase.[5]



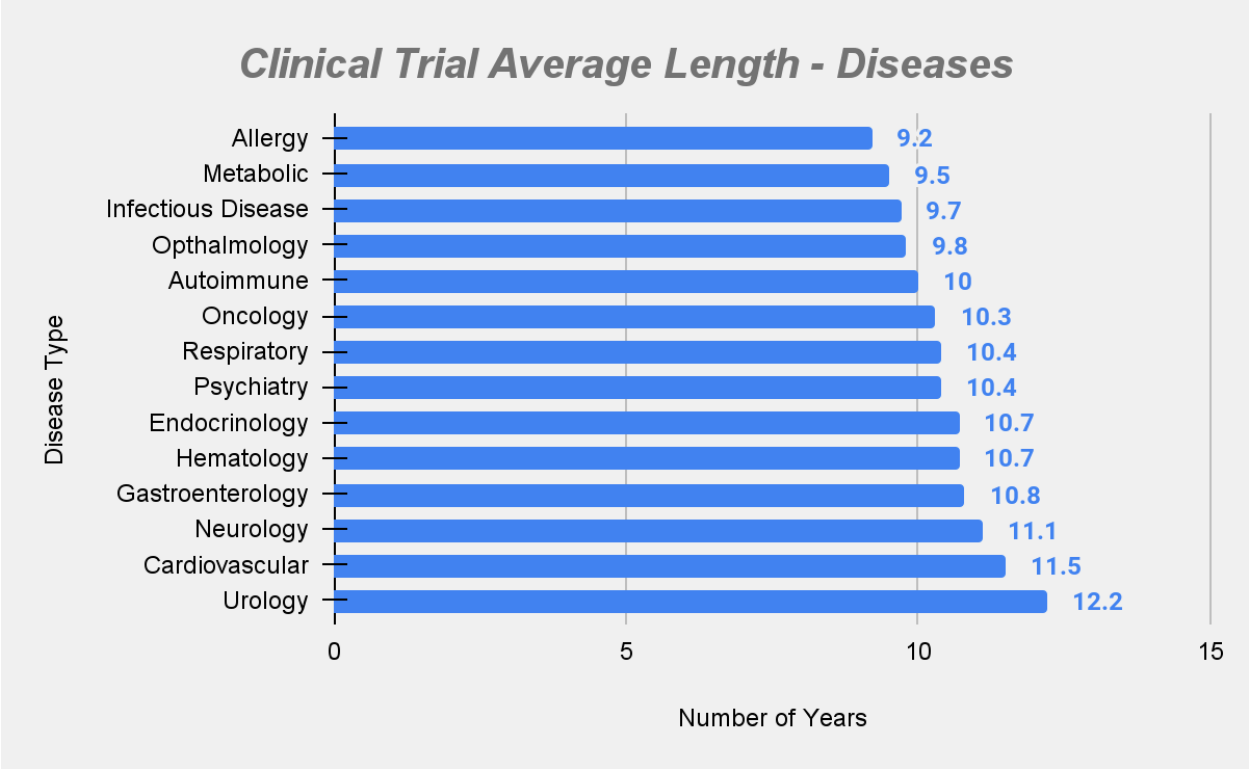
[1] https://www.statista.com/statistics/265085/research-and-development-expenditure-us-pharmaceutical-industry/

[2] https://www.mckinsey.com/industries/life-sciences/our-insights/accelerating-clinical-trials-to-improve-biopharma-r-and-d-productivity

[3] https://phrma.org/policy-issues/Research-and-Development-Policy-Framework

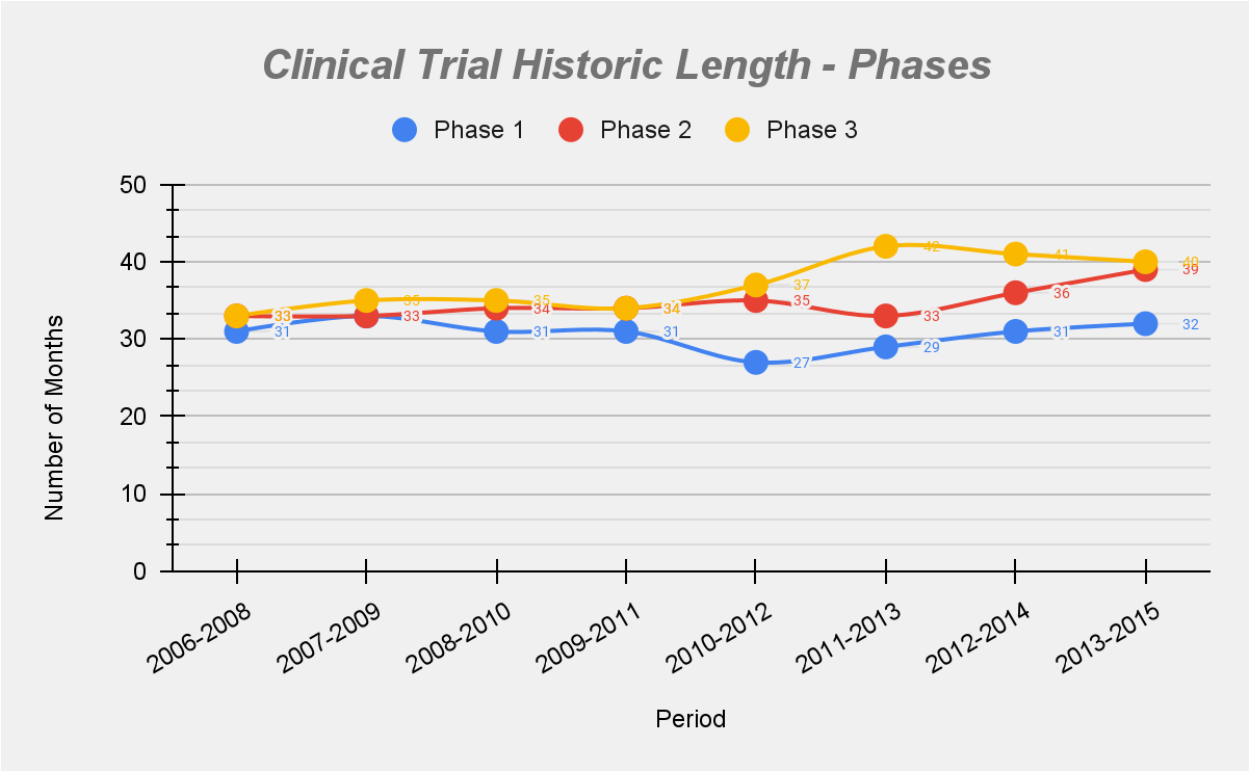
[4] https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/0-9/5-Things-to-Know-about-the-Biopharmaceutical-Ecosystem_2.pdf

[5] https://go.bio.org/rs/490-EHZ-999/images/ClinicalDevelopmentSuccessRates2011_2020.pdf



Another trend in the industry is the increase in total times for clinical trial completion despite the use of technologies designed to improve operational efficiency. Most recent results from KMR Group's *Clinical Trial Cycle Time Study* show that Phase 1, 2 and 3 lengths were similar in the early 2000s with growth rates increasing across all phases from 2010 onwards and at a higher rate for Phase 2 and Phase 3 trials.[6]

[6] Martin, L., Hutchens, M. & Hawkins, C. Clinical trial cycle times continue to increase despite industry efforts. Nat Rev Drug Discov 16, 157 (2017). https://doi.org/10.1038/nrd.2017.21



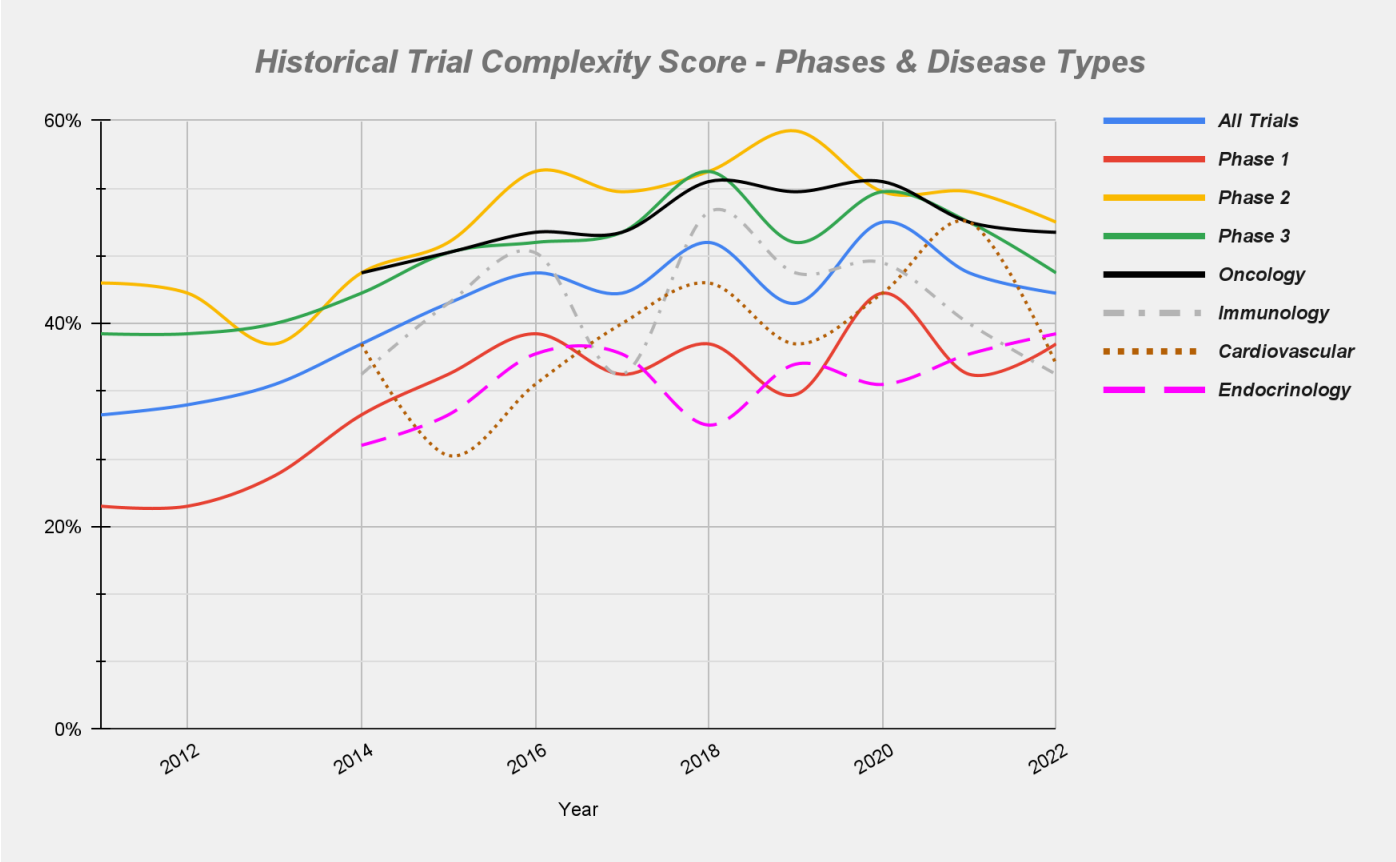
There are a number of reasons for the overall growth in clinical trial timelines as well as that of Phase 2 and 3 timelines.

- One of these reasons is tied to the effects of the COVID-19 pandemic. While the drug development community rallied to complete the process of development and approval for COVID-19 vaccines within a year, the focus on these drugs as well as the general constraints introduced by the pandemic affected the timeline for other existing drugs in the pipeline. A number of trials halted and the start of new trials was delayed during the period. The most direct effect was the reduction of clinical trial enrollment and screening rates by about 70% in the initial year of the pandemic as well as activation of only 57% of the expected trial starts during that period.[7]
- There has been a trend of more complex and time consuming activities and an increase in the number of trial protocols. Protocols include activities such as diagnosis and treatment of undetected conditions, extra testing, data collection and quality assurance activities. These complexities have become especially pronounced for Phase 2 & 3 trials. In 2016, there were 17 average endpoints in an average Phase 2/3 protocol but this increased by 24% to 21 by 2020.[8] The number of procedures involved have also increased by 44%.

[7] McDonald K, Seltzer E, Lu M, Gaisenband SD, Fletcher C, McLeroth P, Saini KS. Quantifying the impact of the COVID-19 pandemic on clinical trial screening rates over time in 37 countries. Trials. 2023 Apr 4;24(1):254. doi: 10.1186/s13063-023-07277-1. PMID: 37013558; PMCID: PMC10071259.

[8] https://www.mckinsey.com/industries/life-sciences/our-insights/accelerating-clinical-trials-to-improve-biopharma-r-and-d-productivity

Phase 2 trials (which have shown the greatest overall growth since 2010) have increased in size from a median number of 88 participants in 2007 to 108 participants by 2015. A metric developed to measure trial complexity - *Trial Complexity Scores* - also demonstrates the increasing overall complexity of trials with an overall increase in complexity of over 10% across all trials.[9] This metric is calculated based on factors to determine complexity such as number of endpoints, number of inclusion–exclusion criteria, number of study arms and number of trial sites. The data also shows the most complex trials over this period are oncology trials. Even trials that historically involve less complexity such as endocrinology and Phase 1 trials have also become more complex over the past decade.



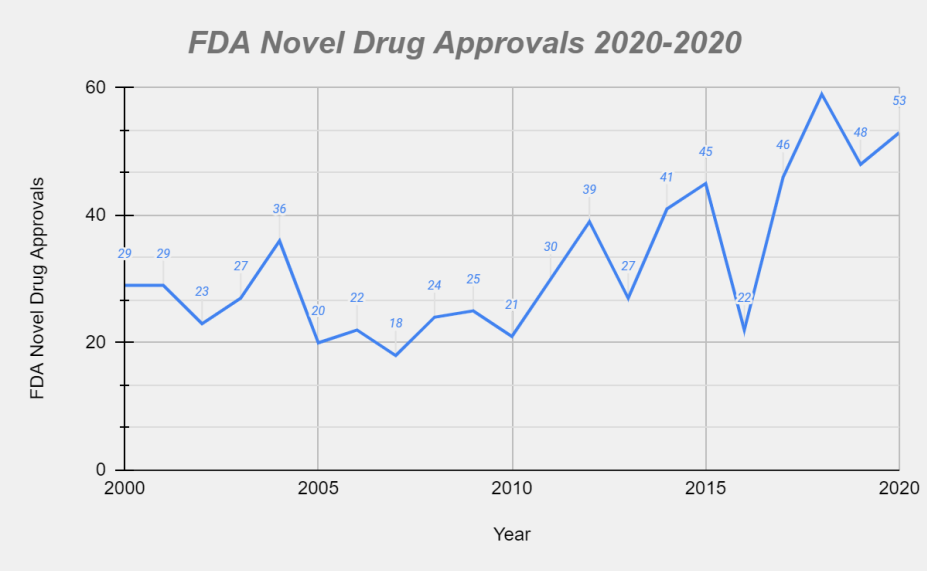
- The increase in the number of trials involving large molecules has also increased the overall time to complete for clinical trials. Biologics such as monoclonal antibodies and recombinant proteins have become the most successful drugs released in recent times with an average approval rate of 13% compared to 5% for small molecule drugs.[10] These drugs involve more complicated clinical trial processes due to targeted mechanisms to ensure stability and effectiveness of formulations and delivery methods as these treatments are derived from living cells.

[9] Markey, N., Howitt, B., El-Mansouri, I. et al. Clinical trials are becoming more complex: a machine learning analysis of data from over 16,000 trials. Sci Rep 14, 3514 (2024). https://doi.org/10.1038/s41598-024-53211-z

[10] https://www.appliedclinicaltrialsonline.com/view/large-vs-small-molecule-success-rates

FDA Approvals

Though there have been longer timelines for approval on average, there has also been a trending increase in annual FDA approvals. 700 prescription drugs were approved between 2000 and 2020 and though this suggests an average yearly approval of 35 drugs, FDA approvals have been at record numbers between 2014 and 2020.[11]



Major reasons for the increase in approvals in the past decade despite increasing clinical trial timelines include;

- While timelines are increasing across most phases, data from the regulatory & approval phase makes it clear that the final push to approval has actually reduced from 13.6 months to 11.7 months. This is mainly due to the increasing proportion of new drugs targeting rare diseases in the pipeline. These drugs are often approved via accelerated timelines.[12] 31 of the 55 new drugs (56%) approved in 2023 were designated as Priority Review drugs while 9 of 55 (16%) were approved via Accelerated Approval. Overall, 36 of the 55 drugs (65%) were filed under one or more of the FDA's expedited timelines - Fast Track, Breakthrough Therapy, Priority Review or Accelerated Approval.
- There is an increasing use of technologies such as AI and 3D bioprinting in the drug R&D process. Precision medicines and targeted therapies approvals have occurred on average 2 years earlier than non-precision approvals with fewer trial participants on average.[13]

The industry is currently focused on finding new ways to conduct clinical trials to enable shorter overall cycles without compromising on quality. Shorter cycles present both societal and

[11] https://phrma.org/-/media/Project/PhRMA/PhRMA-Org/PhRMA-Org/PDF/G-I/Innovation_in_Biopharmaceuticals.pdf

[12] https://www.centerwatch.com/articles/25033-trend-of-longer-trial-timelines-is-likely-to-continue

[13] Pregelj L, Hwang TJ, Hine DC, Siegel EB, Barnard RT, Darrow JJ, Kesselheim AS. Precision Medicines Have Faster Approvals Based On Fewer And Smaller Trials Than Other Medicines. Health Aff (Millwood). 2018 May;37(5):724-731. doi: 10.1377/hlthaff.2017.1580. PMID: 29733717.

commercial opportunities as patients get access to the drugs they need faster while time and cost reductions can potentially allow companies to achieve greater revenue benefits and longer periods of patent-protected sales. The recent clinical trial trends point to a time of innovation in the research and development process that will continue to evolve over the next decade.