PEER REVIEWED

Clinical Trial Feasibility in a Changing World: Current Trends and Prospects

In recent years, there has been an upsurge in the number of (bio) pharmaceutical products under development globally, reaching an estimated 7,471 products in 2021, which represents a 2.3-fold increase compared to 2017 (Figure 1). This unprecedented expansion in the pipeline of innovative therapeutics and vaccines across a broad spectrum of diseases has in turn increased the number of clinical trials. During the same period, the number of industry-sponsored studies increased by 56%, from 6,307 to 9,870 clinical trials (Figure 2). The number of trial participants has also increased, with over four million healthy subjects and patients in COVID-19 and non-COVID-19 studies in 2020 due to the impact of the pandemic (Figure 3).[1]

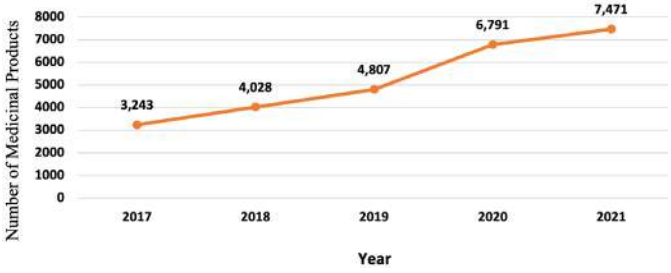

Figure 1 – Number of medicinal products under development from discovery to pre-registration

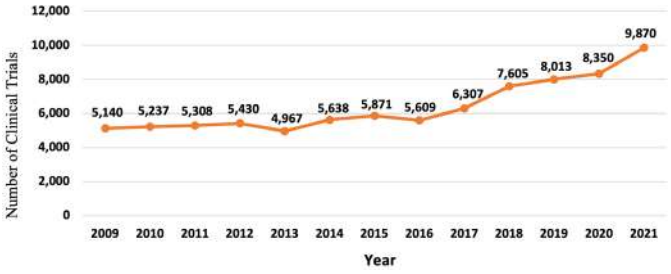

Figure 2 – Number of industry-sponsored clinical trials over time

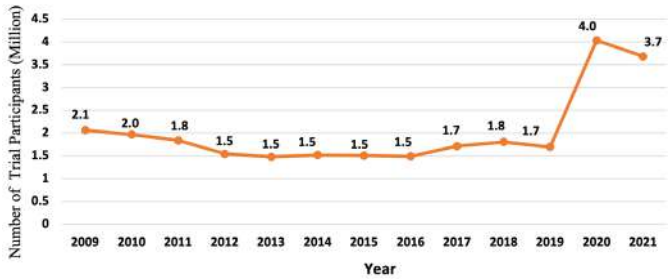

Figure 3 – Number of clinical trial participants over time

A fundamental factor that underpins the successful execution of clinical trials is site quality, and delays in, or the failure of, trial participant enrolment represent significant risks in product development. Therefore, a critical success criterion of clinical trials is the selection of sites with the requisite capabilities: access to a well-characterised population of potential trial participants, experienced and well-motivated investigators and study staff, and adequate site facilities, all located within countries with a favourable regulatory environment.

In this article, we summarise the pitfalls associated with current methodologies of clinical trial feasibility and highlight how SGS Health Science's data-driven and multidisciplinary clinical trial feasibility approach supports many trial sponsors in optimising trial planning across various therapeutic indications.

Recruitment Failure: A Critical Risk to Clinical Trials Globally

Premature termination is a common phenomenon in the clinical trial landscape. For example, approximately 40% of clinical trials in oncology are terminated prematurely.[2] Other authors have estimated that up to 23% of trials cannot follow their patient recruitment as initially planned and fail the study timeline, and about 13% of clinical trial sites do not enrol a single patient in the study.[3] Recruitment failure can seriously impact the product innovation lifecycle, with significant implications in terms of research costs, corporate revenues and delays in access to life-saving innovations.

To assess the contribution of recruitment failure to the global toll of clinical trial termination, we analysed global trends over five years from January 1, 2017 to January 1, 2022 by evaluating all terminated interventional Phase 1, 2, and 3 and industry-sponsored studies posted on ClinicalTrials.gov.

A total of 1,156 studies were included. The results outlined in Figure 4 and Table 1 show that a majority (42%) of clinical trials over the last five years were terminated due to business or strategic decisions. Furthermore, recruitment delays accounted for 22% of trial terminations globally over the previous five years. Other causes of trial termination were lack of efficacy of the intervention (10%), safety (8%), failure to meet the primary endpoint (8%), futility (3%), COVID-19 related reasons (2%) or FDA request (2%). Less common reasons for early trial termination include Data Safety Monitoring Board (DSMB) and Independent Data Monitoring Committee (IDMC) recommendations, investigational medicinal product (IMP) issues, poor pharmacokinetic (PK) data, principal investigator (PI) exit, or no reason was specified.

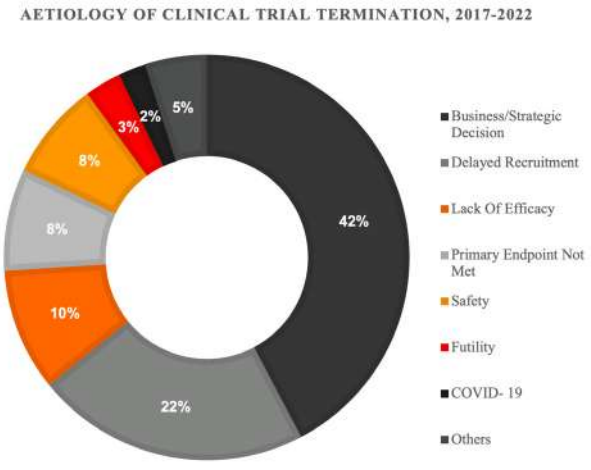

Figure 4 – Aetiology of clinical trial termination: A global view, 2017–2022

Reason For Trial Termination	Number Of Trials	%
Business/Strategic Decision	489	42.3
Delayed Recruitment	253	21.9
Lack Of Efficacy	113	9.8
Primary Endpoint Not Met	94	8.1
Safety	91	7.9
Futility	34	2.9
COVID- 19	25	2.2
FDA Request	17	1.5
IDMC Recommendation	13	1.1
IMP Issues	11	1
No Reason Given	8	0.7
PI Exit	5	0.4
Poor PK Data	2	0.2
DSMB Recommendation	1	0.1
Total	**1,156**	**100**

Table 1: Aetiology of clinical trial termination: A global view, 2017–2022

A Data-driven Approach to Clinical Trial Feasibility Planning

The integration of data-driven analytics and decision-making into the clinical trial feasibility planning process can help maximise the enrolment potential of clinical trials and mitigate the risks of premature termination. Furthermore, the operational efficiencies gained by optimising the feasibility planning process at the trial or portfolio level may potentially reduce drug development costs.

In recent years, attention has focused on a deeper understanding of the data sources that are critical to increasing the accuracy of trial enrolment planning and risk management. The increasing availability and use of digital real-world data (RWD), including electronic health records (EHRs) and insurance claims, has facilitated the application of advanced analytical tools to identify eligible populations and subpopulations of patients with clinical indications of interest.[4] Newer statistical and machine learning algorithms are being deployed to derive even greater insights from existing data.

Furthermore, incorporating data from clinical trial registries like ClinicalTrials.gov, the EU Clinical Trials Register and Japan UMIN-CTR into feasibility planning, combined with well-curated epidemiology and market size information, supports holistic strategic and business decision-making.

SGS Health Science: Delivering Data-driven Clinical Trial Feasibility

Many trials sponsors in the (bio)pharmaceutical industry experience delays in clinical trial completion mainly because their enrolment plans are based on poorly validated information. In many instances, the enrolment rate needed for developing the country/site/patient analysis and subject accrual duration is extrapolated from either raw data from databases without in-depth analysis or directly from site feasibility surveys. However, this linear approach omits several critical components vital for an accurate trial feasibility workflow. Using pharmaceutical intelligence databases without further investigation or heavy reliance on trial investigators' self-assessment of recruitment capacity may result in overly optimistic enrolment estimations. Furthermore, in a recent publication that explored clinicians' perspectives on the persistence of barriers to patient enrolment in Phase 3 oncology studies, some trial investigators considered the completion of site feasibility questionnaires as a very time-consuming activity, often without any guarantee of eventually participating in the study,[5] highlighting the critical role of questionnaire design in the feasibility process.

The workflow of data-driven clinical trial feasibility at SGS Health Science is outlined in Figure 5. The start of the feasibility planning process is based on the receipt of a request for proposal (RFP) from a sponsor. The protocol-related information is reviewed by crucial internal departments, resulting in identifying potential recruitment obstacles, an initial, high-level selection of suitable regions/countries and a first estimation of the anticipated recruitment rate. The overall process is managed by a dedicated feasibility team and supported by medical staff.

Furthermore, a second feasibility evaluation is performed that incorporates critical details like the targeted indications, trial design, subjects' inclusion and exclusion criteria, study assessments, type of investigational medical product, and estimated start and end dates, which are subjected to in-house intelligence and benchmarking analyses incorporating proprietary and publicly available databases as well as relevant published scientific literature. The output is cross-referenced with information collected directly from sites. The result is a detailed clinical trial feasibility assessment report tailored to the sponsor's needs that optimises trial efficiency and minimises the risks of recruitment failure.

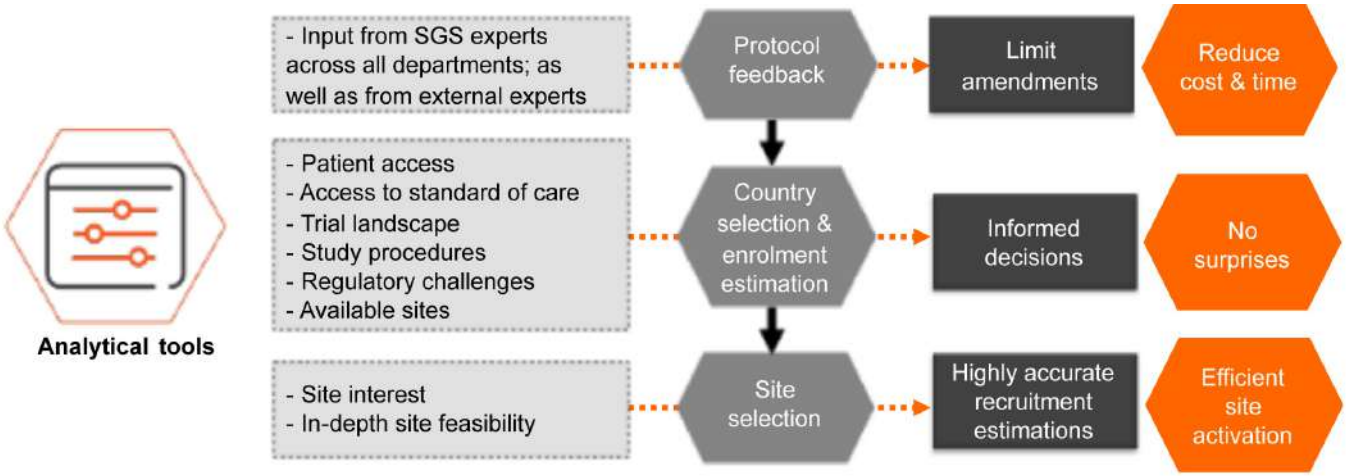

Figure 5 – Workflow of feasibility assessment, SGS Health Science

Clinical Trial Feasibility: Future Directions

There is increasing recognition of the central role of data-driven feasibility in (bio)pharmaceutical product development. Improving efficiencies in targeted feasibility support that meets the innovation cycle needs of evolving personalised and precision medical products represents a critical priority for clinical research organisations. The response of competent authorities to the COVID-19 pandemic – shortening review timelines and providing novel, accelerated pathways – exemplifies the need for adaptation to the emerging patient and public health priorities. Feasibility plans will need constant updating to keep up with these trends.

With the increasing availability of large, patient-level datasets on electronic platforms, a more significant role for artificial intelligence and deep learning algorithms in the feasibility planning process is anticipated.[6] New sources of information on disease incidence, such as social media, are likely to play increasing roles in patient recruitment. Furthermore, as trials become larger and more globally distributed, regional data privacy laws like the European Union (EU) General Data Protection Regulation (GDPR) will become increasingly relevant when it comes to assessing trial feasibility.

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