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Critical path activities in clinical trial setup and conduct: How to avoid bottlenecks and accelerate clinical trials

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Most clinical trials are delayed due to scientific and/or operational challenges. Any effort to minimize delays can generate value for patients and sponsors. This article reviews critical path process steps commonly identified by practitioners, such as during protocol development, site contracting, or patient recruitment. Commonly considered measures, such as adding more trial sites or countries, were contrasted with less frequented measures, such as evidence-based feasibility or real-world evidence analysis, to help validate assumptions before clinical trial initiation. In a broad analysis, we integrated a literature review with a practitioner survey into a framework to help decision makers on the most critical process steps when setting up or conducting clinical trials in order to bring critical treatments to patients faster.

Keywords: clinical trials; critical path; R&D productivity; pharmaceutical industry; trial acceleration

Introduction

The goal of treatment-focused clinical trials is to determine whether a new intervention is safe and efficacious. Hence, these trials play a central role in the drug development process.[1] When planning and conducting clinical trials, practitioners are faced with both scientific challenges and operational complexities, such that delays in clinical trials occur frequently.[2,3] Lengthy timelines can in turn risk trial success and ultimately prolong the delivery of novel treatments to patients.[2,4] Overall, an analysis of clinical trial data from 2000 to 2019 estimated that only 12% of clinical trials are ultimately successful.[5]

The list of possible reasons for delays in clinical trial setup and conduct is long, ranging from production issues with investigational medical products (IMPs), lengthy protocol development cycles, and challenging regulatory landscapes to communication and coordination issues due to the high numbers of involved stakeholders across sponsor organizations, clinical research organizations (CROs), trial sites, lab providers, or patient groups.[2,3,5–8] Furthermore, clinical trial site selection and contracting, authority approvals, or identification of suitable patients can contribute to clinical trial delays.[2,4–6,9]

However, it remains unclear which of these factors are the key drivers of delays during clinical trial setup and conduct. Therefore, we conducted a literature review and a critical path survey among industry experts to answer this question. A critical path analysis is a methodology that can be used to analyze bottlenecks of time-bound operational activities, here to improve drug development, reduce process uncertainty, enable effective resource management, and reduce costs of clinical trials.[10] Critical path activities are process steps that have a high risk of becoming a bottleneck and delaying the full clinical trial timeline.[10] In contrast, noncritical path activities can be carried out in parallel with other process steps because their delay does not necessarily lead to a delay of the overall process.[10] Furthermore, to understand how practitioners notice and counteract delays in clinical trials, we review clinical trial monitoring approaches and possible acceleration levers.

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On the basis of a comprehensive literature review, we developed a clinical trial online survey to validate current academic thinking with a real-world perspective from leading global experts in pharmaceutical (sponsor) organizations and CROs. In a two-step process, the survey was tested with selected industry professionals and academic leaders to incorporate their feedback. Furthermore, to gain insights from a larger audience, we subsequently distributed the online survey globally: 50 responses from industry experts working at different big pharma companies, midsize pharmaceutical companies, biotech companies, CROs, or academic research organizations globally were received. A detailed overview of the participants' demographics can be found in the Supplementary material online.

Finally, we integrated the literature review and survey results into a framework that can help decision makers to focus on the most critical process steps when setting up or conducting clinical trials. Through this effort, we hope to improve clinical trial setup and conduct to bring critical treatments to patients faster.

Protocol development, site contracting, and patient access are crucial critical path activities during the setup and conduct of clinical trials

Overall, the list of process steps and reasons leading to potential delays in clinical **setups** is long (see Supplementary material online), including, for example, selection of appropriate clinical endpoints, protocol development, availability of drug supply, applications to and approval by competent authorities, resolving regulatory differences across different countries (potentially slowing approval timelines), study feasibility and site selection, site contract negotiations, insurances and translations, site activation challenges (i.e., infrequent communication cadences, language differences, and training of site personnel), or simply resource and budget constraints.[2,7,11–14]

Moreover, when **conducting** clinical trials, patient recruiting is an industry-wide challenge (which continues to persist over time) that can be especially pronounced in rare diseases, such that during feasibility assessment, such as at study sites, patient numbers are overestimated frequently, and enrollment targets remain unmet.[4,6,9,12–14] Prolonged patient recruitment and the failure to reach the targeted sample size in time not only could lead to increased cost but also could compromise the reliability and generalizability of the trial results (e.g., if a change in the standard of care occurs while a trial is conducted) and can also lead to ethical questions, such as when no alternative treatment options are available for patients with life-threatening conditions.[4,9,14–16] Furthermore, competing trials, complex study designs, constraints of site personnel resources, protocol amendments, limited commitment of site personnel, insufficiency of principal investigator oversight, and issues with IMP supply are other commonly identified delay reasons during the conduct of clinical trials.[2,5–7,12,17]

To better understand which of these factors are key contributors that create bottlenecks and ultimately delay the overall progression of clinical trials such that they become critical path activities, we surveyed 50 professionals working in pharmaceutical companies, academic research institutions, or CROs. The results of the critical path analysis are presented in Figure 1. Out of this long list of potential reasons delaying clinical trial setup and conduct, the surveyed respondents in particular identified protocol development, IMP supply, site contracting, and patient access as the key critical path activities – the 'four diamonds' (Figure 2).

Prioritizing and improving these critical path process steps (the 'four diamonds') can be beneficial for industry practitioners to avoid bottlenecks and mitigate clinical trial delays. Hence, we summarized improvement and acceleration levers for them in Figure 2 and review them in more detail.

Protocol development: Often unforeseen issues and a high number of review cycles internally and externally (e.g., through competent authorities or ethics committees) can lead to delays in protocol finalization.[2,7] Moreover, protocols of high complexity might necessitate a high number of protocol amendments, lead to lower recruitment rates or compromised data integrity, and ultimately lead to longer trial cycle times and additional costs.[5,8]

Here, Agile teamwork and Lean process management could help to accelerate protocol development, avoiding delays and bottlenecks.[18] The Lean methodology was developed by Toyota as part of their efforts to continuously improve and streamline their automotive manufacturing process by eliminating unnecessary process steps (reducing waste).[19] Both Lean and Agile management methodologies not only have been employed successfully in the software industry or the manufacturing industry but also have helped to achieve operational excellence in different areas of clinical trials.[18–20] For example, the Lean Six Sigma management methodology was used to reduce process error and process cycle time when recording clinical trial data in thousands of case record forms.[20] Furthermore, the Lean methodology was used to refine, improve, and accelerate the hiring process of a clinical research center in such a way that not only the cycle time was significantly reduced from 30 to 22 days but also employee satisfaction was increased.[19]

The next section describes in detail how Agile and Lean could be applied to the protocol development of a clinical trial.

- First, Agile principles could accelerate protocol development by embracing the principle of simplicity, shortening iteration cycles by working in time-boxed sprints and collaborative cross-functional teams that are 100% dedicated and often colocated.[18] Through this, an enhanced stakeholder access across the organization (i.e., governance) can be established that boosts productivity and accelerates the protocol development timeline.[18]
- Second, the introduction of Lean can fast track protocol development. Process mapping could help to eliminate inefficient process steps (e.g., shortening and reducing protocol review cycles) and parallelize activities (e.g., formatting) such that timelines could be compressed.[18,21] Additionally, seeking upfront advice, such as that provided by regulatory authorities, principal investigators, or senior study coordinators, could help to achieve a robust protocol early and reduce the number of iteration cycles or amendments.[2,7] In particular, this requires early decision making to incorporate critical changes in the initial stages of protocol development while

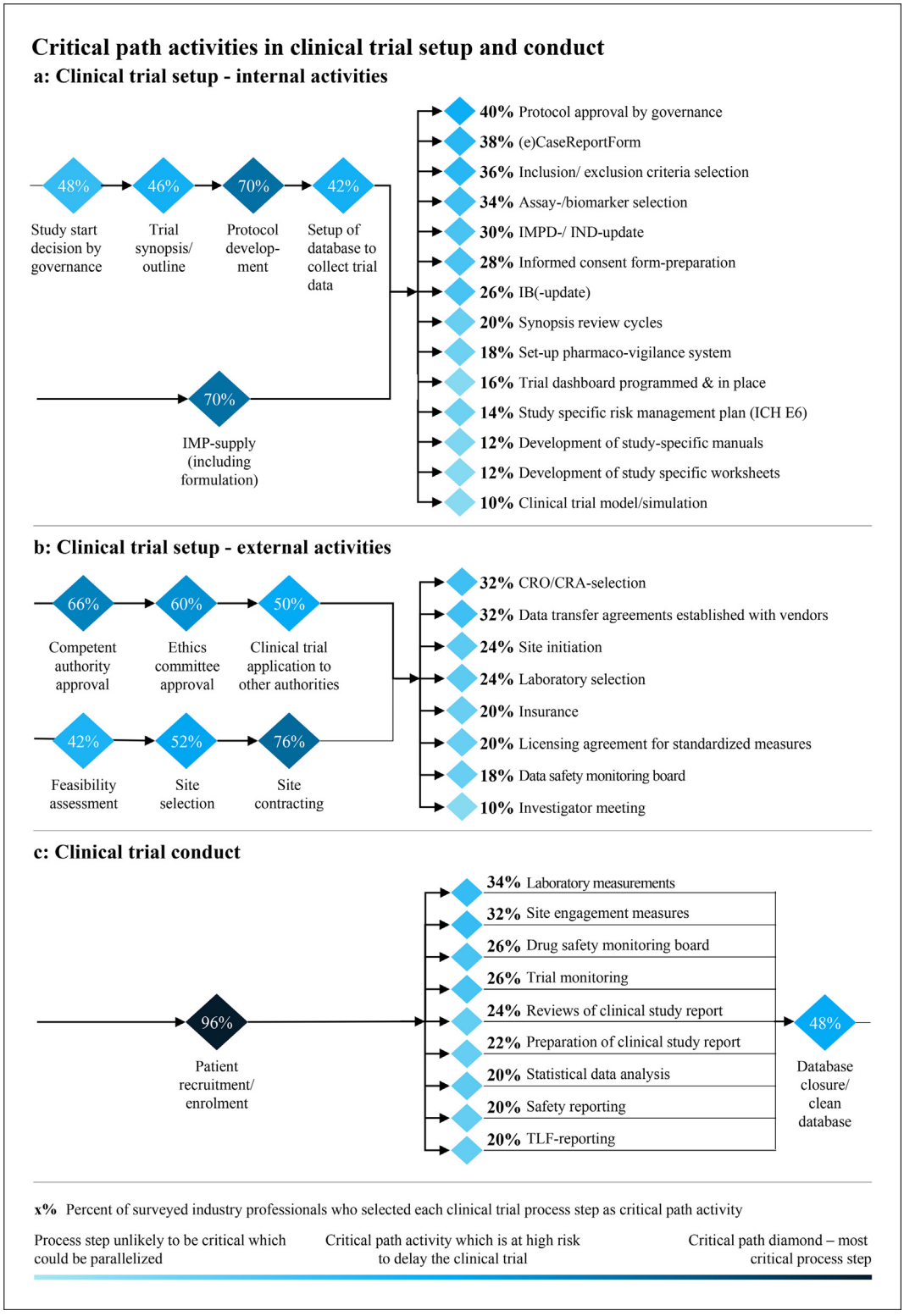

FIGURE 1

Critical path analysis of clinical trial setup and conduct. Insights from a globally facilitated industry practitioner survey including big pharma sponsor organizations, clinical research organizations, and academic institutions about the setup and conduct of clinical trials Phase IIb (classical dose finding trials) (N = 50). Critical path activities are process steps that become bottlenecks leading to delay of the full clinical trial. The percentage values indicate the share of industry practitioners who identified each process step as a critical path activity (multiple answer option: a–c). As key critical path activities industry experts observe **(a)** protocol development, **(b)** site selection, and **(c)** patient recruitment/enrollment. The latter is faced by almost all industry practitioners. Abbreviations: CRA, clinical research assistant; CRO, clinical research organization; IB, investigational brochure; IMP, investigational medical product; IMPD, investigational medicine product dossier; IND, investigational new drug; TLF, tables, listings and figures.

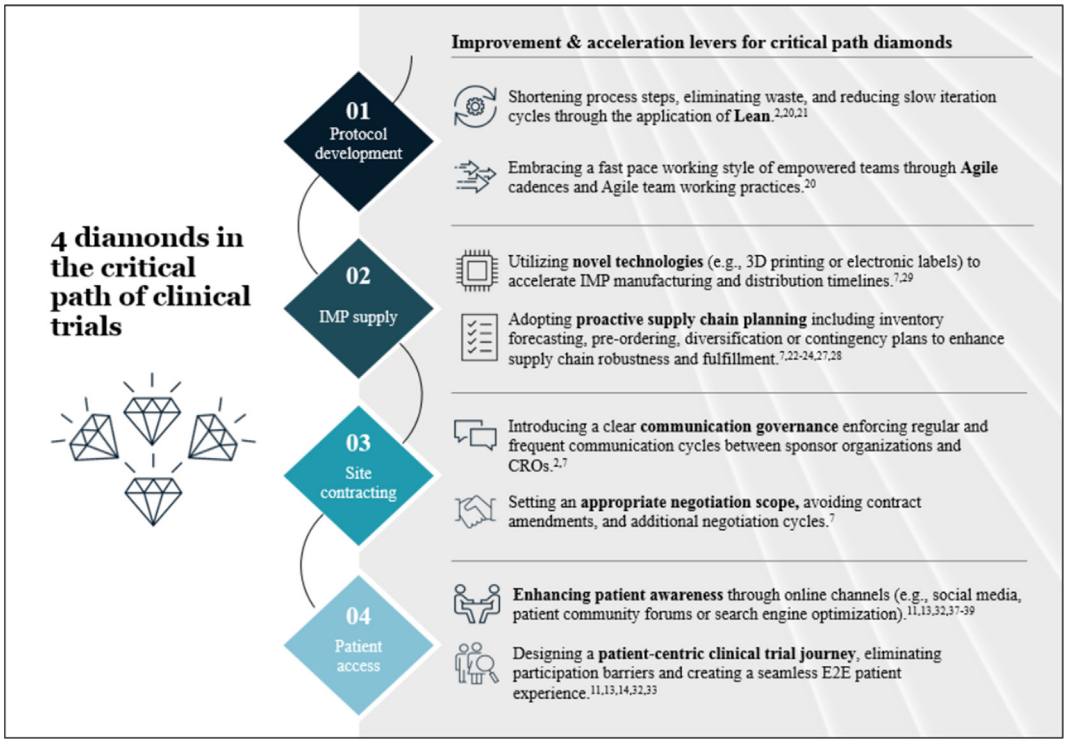

FIGURE 2

Prioritization framework for decision makers – the four diamonds in the critical path of clinical trial setup and conduct. The box reviews acceleration levers for the four most critical process steps (the four diamonds) when setting up and conducting clinical trials of Phase IIb (classical dose finding trials): protocol development,[2,20,21] investigational medical product (IMP) supply,[7,22–24,27–29] site contracting,[2,7] and patient access.[11,13,14,32,33,37–39]

minimizing optional 'nice-to-have' aspects in the protocol (with the potential to add them after initial approval as non-substantial amendments).[2]

- Of course, when aiming at accelerating the protocol development or clinical trials in general, it is important to define clear metrics that would capture what benefits can be achieved by acceleration; otherwise, the acceleration could yield limited results.[18] Moreover, it needs to be considered that both Agile and Lean methodologies have limitations or face practical considerations when choosing to implement them. Transitioning from traditional workflows to Agile or Lean operations cannot be implemented overnight but require long-term commitment from senior management.[20] Overall, further research needs to quantify in more detail the expected process improvement rates that can be achieved by adoption Agile or Lean management methodologies in a research setting because available data remain limited.[19]

IMP supply: Delivering IMP supplies globally is an additional common factor delaying clinical trial launches.[7,22] Manufacturing challenges (quality, stability), lacking harmonization of regulation (country-specific import/export regulations or data requirements for drug labels), coordination of multiple stakeholders (manufacturing facilities, couriers, hospital personnel, etc.), or deliveries to remote regions introduce logistical challenges and significant lead times for IMP supply deliveries.[7,23,24] With the industry shifting from traditional small molecules toward novel therapies (biologics, radiotherapies, or cell and gene therapies), additional supply chain complexities are introduced: strict cold chain and time constraints, customization, and patient-specific manufacturing.[23] The COVID-19 pandemic has led to additional supply chain interruptions for IMPs and subsequent shortages and delays.[22,23,25–28]

To mitigate the risk that IMP supply becomes the bottleneck of clinical trial setup and conduct, it is recommended to leverage novel technologies and implement proactive planning strategies[7,23,24,27,29]:

- Using novel technologies such as three-dimensional (3D) printing in pharmaceutical formulation development or electronic labels could accelerate manufacturing and distribution timelines of IMP supply and enhance supply chain flexibilities.[7,29] 3D printing is a rapid manufacturing technology that is promising for small batches of pharmaceutical formulation because it is very flexible (tailoring of doses, shapes, release characteristics), faster, less costly, and less resource-intensive than traditional manufacturing routes.[29] Furthermore, adopting electronic labels for IMP supply is expected to reduce lead time for the packaging and labeling of drug supplies from 30 weeks to 16 weeks.[7]
- Proactive supply chain planning could enable organizations to build robust supply chains and ensure sufficient stock levels even when unforeseen events occur.[7,22–24,27,28] Monitoring of local import and export regulations, inventory forecasting,

implementation of good cold chain strategies, preordering, and close coordination of both internal and external distribution stakeholders build the foundation of a robust supply chain,[7,22–24,27] whereas the preparation of contingency plans and the diversification of supplier networks protects organizations against unforeseen global disruptions.[23,28]

Site contracting: Contract negotiations between sponsor organizations and CROs can run over months and are described as critical path activity commonly delaying clinical trial setup.[2,7,17] Prolonged negotiation timelines could be driven by incompatible regulatory policies, diverging terminology, or long turnaround times due to resource constraints (e.g., at academic sites).[2,6,7] Further contributing factors could be difficulties in finding experienced staff, inadequate budget templates, limited negotiation parameters, or prolonged legal reviews.[7] Every renegotiation iteration will lead to delays[6]; thus, alternative levers need to be applied to overcome lengthy site contracting endeavors:

- For both sponsors and CROs, it may be beneficial to begin contract negotiations early on (e.g., in the form of master service agreements with indication-specific centers) and to jointly define a communication governance that includes the definition of clear points of contact, the alignment on target timelines, and the introduction of frequent communication cycles to accelerate contract negotiations.[2,7]
- Moreover, setting an appropriate negotiation scope and concrete negotiation parameters from the beginning could speed up the overall site contracting process.[7] Leveraging previously negotiated contracts and budget terms may provide an additional opportunity to reduce negotiation cycle times.[7]

Patient access: Almost all industry practitioners evaluate patient access as their most prominent challenge and critical path process step when conducting clinical trials (Figure 1). Effective patient recruitment and enrollment are fundamental for a successful clinical trial completion and the generation of reliable and generalizable results.[9] However, often the predicted recruitment is overestimated, and targets are not met.[4,6,9,12–14,17] Only approximately 31% of clinical trials meet their originally predicted recruiting rate.[30] Contributing factors to unmet recruiting targets could be high screening failures, high number of competing trials, and high patient dropout rates [e.g., due to complex and burdensome (for patients or site staff) protocol designs].[5,12,15,31]

However, opportunities exist to improve patient access and mitigate the risk of delays through enhancing patient engagement (e.g., during the design phase of the protocol) and strengthening patient-centricity when setting up and conducting clinical trials.[11,13,14,32–34] Recent research has found that the implementation of effective patient engagement strategies can accelerate clinical trials and yield significant financial benefits. For example, it was found that for a typical oncology pre-Phase II project, the cumulative impact of patient engagement activities was deemed to yield an increase of $62million in net present value and an increase in $35million in expected net present value (ENPV). Consequently, for $100,000 investments in patient engagement activities that avoid one protocol amendment, define more meaningful end points, improve patient enrollment, adherence, and retention, the increase in ENPV would exceed 500%. This financial benefit in increased ENPV is equivalent to accelerating a pre-Phase II product launch by 2.5 years.[34]

- Embracing strong patient-centricity in clinical trial setup and conduct could enhance patient access and improve trial outcomes, which leads to greater medical benefits for patients.[13,32] Engaging patients early in the clinical trial design and planning process could unlock valuable improvements, leading to a more seamless end-to-end clinical trial patient journey, increasing enrollment, and reducing dropout rates. For example, participation barriers such as burdensome logistics could be removed; inclusion and exclusion criteria could be optimized to enable higher screening success rates; and communication targeting patient groups could be customized to the patients' preferences, needs, and priorities.[11,13,14,32,33] Additionally, the adoption of new technologies or other supportive solutions can further help to boost enrollment, patient engagement, care, and overall satisfaction. These can range from low-tech concierge services, prepaid travel expenses, and childcare to more high-tech solutions, such as wearable devices or smartphone apps.[35]
- Furthermore, adopting a multichannel digital communication strategy could help to enhance patient awareness and identify untreated patients, such as targeting patient groups that organize on social media platforms, communicating in forums, or seeking information through online search engines.[13,32,36] Technologies such as search engine optimization or telemedicine could be effective in putting such strategies into practice and broadening patient access.[11,37–39]

Of course, when designing patient engagement strategies, it should be taken into account that patient appetite to engage with new technologies or support services varies across age groups, regions, or ethnicities.[35]

Overall, it is expected that improving the key critical path process steps protocol development, IMP supply, site contracting, and patient access – the 'four diamonds' – can help industry practitioners to prevent or mitigate clinical trial delays. Lean practitioners could use the developed framework to benchmark their organization, identify room for improvement, and start adopting strategies outlined above. It requires further research or data collection to measure the impact of the implemented managerial or process changes on the duration of clinical trials. Therefore, in the next section, we review how industry practitioners approach monitoring of clinical trials and what are common practices to further accelerate clinical trials.

Clinical trials can be monitored using a risk-based approach and counteract delays by adding additional sites, intensifying site interactions, or sharing best practices

Regular **monitoring** of the advancement of clinical trials is critical to tracking a site's operational performance and identifying potential clinical trial delays.[9,15,40] Comparing actual patient enrollment rates with rates stated in the site's feasibility question-

naire could provide an early indication of clinical trial delays.[6,9,15,40] This is recommended because patient enrollment rates are often overestimated during trial planning.[6,7,9,17] Overall rigorous monitoring could enable performance comparison across sites and the establishment of benchmarks.[9,41] This could enable the detection of inefficiencies and foster more effective resource allocation and balancing of workload across staff, which in turn could lead to process improvements and trial acceleration.[9,41]

Although traditional clinical trial monitors have analyzed all the data generated in a clinical trial, risk-based approaches also advocated by regulatory agencies have embodied the principle to 'focus on things that matter' and have adapted monitoring frequencies based on the risk level.[42,43] Through this, risk-based monitoring is considered to be more time and cost efficient.[43]

Among the surveyed industry experts, risk-based monitoring has been cited as common practice (Figure 3). Most of the surveyed experts monitor specifically patient-focused metrics such as recruitment rates, screening failures, total number of enrolled patients, or screening failures during weekly or monthly review meetings, on dashboards, or in summary reports. Financial metrics such as 'spent per patient' seem to be less important to the surveyed industry experts (Figure 3). Also, recent academic research finds that the cost of running a clinical trial are considered as secondary if the site accomplishes the patient recruitment in the agreed timeline.[6]

To source more patients and **accelerate clinical trials**, organizations most commonly share best practices, add additional sites, or engage more frequently with site personnel (Figure 2):

- Sharing best practices across clinical trial sites and the engagement of operational excellence teams can be helpful to shorten clinical trial lengths.[44] Practices such as gemba walks (visit and analyze actual frontline processes) or kaizen (process improvement) workshops could be suitable techniques to identify process inefficiencies, ideate improvement ideas, and cocreate the vision of the ideal clinical operation processes.[21,45,46] Because these methodologies rely on a high level of stakeholder engagement, they are expected to lead to a quick adoption of improved operational processes that could accelerate clinical trials.[21]
- Selecting additional sites that are most promising to yield clinical trial acceleration remains a challenge, and the competition for good, experienced clinical trial sites intensifies.[6,7,12,47] In order to achieve the desired clinical trial acceleration, organizations may prioritize additional sites based on criteria such as their activation speed, patient access, and throughput potential.[6,7,9,14,15,30,47] Further details about site selection criteria are reviewed in the next section.
- Intensifying sponsor, CRO, and site interactions to enhance engagement with local investigators but also across the complete trial 'value chain' can improve recruitment efficiency and mitigate clinical trial delays.[17] It will allow recognition of problems promptly and finding remedial actions.[17]

As described above, clinical trial site selection remains an industry-wide challenge to better understand which key criteria guide industry practitioners in their decision. We review this topic in detail in the next section.

Clinical trial site selection is mainly based on knowledge, patient access, and working culture

Clinical trial site selection is pivotal to the pharmaceutical industry because it impacts the trial timeline, its success, and ultimately the delivery of medical care to the patient.[6,12,17] However, in practice, still approximately 19% of initiated sites do not recruit any patient.[30] Hence, prioritizing and selecting the most promising trial sites from the beginning is of great importance to reduce the risk of trial delays, limit the risk of data quality issues compromising scientific integrity, and mitigate cost inefficiencies.[6,15,47] As described above, most commonly, industry practitioners counteract clinical trial delays by expanding to additional trial sites.

Besides the key criteria – activation speed, patient access, and throughput potential – additional criteria play an important role in the clinical trial site selection: the level of training of site personnel and experience in conducting clinical trials, communication skills of site personnel, interest in participating in the study, level of engagement of the principal or lead investigator, academic standing and expertise of key opinion leader, or data collection procedures.[6,7,12,14,15,30,47]

Out of this set of selection criteria, the majority of industry experts base their decisions on three dimensions (Figure 4):

- Knowledge, i.e., the site's experience in conducting trials or therapeutic specialization in target indication
- Patient access, i.e., the site's historic patient recruitment performance or access to required patient population
- Working culture, i.e., the site's interest and commitment to drive clinical trials on time

Often feasibility assessments are carried out in a hurry such that patient enrollment rates are overestimated.[7,17] Hence, achieving more realistic and evidence-based feasibility assessments is an enabler for a robust site selection decision.[9,14,30] Moreover, to ensure appropriate site selection, it might be beneficial for industry practitioners to define an ideal site profile describing the required investigator experience, site capabilities, site infrastructure, institutional resources, and target population access.[14] In particular, assessing the target patient population using specific criteria such as seasonal fluctuations, disease stage, public awareness, disease rarity, and satisfaction with current therapies could lead to a more realistic estimation.[14]

Furthermore, historically well-performing trial sites are also likely to perform well during subsequent trials.[12] Thus, analyzing a site's historical performance and leveraging information from site recruitment rate databases, public databases (e.g., clinicaltrials.gov), or electronic health records can enhance decision making in clinical trial site selection such that the trial feasibility evaluation becomes data-driven and evidence-based.[12,15,30,40,44,47,48]

Concluding remarks

The setup and conduct of clinical trials are operationally complex. Inefficiencies in clinical trials not only can lead to delayed timelines and additional costs but also can yield ethics questions, risk trial success, and ultimately prolong the delivery of treat-

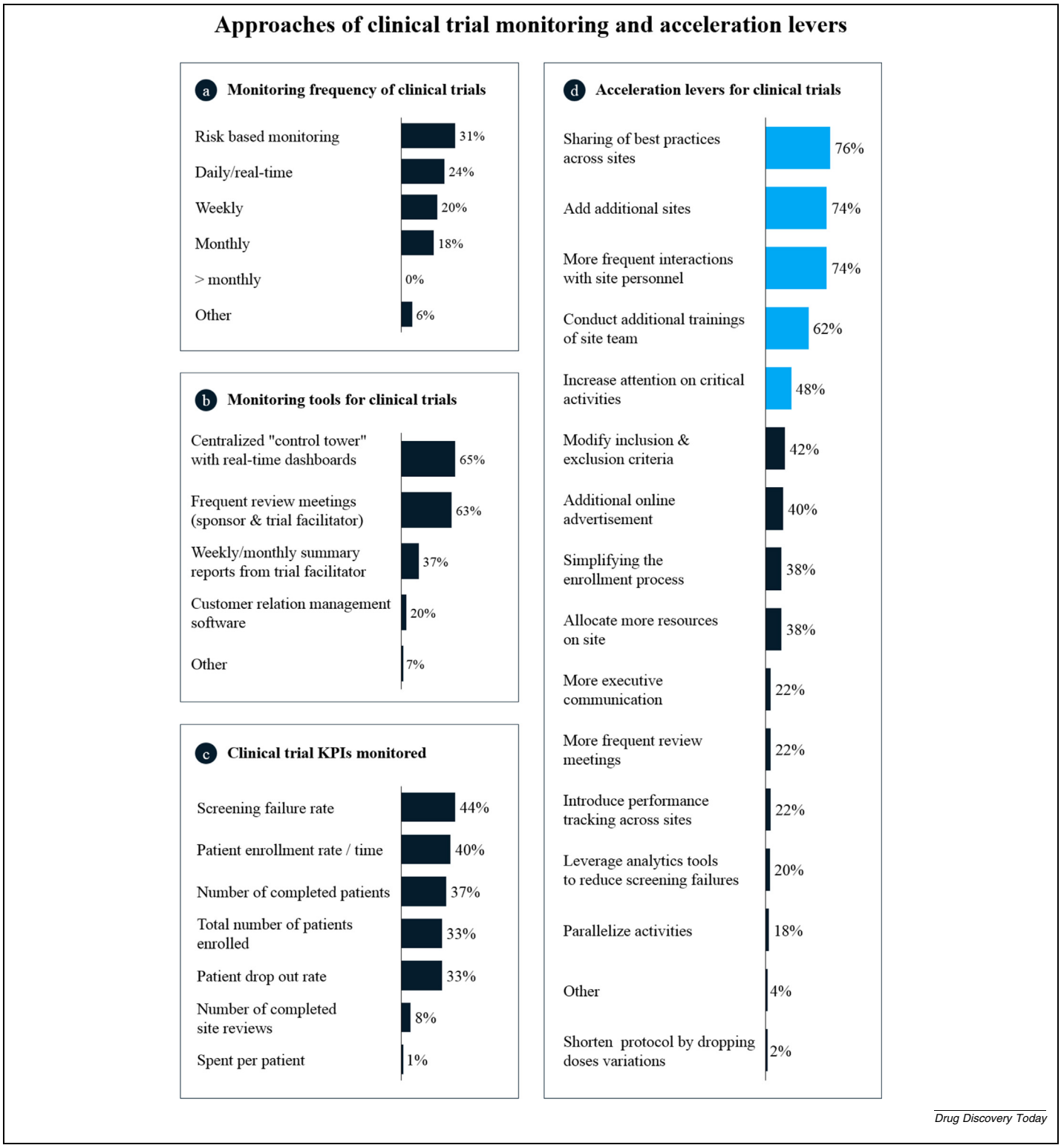

FIGURE 3

Approaches to clinical trial monitoring and applied acceleration levers. Insights about approaches to clinical trial monitoring and acceleration from a globally facilitated industry practitioner survey including big pharma sponsor organizations, clinical research organizations, and academic institutions about clinical trials Phase IIb (classical dose finding trials) (N = 50). The percentage values indicate the share of industry partitioners who selected each option (single answer option: a, multiple answer option: b–d). Industry experts most commonly monitor clinical trials risk-based **(a)**, for which they leverage centralized control towers, or facilitate frequent review meetings **(b)** to evaluate recruiting key performance indicators (KPIs) such as screening failure rates, enrollment rates, or number of patients who completed the trials **(c)**. To accelerate clinical trials, organizations mostly rely on sharing best practices across sites, adding additional sites, or intensifying interactions with site personnel **(d)**.

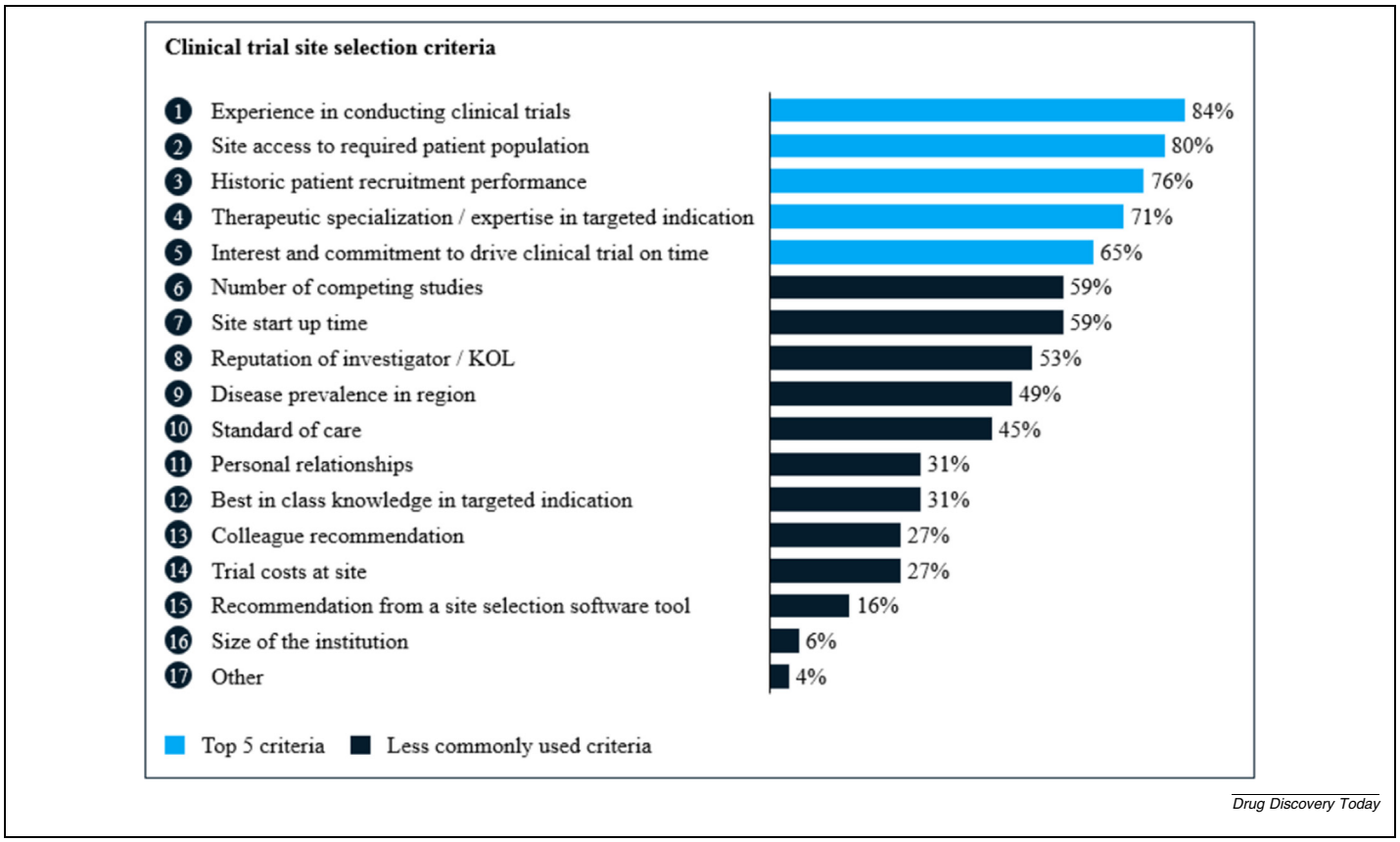

FIGURE 4

Clinical trial site selection criteria. Insights about clinical trial site selection criteria from a globally facilitated industry practitioner survey including big pharma sponsor organizations, clinical research organizations, and academic institutions about clinical trials Phase IIb (classical dose finding trials) (N = 50). The percentage values indicate the share of industry partitioners who selected each option (multiple answer option). Industry experts select clinical trial sites most commonly based on the site's experience and expertise in target indication, its access to patient populations, and the personnel's interest and commitment to drive the clinical trial on time. Abbreviations: KOL, key opinion leader.

ments to patients. Literature review and critical path analysis shows that the four most prevalent critical path activities for clinical trial setup and conduct are protocol development, IMP supply, site contracting, and patient recruiting/enrollment – the four diamonds in the critical path of clinical trials.

To avoid or mitigate bottlenecks, clinical trial sponsors and CROs should give heightened attention to these critical process steps, plan with buffer time, build governance around them, adopt agile working models, leverage novel technologies accelerating processes, and pay attention to improved communication and coordination of the different stakeholders making the planning, setup, and conduct of clinical trials more robust against disruptions.

Because patient recruiting remains a key challenge for practitioners of clinical trials, further research is required to better understand how to reach especially patient populations in orphan indications or very specific subpopulations, efficiently select the best clinical trial sites, realistically evaluate projected patient enrollment rates, or enable patient-centric trial designs to achieve seamless patient journeys. Involving patients early in the clinical trial design process could not only lead to higher patient enrollment numbers and faster trial timelines but also yield better medical outcomes and benefits for patients. Investments in patient engagement strategies are therefore expected to yield significant financial benefits and clinical trial acceleration.

Finally, unlocking the benefits from the presented frameworks and recommendations in practice requires both sponsor organizations and CROs to embrace improvements to their current operating model. Both the sponsor organizations and the CRO should clearly articulate whose responsibility it is to address which bottleneck, such as during protocol development or securing IMP supply, might be the sponsor's responsibility while accelerated site contracting and better patient access could be addressed by the CROs.

Declaration of interests

L.B., M.Z., and F.D. participated in this project while on academic leave from a large international consulting firm. H.T. is employed by AiCuris AG, which engages in anti-infective new drug development. Furthermore, H.T. is the founder of The Knowledge House GmbH, which focuses on the support of biotech and medtech companies. The study was executed during the authors' personal time. Neither the consulting firm nor any

of the mentioned other companies were at any point involved in the research, and no funding was provided.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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