

Improving Pharma R&D Efficiency:

The Case for a Holistic Approach to Transforming Clinical Trials



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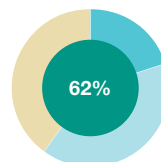
Introduction

Declining research and development (R&D) efficiency is one of the biggest challenges pharmaceutical manufacturers face today. Total sponsor cost per new drug approved in the US jumped 145 percent in just 15 years to more than \$2.5 billion in 2014, according to the Tufts Center for Drug Development. At the same time, just seven percent of first-in-human drugs gained FDA approval.¹ The costs and risks of drug development have never been higher in both financial and human terms.

These inefficiencies largely result from an outdated clinical trial model. Nearly \$1.5 billion per approved new drug is attributed to clinical development, the majority of which is for clinical studies. The traditional approach of three discrete, fixed trial phases designed for testing mass-market drugs often is not viable in today's increasingly competitive, value-based therapeutic markets. It lacks the flexibility, analytic power and speed required to develop complex new therapies targeting smaller and often heterogeneous patient populations.²

A new survey of pharmaceutical executives and professionals by ICON and Pharma Intelligence provides valuable insight into current clinical trial challenges and potential solutions. The challenges most frequently cited are patient enrolment, site start-up and regulatory approval delays and changes. These operational issues reflect the difficulty of designing studies that address critical patient and investigator needs, as well as evolving regulations.

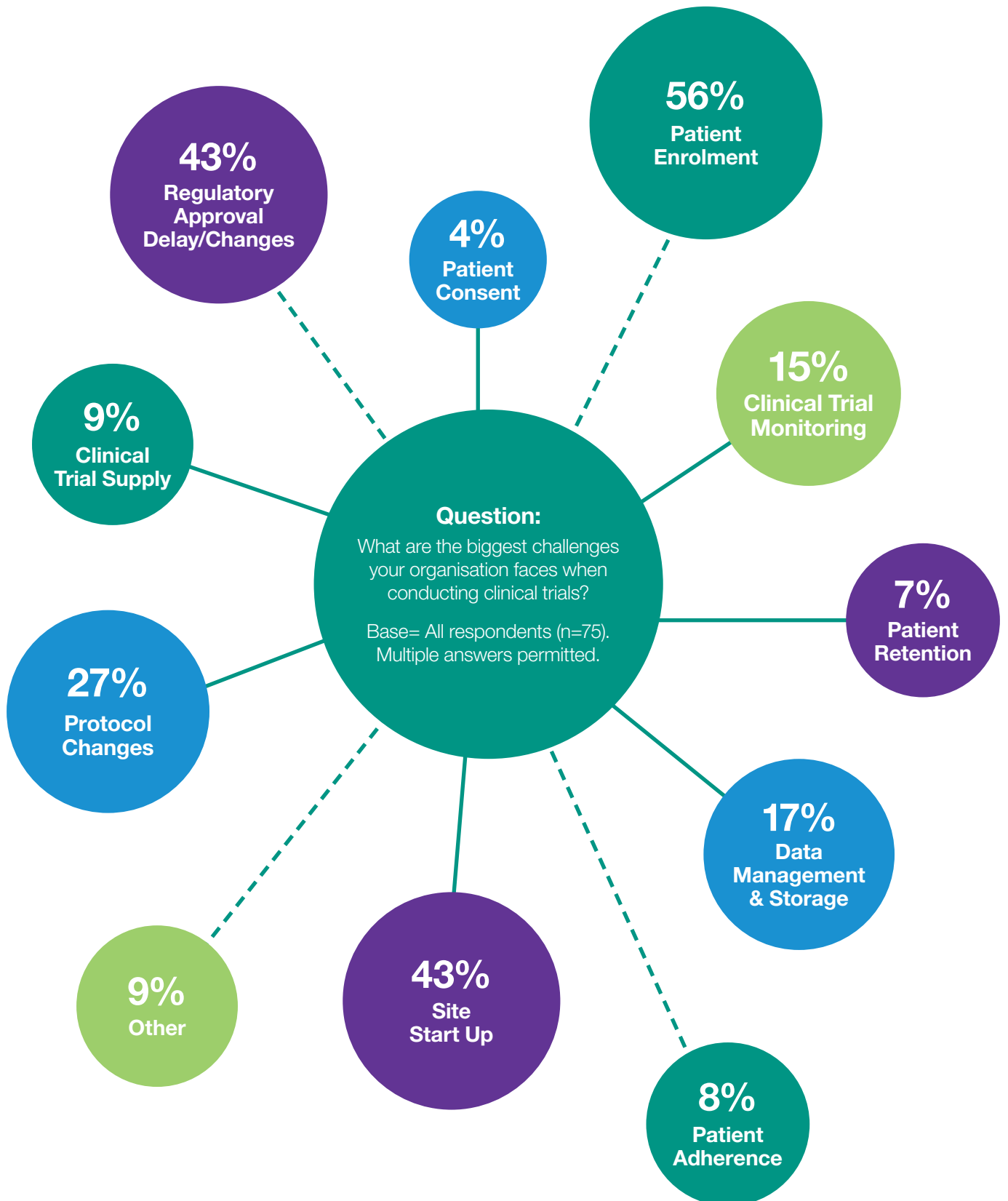
In this white paper we examine in more detail the challenges facing clinical trials, and propose a three-part framework for addressing them that leverages key emerging technologies and capabilities. We then make the case for a holistic, integrated approach to transforming trials that breaks down obsolete organisational, functional and information silos, as necessary, to improve R&D efficiency, putting sponsors on the path to reducing both the costs and risks of developing needed new therapies.



More than one in five survey respondents reported that an integrated effort to drive clinical trial transformation was already in place in their organisation. Another 40 percent plan to launch one in the near to intermediate future (up to 3 years or more).

Top Challenges

Patient enrolment, site start up and regulatory approval delays/changes are the biggest challenges that organisations face when conducting clinical trials.

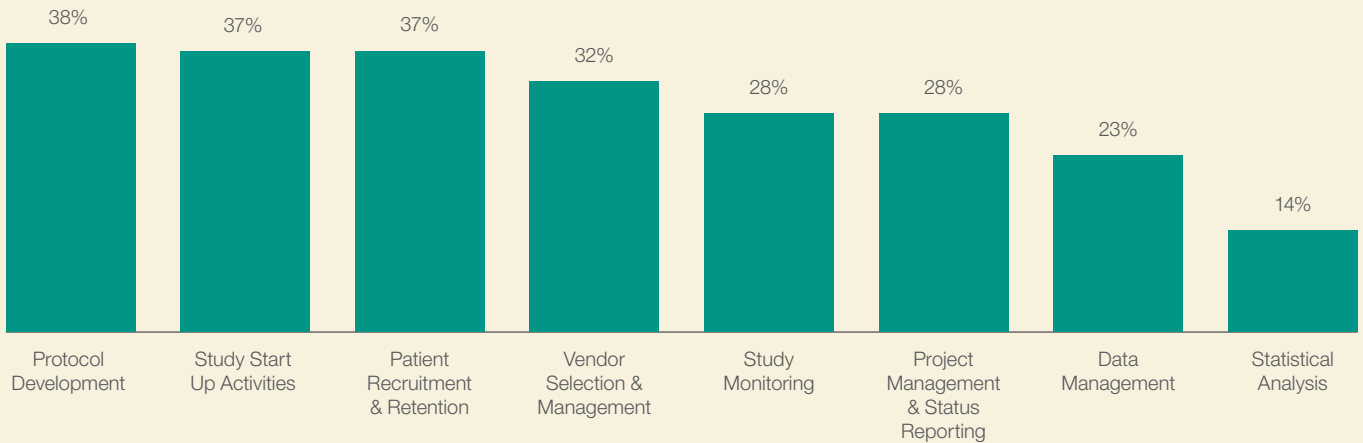


Areas identified as having the most potential for generating savings and improving trial efficiency corresponded closely with perceived challenges. Protocol development, study start-up activities, and patient recruitment and retention virtually tied for first place.

Vendor selection and management, study monitoring, and project management and status reporting clustered not far behind, suggesting awareness of the value of developing and maintaining key operational capabilities, both internally, and through partnerships.

Potential for Efficiency Savings

Respondents see the potential for efficiency savings in various areas of the clinical trial process.



Question: Where do you see the biggest potential for efficiency savings?

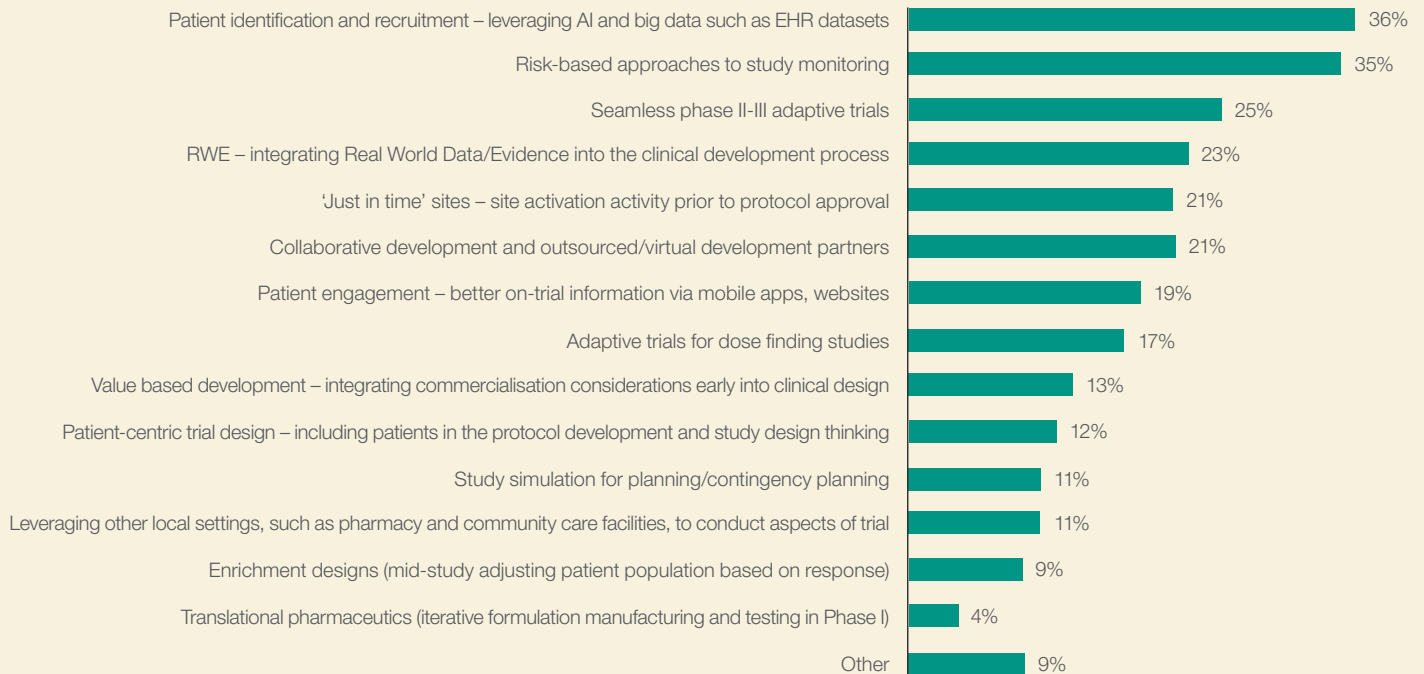
Base= All respondents (n=74). Multiple answers permitted.

Emerging technology capabilities are expected to play a vital role in transforming clinical trials – including leveraging big data and predictive analytics – which can enable the efficient identification of promising study subjects and sites, as well as risk-based monitoring of trial performance in real time. Integrating study and electronic health records (EHR) may increase data collection reach and efficiency, and help better integrate trials into clinical practice. Patient-focused technologies, including mobile sensors, smartphone apps and telemedicine, were seen as ways to collect richer patient data, develop new endpoints and help design novel kinds of trials that may better demonstrate real-world clinical and functional value.

Survey responses reflect a growing understanding that improving R&D efficiency and return on investment will take more than gradually adopting a number of new technologies. It will require a holistic approach to transforming trials, rethinking and redesigning the trial product itself and the enterprise that supports trials from the ground up.

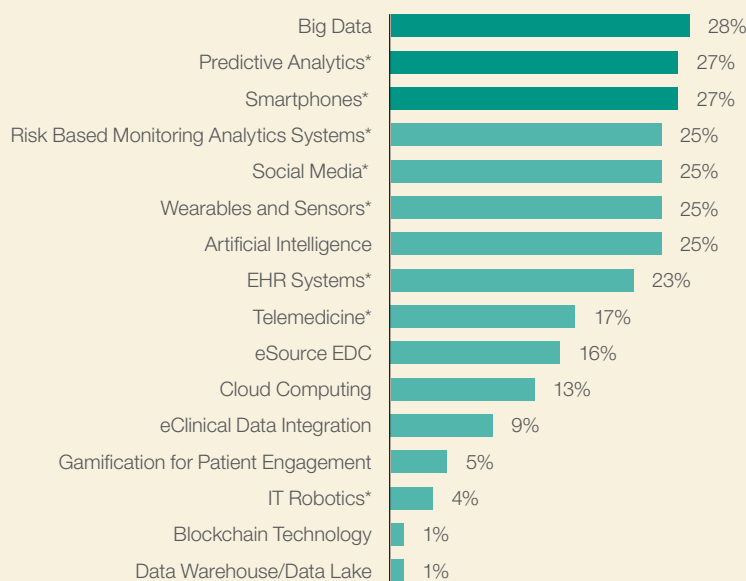
Impact on Clinical Trial Operations

Patient identification and recruitment and risk-based approaches to study monitoring are expected to have the most impact in transforming the efficiency, speed, and productivity of clinical development.



Question: Which of the following will have the most impact in transforming the efficiency, speed and productivity of clinical development? Select up to three. Base = All respondents (n=75).

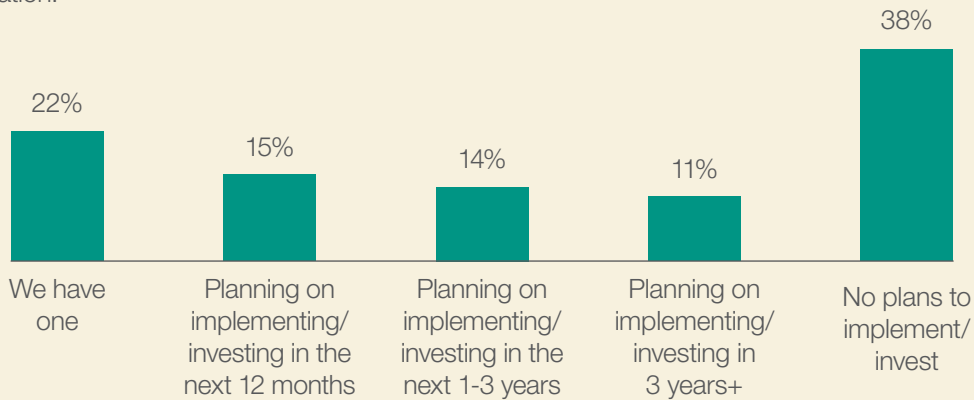
Respondents vary in their opinions of which disruptive technology trends will have the greatest impact on clinical trial operations.



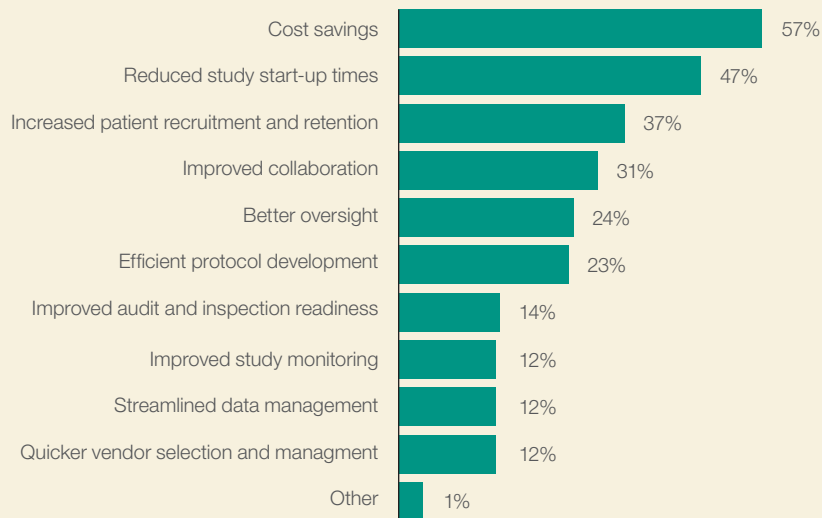
Question: Which of the following disruptive technology trends do you think will have the greatest impact on your clinical trial operations? Select up to three. Base= All respondents (n=75). *See notes on back page.

Clinical Trials Transformation Initiative

More than one in five respondents currently has a holistic/integrated initiative to drive clinical trials transformation. An additional 40% plan to implement or invest in this initiative. Cost savings, reduced study start-up times and increased patient recruitment and retention are considered the top three benefits of a holistic/integrated initiative to drive clinical trials transformation.



Question: Does your organisation have a holistic/ integrated initiative to drive clinical trials transformation?
 Base= all respondents (n=72).



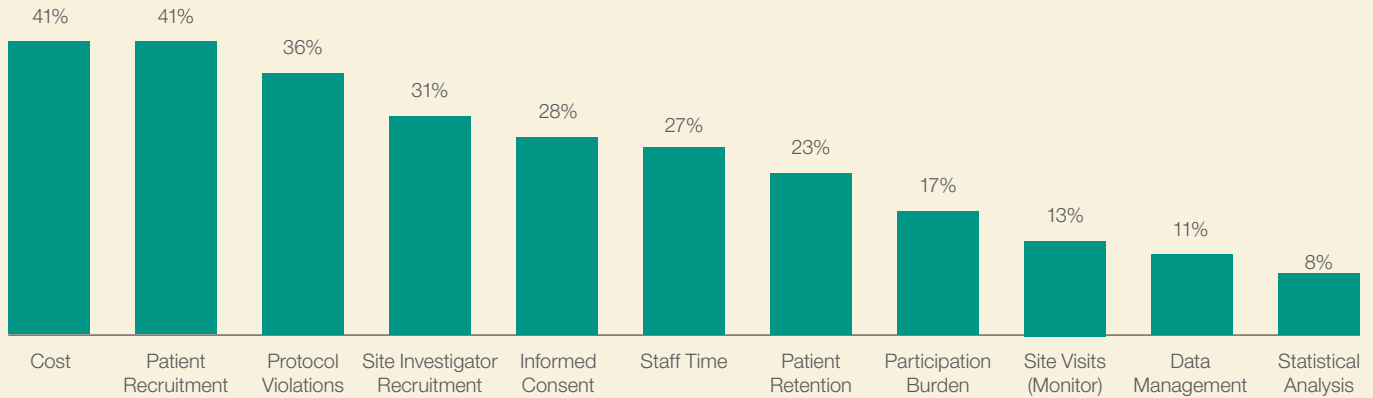
Question: What do you consider the top three benefits of implementing an initiative to drive clinical trials transformation?
 Base=All respondents (n=74).

Key Challenges

Changing market needs require establishing new goals for clinical trials.

Negative Results of Increased Protocol Complexity

Cost, patient recruitment and protocol violations are most negatively impacted by increasing protocol complexity.



Questions: Which of the following activities are most negatively impacted by increasing protocol complexity? Select up to three. Base= All respondents (n=75).

Declining pharmaceutical R&D efficiency and the resulting deterioration in return on investment is largely driven by lengthening development cycles. These, in turn, typically involve increasing trial complexity and regulatory approval delays. Drilling down further, these complexities and delays are symptomatic of deep structural changes in therapeutic markets that conventional clinical trials are simply not designed to address. These market changes include:

Smaller Targets

The traditional three-stage randomised clinical trial structure was built to study drugs intended to treat large populations. The numbers involved made it relatively easy to recruit for very large trials, while mass market potential made it economically feasible to conduct them. Today's markets are different. Driven by scientific advances in areas including biochemistry, genomics and biomarkers, the market for new therapies has moved toward targeted therapies and orphan indications, with big gains in approvals for neoplastic therapies and declines in cardiovascular and broad spectrum anti-infectives since 1980.⁴ The smaller potential markets mean the R&D enterprise – and clinical trial designs and procedures – must be tightly focused on patient needs, relevant clinical and research expertise, and maximising efficiency in demonstrating safety and efficacy.

Personalised Medicine

Taking the smaller target trend to its logical conclusion, the market for personalised medicine is growing exponentially. New product offerings target specific biomarkers, such as biologic chemotherapy agents, or even individual patients, such as CAR-T immunotherapy. Similarly, therapies that combine mobile sensors and devices with drugs and delivery devices, such as an artificial pancreas or apps assessing the daily effects of Parkinson's or other mobility-restricting conditions, require evidence of real-world efficacy and safety that cannot be generated in a controlled environment.

Value-Based Care

Rising healthcare costs as a percentage of GDP is driving greater scrutiny of the economic value of new treatments by government and private payers. In addition to efficacy and safety, clinical trials increasingly must demonstrate a meaningful impact on patients' lives. This is particularly true for high-cost therapies targeting smaller patient groups, many of which struggle to be covered by national health systems and private insurers. Screening patients to identify potentially better responders and linking payments to individual patient outcomes are among the measures payers are negotiating with sponsors to ensure they are getting value for the money they spend.⁴

New market needs require new ways to generate evidence

The traditional three-stage randomised control trial (RCT) model is not designed to collect information that meet emerging market needs. In some cases, the populations involved are too small to conduct randomised trials, noted Rob MacKenzie, executive vice-president and chief development officer with Pfizer, speaking at a “Transforming Clinical Trials” session at the ICON sponsored Financial Times Global Biopharmaceutical conference.⁵ Similarly, collecting real world data (RWD) to expand label indications, or to truly personalise therapies, cannot be done in a strictly controlled trial structure. Demonstrating value also requires collecting real-world clinical information, as well as non-clinical data on costs.

Alternatives to RCTs are needed to develop products that address these needs, noted Janet Woodcock, director of the US FDA Center for Drug Evaluation and Research, at a recent National Academies of Sciences, Engineering and Medicine meeting. “Our inability to generate the needed evidence efficiently and in a cost-effective manner will continue to be a barrier to innovation and to quality care around the world”.⁶ While RCTs are likely to remain the gold standard for validating the safety and efficacy of new compounds for initial registration, innovative trials using real-world data are likely to play an increasing role in defining new, patient-centred endpoints and expanding and refining indications.

A clinical trial model integrated with the broader healthcare delivery system presents a transformative opportunity. It would be one way to address patient enrolment, the top challenge to conducting trials identified in the joint ICON-Pharma Intelligence survey, by making more patients available.

According to the landmark EDICT project, depending on location and trial type, only about three percent of eligible patients have the option to participate in a clinical trial.⁷ Increasing this percentage to even five percent would nearly double eligible patient pools and could speed up recruitment and shorten start up times, which are usually the longest trial components. Expanding recruitment pools could also help ensure traditionally under-represented groups, including older and younger patients, and ethnic minorities, are included. Making clinical trials available as a treatment option when patients present for primary care, secondary care, and at the consultant level could greatly expand participation. Organisations such as PMG Research address this gap by partnering with physician networks to provide sophisticated trial support in community settings.⁸

Pragmatic trials, which take place in real-world conditions rather than tightly controlled settings; virtual trials, which monitor patients remotely; and concurrent open-label trials, which allow testing a therapy’s effect on a population more representative of typical patients, are potential alternatives for more efficiently capturing data needed to target smaller patient groups, individual needs and demonstrate value outside the narrow population and controls required for RCTs.⁹

“The traditional three-stage randomised control trial (RCT) model is not designed to collect information that meet emerging market needs. In some cases, the populations involved are too small to conduct randomised trials”

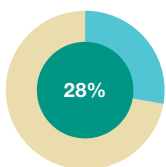
– Rob MacKenzie, Executive Vice-President and Chief Development Officer, Pfizer

New capabilities for transforming clinical trials must be validated

A wide range of new technologies are available, which are already being used to transform the efficiency and scope of clinical trials. While the use of big data, mobile sensors, social media and advanced analytics are in their early stages, survey participants clearly sensed their potential.

When asked what technologies would have the most impact improving clinical trial efficiency, leveraging big data and AI was the top answer at 36 percent. Risk-based trial monitoring, seamless Phase I-II clinical trials, and integrating real-world outcome data filled out the top four. Yet making effective use of each of these technologies carries challenges as well. Matching technologies to trial needs is vital, as is standardising and validating their use for specific purposes. Among the most promising:

Big Data



28% say big data will help improve clinical trial operations.

The world's capacity for producing data is expanding exponentially, and that data, from medical and non-medical sources, has the potential to greatly increase the efficiency of clinical R&D. ICON already is working with IBM Watson to help sponsors extract data from networked medical records that can be used to identify potential trial participants and sites, and help design protocols that will work for them.¹⁰ Medical record and daily activity data can help track post-market therapy performance. Financial data and information on patients' daily activities can help demonstrate therapy value, how a therapy might be improved and identify new therapeutic opportunities.

However, establishing and structuring data sourced from diverse systems is required, and this can be technically daunting. Pfizer's MacKenzie said. Outcomes based on such data also must be modelled and validated, and this, too, requires significant expertise.

“Although people can access a lot of data, making it talk to one another is an unsexy but really important piece of work that needs to be done,” – Rob MacKenzie, Executive Vice-President and Chief Development Officer, Pfizer

Wearables & Mobile Devices

Life in the 21st century has changed dramatically for patients, who, with the power of the internet, have become better informed, have educated themselves about their disease and share their knowledge with each other.



1 in 20

Today, 1 in 20 Google searches are for health-related information.¹¹

Patients want to have more input into research and treatment of their condition and its impact on their lives. This can benefit clinical research in many ways.

Focused patient advocacy groups can help define new therapeutic targets, plan and recruit patients to trials, and demonstrate the value that new therapies bring to their lives. Within trials, mobile apps and sensors can measure key symptoms and signs, such as tremor, blood pressure, blood sugar or activity level, while diagnostic apps, reminders and telemedicine can help keep patients engaged and on protocol.

Sensors also may support development and measurement of new endpoints that are more relevant to patient needs, such as the ability to walk to the corner grocery store or to work eight hours. Specialised sensors also are coming to market, such as the recently approved Abilify MyCite, an embedded device that tracks drug ingestion and communicates via a smartphone to track adherence for patients being treated for bipolar disorder or schizophrenia.¹² As with big data, though, new outcome measures and endpoints using mobile devices must be rigorously validated, as must the use of any mobile device supplied by patients to support any apps and sensors used in a clinical trial.

Statistical Analysis & Artificial Intelligence (AI)

AI is another area evolving alongside the data explosion – AI-enabled measures include data integration, data management and interpretation. These can improve trial performance at every level, from enabling risk-based trial monitoring to modelling investment return at the portfolio level.

\$13 billion

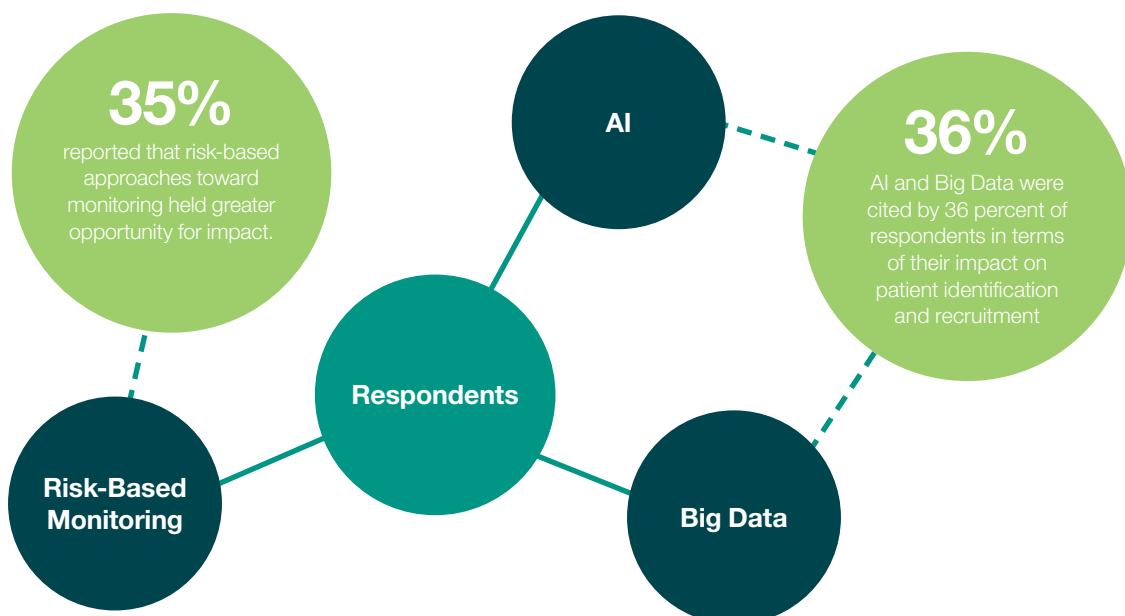
Projected benefits by 2026 in clinical trial participant identification.

Powerful statistical approaches, including Bayesian statistics for guiding trial design based on accumulating evidence and MCP-Mod for dose-finding, can greatly increase the efficiency of trials, making smaller trials possible by achieving adequate statistical power with fewer subjects. Regulators increasingly are embracing these advanced features, as evidenced by the FDA’s designation of MCP-Mod as ‘fit for purpose’ to improve dose finding efficiency¹³, and are being incorporated into powerful trial design software packages such as ADDPLAN.¹⁴

When asked what components have the largest impact on clinical development, AI, Big Data and risk-based monitoring were among the top technologies mentioned in the survey. AI and Big Data were cited by 36 percent of respondents in terms of their impact on patient identification and recruitment, while 35 percent reported that risk-based approaches toward monitoring held greater opportunity for impact.

These features make possible seamless phase I-II trials, and adaptive dose-finding trial and study simulation, which were named in the survey by 25 percent, 17 percent and 11 percent of respondents respectively as technologies likely to improve study efficiency. Here again, applying AI and advanced statistical methods requires effort, often including extensive process modelling, and a high degree of specialised skill to achieve results useful for development and acceptable to regulators.

While the technical challenges of applying these new technologies to clinical trials are significant, their value already has been confirmed in many studies, saving millions in development costs.^{15,16} They make possible innovations that are fundamental for transforming clinical trials, such as seamlessly combining phase I and II of clinical trials, developing novel patient-centered endpoints, and collecting and analysing real world data.



Key solutions

The range of techniques for transforming clinical trials is broad, diverse and disjointed to the point of confusion, raising questions about what technologies should be adopted and how.¹⁷ But the goals are straightforward – increase clinical trial efficiency and return on investment, while addressing patient needs. This white paper proposes a three-part framework for guiding strategy in transforming clinical trials.

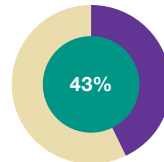
Adopt a Radical Patient Focus

Identifying and addressing unmet patient needs is, and always will be, the ultimate goal of pharmaceutical R&D. Therefore, new clinical trial models and the technologies behind them should be harnessed to achieve those goals. In many cases, technology that allows constant monitoring of, and communication with, patients in real time creates the possibility to assess the results of therapies at a level of granularity and over a range of real-world conditions never before imagined – and to intervene in real time if necessary to improve patients' lives.

Involving patients in developing new therapies and trial designs, and engaging them throughout the development and post-market process not only will help recruit and retain patients, but also will generate irrefutable evidence of the value of therapies to real patients in the real world. This is the goal of initiatives such as the Patient-Centred Clinical Research Network (PCORnet). Established by the Affordable Care Act in the USA, PCORnet brings together clinicians, patients, community representatives and data from electronic health records to transform “the culture of clinical research from one directed by researchers to one driven by the needs of patients and those who care for them.”¹⁸ Among the possibilities for making trials more responsive to patient needs is:

Data-Driven Recruitment

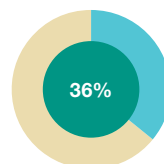
Industry data indicates that close to 80 percent of clinical trials are delayed as a result of slow patient enrolment. A Tufts CSDD study found that half of trial sites do not meet recruiting targets, with 39 percent under-enrolling and 11 percent failing to enrol a single patient. On average this nearly doubles study timelines.¹⁹ These issues were reflected in the survey, in which 43 percent said trial start up delays are a major challenge.



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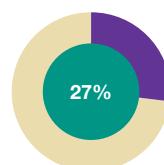
Vast troves of EHR data can make patient recruiting far more effective and efficient. Big data reveals where high concentrations of patients reside, which helps find study sites that can meet recruitment targets on schedule. Focusing on these targeted site prospects can significantly reduce site selection and preparation costs.

EHR data also enables direct outreach to patient candidates. Our experience suggests that increasing the proportion of eligible patients contacted from about three percent typically seen today to five percent would significantly speed up trials. Finding patients also helps find sites that may be suitable for a study, reducing delays and costs associated with preparing sites that are not able to recruit enough patients, and focusing resources on supporting those with the best prospects.



36% say leveraging Big Data and AI to identify patient recruits will improve clinical trial efficiency.

More than one-third of respondents in the joint ICON-Pharma Intelligence survey identified leveraging AI and big data to assist patient identification and recruitment as the one move that would most improve trial efficiency. However, substantial effort is required to convert patient leads into enrolled trial participants. Implementing this recruiting infrastructure requires skill, planning and coordination with clinical sites.



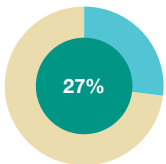
27% say using analytics to predict site performance and subject retention will improve trial operations.

Develop Patient-Focused Endpoints & Patient-Reported Outcomes

Developing patient-centred trials is the focus of initiatives such as PCORnet, and this requires new endpoints. Mobile health, or mHealth, devices connected to EHR networks are increasingly used to support the development and measurement of study endpoints that are more pertinent to patient needs.²⁰

For example, functional fitness, defined as how long a patient can engage in moderate to vigorous exercise, is often used as an outcome measure for COPD treatment, and as an indicator of how much the condition restricts daily activities. However, for many COPD patients, vigorous exercise isn't desirable or even possible, though walking is. Mobile devices make it possible to measure their free-living activities directly, by assessing whether they can maintain a steady walk for several minutes or even counting the number of steps they take daily. But is an improvement of 100 steps, or 1,000, meaningful to the patient?

Comparing data from mobile devices with patient perceptions of how their progress affects their lives will make it possible to determine thresholds for change that can be used to construct robust, statistically validated, patient-centred endpoints.²¹ Standardising the collection and interpretation of mobile data is essential for use in clinical trials, particularly for interventional trials and registering new therapies, and this requires a high level of expertise.²⁰



27% say using smartphones, developing novel outcome measures and remotely collecting data will improve trial operations.

Connected mHealth devices also provide richer data, as well as increased access and more frequent acquisition of data. For example, symptoms used to assess chronic disease, such as blood sugar, blood pressure, oxygen saturation, heart rhythm or intraocular pressure, may be monitored continuously in the real world rather than periodically in the doctor's office. This leads to a better understanding of treatment effects, such as diurnal fluctuations, that are too expensive or impossible to observe in a controlled study setting.



ICON Wearables

Wearables and sensors offer great potential in the collection of richer data and insights to enhance our understanding of the effects of treatment through the collection of objective measures of intervention effects both in-clinic and in remote free-living settings. However, implementing wearables and sensors brings new challenges to clinical trial conduct, data management and interpretation.

Leverage wearable devices and sensors for remote monitoring in your clinical trials. ICON can help you understand and successfully address the complexities of implementation of wearable devices in trial design, execution and reporting.

[ICONplc.com/wearables](https://www.iconplc.com/wearables)

Mobile devices also are better at detecting intermittent symptoms. The result is earlier, better informed assessments of product safety and efficacy, enabling earlier, more reliable product development and go/no-go decisions. This can reduce product development costs and cycle times.

Integrated with RWD on health and cost outcomes, mHealth can powerfully make a reimbursement case for new products payment – a critical success factor as payers move to value-based payment models.²¹ In our survey, one quarter of respondents indicated using mobile sensor data could improve trial operations, while one in five believed it is a key technology for improving study efficiency.

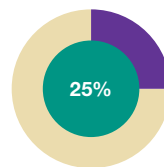
Use E-visits & Telemedicine

The burden of frequent clinic visits is a significant factor limiting patient participation in clinical trials. Recent data suggest that about 18 percent of clinical trial patients drop out after enrolling²², and difficulty reaching clinics is a major factor.²³ Clinic visit requirements can be more than just a matter of convenience; they can make large portions of the world's population ineligible due to their remote location and lack of transportation. E-visits and telemedicine can greatly expand the potential patient pool while allowing identification of new therapeutic needs in populations previously too remote to study.

E-visits and telemedicine also ease participation in areas close to clinical sites, and can lower costs as well. Often, clinical trial protocols only need a handful of data points, perhaps just beginning and end readings with one midpoint, to demonstrate their endpoints. However, several interim appointments are often scheduled because frequent interaction has been shown to improve patient adherence with day-to-day treatment protocols. Greater use of smartphone, online portals and wearable devices could reduce a six-visit trial to two visits, while actually improving adherence and data collection. Our experience suggests the cost of an office visit is about \$450 per visit, so this approach may reduce a trial's direct costs substantially.

Pfizer's MacKenzie believes easing the burden of participation may be especially useful for studying asymptomatic conditions. "We are contemplating a trial right now, designing it, and our idea is that they come in at the beginning and only at the end. In this particular indication, people are otherwise healthy and they don't want to be coming into the clinical sites, once every week, once every two weeks."

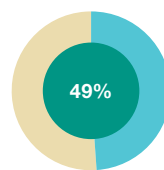
Other benefits of virtual trials might include millions saved by shortening development time and reducing patient attrition. Some sponsors are already vigorously pursuing virtual trials for these reasons. For example, in 2017 Sanofi partnered with a remote research technology company, Science 37, to develop remote trials enabling patients to participate from home with the expectation that this will speed up the development timeline.²⁴



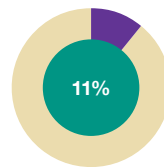
25% say wearables and remote sensors will collect richer patient data that will improve trial operations.

Integrate Trials into Day-to-Day Medical Practice

Offering trials to patients through their personal physicians and health systems is another way to get closer to patients for purposes of designing relevant endpoints and generating real-world outcomes data, and increasing the pool of patients available for trial. The FDA's Woodcock sees integrating the research and care delivery realms as critical for innovation that will reduce costs and improve care. This is also the goal of initiatives such as PCORnet.¹⁸



49% say finding the right sites is a challenge in recruiting patients.



11% say leveraging pharmacies and community care settings will improve clinical development efficiency.

FIRECREST

FIRECREST is a multi-award winning web based suite of digital products designed to enhance patient engagement and support investigators, patient recruitment and retention. It is deployed for more than 1,200 studies with over 500,000 active users, including the top 10 global pharmaceutical companies, and comprises several solutions.

Firecrest Patient eConsent employs easy-to-understand videos and visual aids to explain the complex scientific concepts and medical terms that are found in initial protocols. Multimedia materials are designed with evidence-based research from Carnegie Mellon University, which greatly enhances patient knowledge, recruitment and retention – particularly for children.

Despite intensive and costly monitoring, 5% of all FDA findings are due to errors in the consenting process. Firecrest's eConsent virtually eliminates these errors while providing a real-time view of your trial compliance.

ICONplc.com/eConsent

Greater use of adaptive clinical trials and other alternate trial models

Broader use of adaptive trials, which modify study protocols in predetermined ways based on interim patient data, have the potential to eliminate many unanticipated risks that undermine efficacious drugs and unnecessarily extend development timelines. For example, adaptive approaches can often deliver trial dosing information in a single two-year combined Phase II/III, that might otherwise require three or more consecutive conventional trials over three or more years.¹³ In addition to shortening development time, such seamless trials may reduce the total sample size needed by using the same patients in more than one stage.

Other advantages of adaptive trials are enabling early stopping, change of allocation rates, and reassessment of the sample size, patient subgroups or specific treatment arms. These all improve efficiency.

Adaptive designs can increase the probability of success and decrease development time by reducing the need for trial protocol amendments. According to research by Tufts CSDD, the implementation of each amendment in clinical trials costs organisations nearly \$500,000 in direct costs and requires 61 days to implement.²⁵

ADDPLAN

Software suite for adaptive trials

ICON is the only CRO to offer a validated design, simulation and analysis software platform for adaptive clinical trials.

ADDPLAN® is currently licensed by regulatory agencies, including the U.S. Food and Drug Administration (FDA), the European Medicine Agency (EMA) and Japan's Pharmaceuticals and Medical Devices Agency (PMDA).

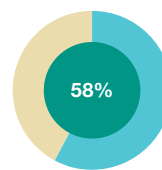
ADDPLAN is also used by leading pharmaceutical and medical device companies and numerous academic researchers. It is the first statistical software package to incorporate a majority of the requirements detailed by the FDA in its draft guidance on adaptive design.

[ICONplc.com/ADDPLAN](https://www.iconplc.com/ADDPLAN)

Our research suggests that the use of adaptive trials across a portfolio – which is encouraged by regulatory agencies in Europe and the US – could reduce trial costs by 25 percent. Combining efficiency-increasing adaptive with other technology enabled trial features and models can further increase efficiency. Some key opportunities are:

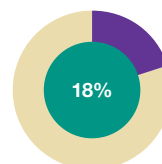
Adopt Data-Driven Protocol Design & Focused Data Collection

Traditionally, trial protocols are developed by clinicians based on their expertise and relevant studies, even when such studies are limited. As a result, enrolment criteria often specify combinations of clinical inclusion/exclusion criteria, signs, and symptoms that make it difficult to find qualified subjects. A more effective approach is validating trial protocol feasibility using actual patient data. Proposed criteria can be screened against data from millions of EHRs available through commercial data aggregators. This enables development of realistic enrolment protocols in hours on the desktop instead of months in the field.



58% say finding patients who meet eligibility criteria is the top patient recruitment challenge.

Most clinical trials collect far more data than is relevant to their clinical endpoints.²⁶ Industry experience suggests that data collection and monitoring could be reduced by as much as 50 percent by doing away with non-functional requirements from protocol templates and information that might be interesting but are not related to product development, regulatory or payer needs. Reducing protocol complexity also could help recruit and retain patients.

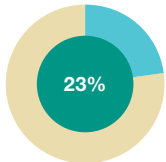


18% say protocol complexity is a challenge for recruiting patients.

Use Pragmatic, Virtual & E-trials

A range of new trial options are emerging that may be better suited to testing therapies in remote settings and generating better information on how they perform in real-world settings. These include pragmatic trials, which are conducted in real-world patient settings; virtual trials, which are conducted remotely; and e-trials, which are conducted using electronic data collected from medical records and other sources. These may supplement or in some cases replace traditional RCTs.

However, a great deal of work must be done to determine how such new approaches can be integrated into the R&D cycle, particularly with regulatory agencies. Pfizer's MacKenzie commented that in the US there are mandates designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently – including the 21st Century Cures Act and Prescription Drug User Fee Act (PDUFA) VI – and new guidance is expected along with public consultation. The US FDA is open to new ways of collecting and interpreting data, and this has led to early provisional approval of drugs. MacKenzie particularly acknowledged the work being done by the oncology division of the FDA as 'pioneering' in trying to get breakthrough medicines to patients when they need them most.



23% say incorporating real world evidence will improve the efficiency of clinical trials.

Pool Related Trials & Data

Combining data from related clinical trials so that all may share the insights can reduce overhead, duplication of effort, and unnecessary competition for patients and physicians. It also helps guide the early clinical decisions that hold so much potential for increasing the effectiveness and speed of drug development. According to clinicaltrials.gov more than 9,000 drug trials are currently active in oncology alone, and many involving multiple drugs, suggesting plenty of opportunity for further collaboration. Major players including Novartis, Lilly, and Pfizer are developing a portal that allows patients to search for clinical trials.⁹

Automate Data Collections & Analysis

Replacing fragmented data collection with automated work flow tools that enable seamless data flow from trial site EHRs to an electronic trial master file (eTMF) is essential for optimising adaptive clinical trials. Integrating EHR data flows was identified by nearly one-quarter of respondents to the survey as important for improving trial efficiency, while another nine percent mentioned eClinical data integration. Our experience suggests that directly flowing clinical outcomes data reduces transcription errors and data loss, and can reduce overall data handling cost by 10 percent. Automated data collection also enables:



18 months

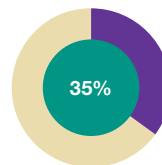
It is estimated that the data generated from clinical trials doubles every 18 months.

Real-Time Clinical Decisions

Automating protocols and data reporting in clinical site EHRs using data structuring systems enables real-time management of clinical trials. Major problems, such as not recruiting enough patients, and smaller problems, like data entry errors, can be detected and addressed immediately. This reduces the need to oversubscribe trials in anticipation of data loss.

Risk-Based Trial Monitoring

Algorithms that can spot data deviations, such as missing or duplicate data entries, improbable clinical results or missed patient appointments, that indicate a trial site is having problems can greatly increase the efficiency of research associates by focusing their attention where it is needed most. This, too, can reduce trial attrition.²⁷ Risk-based monitoring was identified by the ICON-Pharma Intelligence survey as one of the most effective ways to improve trial efficiency, but it requires an automated data collection system is in place.



35% say risk-based trial monitoring will improve the efficiency of clinical trials.

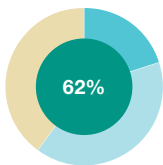
Automated Post-Market Surveillance

With greater emphasis on delivering value, and development strategies shifting toward expanding indications, post-market surveillance is increasingly needed. EHR tools could allow tracking virtually all patients receiving a particular therapy, while saving money on patient visits, mail-in cards and periodic phone calls. This gives a much more rounded view of patient adherence and outcomes in the real world, which could be used to further develop drugs and delivery methods. Pragmatic trials, which blend traditional clinical trials with RWD are the bridge to this new approach.

The need for a holistic approach for Transforming Trials

While adopting the individual tactics detailed above can significantly improve clinical trial efficiency, the potential is even greater when they are applied in a coordinated fashion to reimagine and reinvent the R&D enterprise. The issues affecting the market and the response must be systemic to best address them.

The ICON-Pharma Intelligence survey shows that companies realise the need for a holistic effort to transform trials. To achieve an organisation that is data-driven in every aspect in many cases will require changing both internal and external relationships.



62% of respondents have started or plan to start such a holistic strategy to transform clinical trials.

Interdisciplinary Collaboration

Internal collaboration is essential to bring about clinical trial transformation. “The dangers of silos may not always have been obvious, but today, with more stringent regulatory requirements, greater oversight of healthcare spending, and more demanding patient and doctor constituencies, there is much less room for inefficiency and waste,” noted Jo Pisani and Myrto Lee in a January 2017 PwC report, “A critical makeover for pharmaceutical companies: overcoming industry obstacles with a cross-functional strategy.”²⁸

Speaking at a roundtable organised to discuss the survey findings, held at SCRIP offices in London, Nermeen Varawalla, senior vice-president, head of clinical development at BTG, agreed. “You would be surprised how often it is that commercial teams do not really talk to clinical teams and when suddenly someone from commercial will look at the protocol and say ‘oh my gosh, you have not included this’.

“There needs to be collaboration between sites, investigators and protocol design. Now, many would say that patient enrolment and protocol design are linked.”

We see many ICON client partners moving in this direction, actively engaging patients as they design the protocol and, in particular, as they outline the endpoints. More strategically, many are reexamining how broad or targeted they want their portfolios to be. Leading firms have explicit therapeutic area focus, deep therapy area expertise, and targeted populations where value can be maximised. The industry is moving towards more, smaller commercial launches and expanding indications.²⁹ To support value claims, many organisations are collecting economic data, including the impact a therapy has on patients’ need for other health services, earlier in the development cycle.

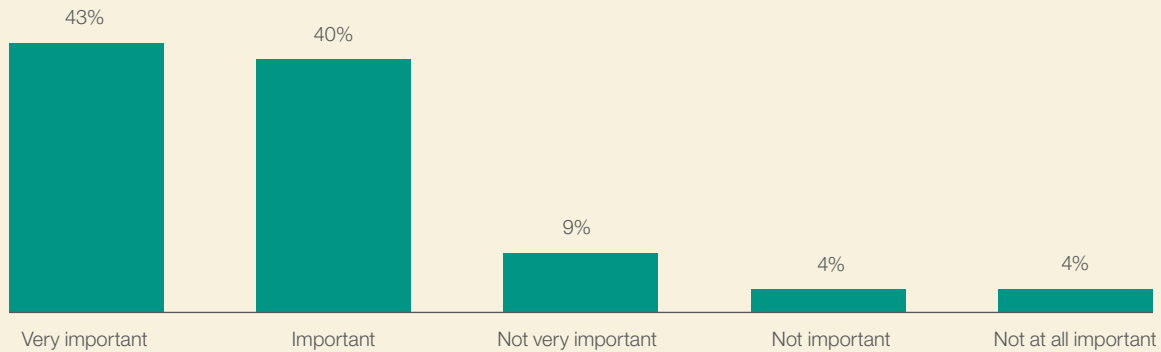
Strategic Partnerships

External partnerships are also critical. According to Tufts, the role of CROs is becoming increasingly significant as they become more involved in clinical research and are seen more as strategic partners, providing access not only to specialised expertise, but also to patients around the world. Deloitte believes that giving control for management of the trial process to external partners with expectations set around outcomes is an effective way for sponsors to make full use of their external partners' depth of knowledge gained from repeatedly executing the service.²⁹

CROs can provide a range of expertise to bring know-how and solutions to the highly technical challenges of transforming clinical trials. Sponsors recognise the value of CRO partnerships; it is estimated that by 2020, 70 percent of all clinical trials will be outsourced to CROs.³⁰

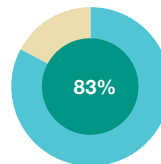
Many CROs already have adopted various technologies essential to improve trial efficiency, including electronic data capture, clinical trial management systems and electronic master files, real time analytics and a wide range of data applications. These are incorporated into ICON programmes including partnerships with IBM Watson and other large databases to help recruit patients and sites, ADDPLAN software for planning and simulating adaptive trials, ICONIK for real time data collection and trial management, remote site monitoring, as well as functional services for improving site payment and logistics management, and consulting to support commercialisation. With the growth in specialisation of clinical research, partnerships between sponsors and CROs are likely to grow in value.³¹

Importance of Strategic Partnerships with CROs

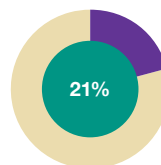


Questions: How important will strategic partnerships with CROs be to the success of your clinical trials in the next 5 years?
Base= All respondents (n=75).

Collaboration among competing sponsors to solve common problems, and even share data, is growing as well. The industry is increasingly seeing the emergence of initiatives and consortia among competitors. The Clinical Trials Transformation Initiative has just launched a new project to accelerate the use of RWD in clinical trials. This radical collaboration is a public-private partnership to develop and drive the adoption of practices that will lead to improved quality and efficiency in clinical trials. It now comprises more than 80 organisations from across the clinical trial landscape including government/regulatory agency representatives, the biopharma industry, patient advocacy groups, professional societies, investigator groups, academic institutions and other interested parties.



Overall, 83% of respondents believe strategic partnerships with CROs will be important to the success of clinical trials over the next 5 years.



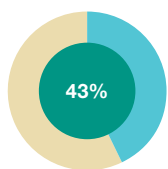
21% say collaborative development with outsourced/virtual development partners will help improve clinical development efficiency.

With regulatory approval delays identified as a challenge by 43 percent of respondents in our joint ICON-Pharma Intelligence survey, better collaboration with regulators also is essential. New guidance is needed to support 21st century clinical trials and the technologies that underpin them. Regulatory authorities are encouraging the use of new technologies.

Pfizer's MacKenzie emphasised the importance of collaborating with regulators in developing new trial procedures and outcomes, which helped the firm gain early approval for a new breast cancer drug based on a novel data collection process.

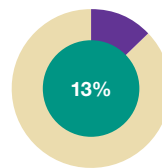
"We were able to work with regulators to get a conditional approval two years before we would normally have had it," said MacKenzie. "And in those two years, about fifty thousand women and many men were actually able to benefit from the drug...I give the regulators great credit; and particularly the oncology division of the FDA, I think, have been pioneering in recent years in trying to get, particularly, breakthrough medicines to patients when they need them most."

FDA Commissioner Scott Gottlieb recently vowed to take steps to modernise the agency's activities in this area, saying its goal is to "make sure that our policies are as scientifically advanced as the products we are being asked to evaluate."



43% say regulatory approval delays and changes are a major challenge.

Anticipating payer requirements and working with payers on pricing arrangements that demonstrate value is gaining importance as well. In its Outlook 2016, Tufts CSDD noted that payers are increasingly adopting cost-sharing incentives for patients that encourage them to choose equivalent products that the insurer deems deliver higher value.⁴ Our experience shows that collecting data on direct costs of new therapies, as well as how they affect total healthcare costs – such as the need for hospital, emergency room or other expensive services during clinical trials – can reduce or eliminate delays in payer approval.³²



13% say value-based development and incorporating commercialisation data collection into early clinical design will increase the efficiency of clinical development.

Ultimately, transforming clinical trials will mean transforming organisations. Strategic leadership, dynamic change management skills, and technical expertise will be required. Higher returns on R&D investments, and more effective therapeutic products serving unmet patient need will be the payoff.

ICON is ready to help through our Transforming Trials initiative. This comprehensive reimagining of the entire clinical trials process uses new approaches and existing, tested technologies to substantially reduce the risk and cost of clinical drug development.

About the ICON Transforming Trials survey

Designed, conducted and analysed by Informa Engage using accepted market research methods, 76 members of the Pharma Database responded to the emailed survey between Oct 16 and 30, 2017. Half of respondents were director level or higher, 24 percent managers, and 26 percent clinical trial professional personnel with no direct reports. A roundtable of invited pharmaceutical industry executives was held at Informa offices in London in November 2017 to discuss the survey results. The survey data, and roundtable discussion, were complimented by extensive desk research, in part conducted by ISR Research.

Notes

- **Predictive Analytics** – Predict site performance or subject withdrawal
- **Smartphones** – Collect novel outcome measures remotely to better and faster understand treatment effects (e.g. Apple Research Kit)
- **Risk Based Monitoring Analytics Systems**
 - **Social Media** – Listening for insights into patient perceptions of treatment and trial participation to optimise patient recruitment outreach
 - **Wearables and Sensors** – Collect richer data and monitor patients remotely
 - **EHR Systems** – Data integration to eliminate duplication with EDC
 - **Telemedicine** – Using video and virtual visits to reduce the number of on-site patient visits
 - **IT Robotics** – Enabling automated processes

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