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Decentralised Clinical Trials: Achieving Our Ambition?

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DECENTRALISED CLINICAL TRIALS: **ACHIEVING OUR AMBITION?**

EXECUTIVE SUMMARY

Decentralised Clinical Trials (DCTs) present a biopharmaceutical company with a series of opportunities and challenges. We highlight the challenges and examine the value the individual DCT elements may create for patients, investigators and site staff, regulators and ethics committees, and the sponsor. We also contend that for a DCT to be truly patient-centric, the patient must be provided with flexible, pragmatic options when taking part in a clinical study.

Our research suggests that there are elements of DCT that are yet to evolve, with less than 0.1% of ongoing industry-sponsored interventional studies including a wearable or biosensor.

Finally, we lay out an operating model framework and set of critical success factors to support a biopharmaceutical company in its enablement of DCTs.

1. THE RISE OF THE PATIENT-CENTRIC CLINICAL TRIAL

Patient-centric Research and Development

In today's biopharmaceutical landscape, you would do well to find a company that did not cite the concept of 'patient centricity' within their strategic vision, mission, or objectives. Patient centricity focuses on putting the patient, and their insights, at the centre of the industry's ways of working.

Research into the future of patient centricity found that 27 industry leaders agreed with the importance of integrating patient-centric approaches much earlier in the value chain in R&D[1]. Approximately 1,300 new trials with a decentralised and/or virtual component were predicted to start in 2022, an increase of 28% on the previous year[2]. Therapeutic areas that comprise the vast majority of DCTs or hybrid clinical trials include CNS, metabolic disorders, infectious diseases and respiratory. However, there is also an intent within industry to include elements of DCTs in clinical trial populations previously considered more challenging[3]. In a survey of 85 oncology executives, three quarters planned to run DCTs or hybrid clinical trials in the next 12 months[4].

Patient-centred clinical trials have the potential to transform patient lives by ensuring patient knowledge and experience of their disease are reflected in the design of the study protocol.

Insights from patients, patient advocates and patient groups may contribute to a more patient-friendly protocol, enhancing patient recruitment and retention in a clinical trial.

[1]Deloitte Insights (2020). Striving to become more patient-centric in life sciences.

[2]Hillman, Kezia Parkins and Andrew Hilman (2021). 2022 forecast: Decentralised trials to reach new heights with 28% jump. Clinical Trials Arena.

[3]GlobalData (2022). Clinical Trials – The Movement Towards Decentralized Clinical Trials.

[4]Science37 (2022). How Agile Clinical Trials are Impacting Oncology Research. Agile Trials and Oncology.

In parallel, patient-centric digital innovations are transforming the patient experience. Wearable sensors, software applications, telemedicine, eConsent, ePRO and eCOA all have the ability to enrich information gained from a clinical trial. Patient centric approaches and digital capabilities synergise to enable patient visits, healthcare provider interactions, laboratory procedures and the administration of investigational medicinal products (IMP) to occur in the patient's community, often within their own home.

The COVID-19 pandemic significantly impacted the start-up and recruitment to new clinical trials. Sponsors and regulators needed to adapt processes to enable clinical trials to continue at a time when patient access to clinical trial sites and hospital priorities were forced to change. Monitoring plans were adapted, IMP could be shipped to a patient's home, investigator site staff contacted patients by telephone and sponsors monitored clinical trial data at a distance. As we slowly emerge from the COVID-19 pandemic, there is a receptiveness to, and continued adoption of, technologies for DCTs.

Adoption of many decentralized clinical trial elements occurred prior to the onset of the COVID-19 pandemic. The first fully 'virtual' Phase IV clinical study was conducted by Pfizer in 2011. The aptly named REMOTE study (The Research on Electronic Monitoring of Overactive Bladder (AOB) Treatment) originally enrolled over 200 patients, terminating early in 2012 and publishing data from 18 participants.

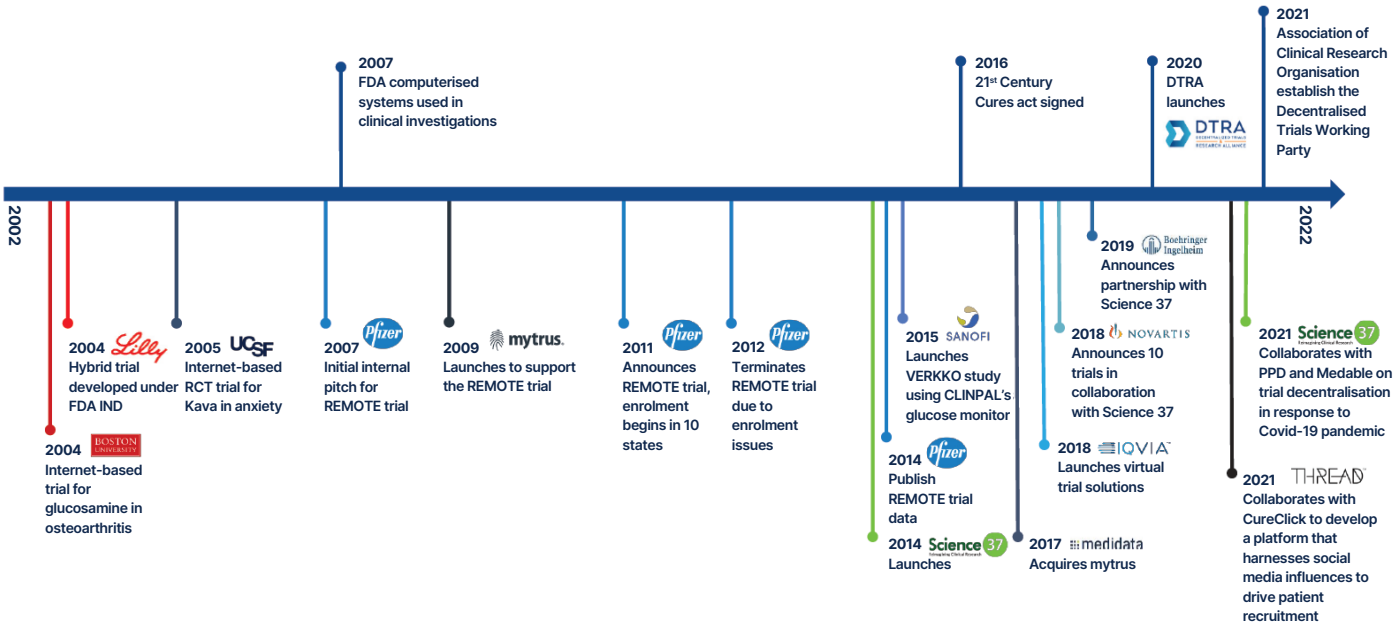


Figure 1. Development of landscape for DCTs over the past two decades

2. DECENTRALISED CLINICAL TRIALS

For a clinical trial to be considered fully decentralised all elements of the clinical trial must be accessible to all patients from a remote location. This is rarely, if ever, achieved. In practice, we see the adoption of elements of DCTs for some of the patients, sometimes described as a hybrid clinical trial. These hybrid clinical trials utilise some or all of the elements defined in Table 1.

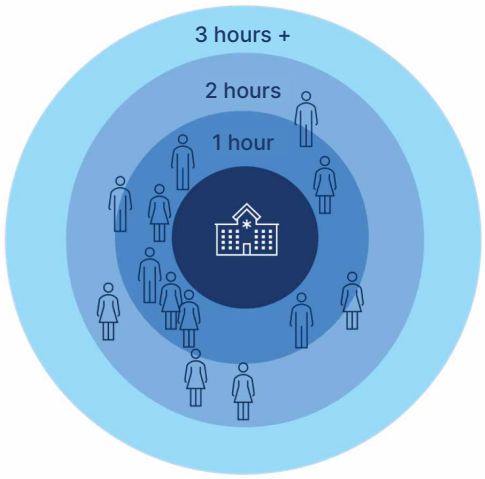
Hybrid Clinical Trials – the pragmatic alternative to a full-DCT

The use of DCTs is dependent on the patient's ability and willingness to successfully adopt and interact with technology, as well as a certain comfort with being remote from the investigator and site staff. Other factors that need to be considered include the use of scarce, capital equipment e.g., Magnetic Resonance Imaging (MRI) which are typically found in the secondary and tertiary healthcare setting.

There are a number of hybrid models that can be adopted depending on the individual needs of the patient, complexities of the treatment and the design of the clinical trial protocol. These fall into two main categories.

MODEL 1

A clinical trial which utilises a combination of both investigator site and home visits for each participant. This can broaden the use of DCTs to include more complex therapy areas where specialised equipment is needed to monitor disease progression.



MODEL 2

A clinical study that offers different elements of DCTs to each participant, based on patient preference. Sponsors may also choose to engage a single clinical trial site, managing patients country-wide, or multiple clinical trial sites dependent upon the model they choose.

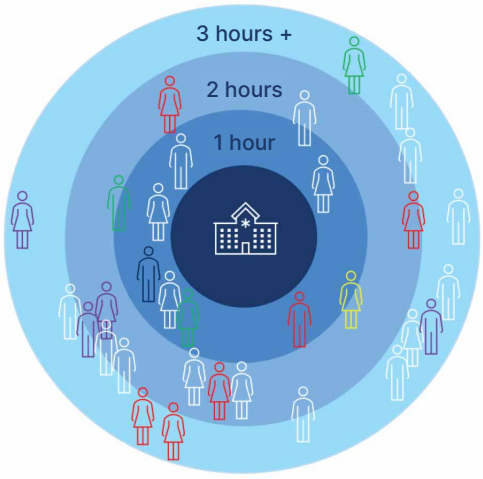


Figure 2. Schematic to demonstrate two models for DCTs

MODEL 1

For conditions which require routine access to capital equipment and expertise at the investigator site. DCT elements can be included in the study design to reduce travel to the investigator site e.g. use of telemedicine or home health care to reduce the patient burden.

MODEL 2

For conditions where the patient involvement in a clinical study can be managed by the investigator remotely, leveraging eConsent, telemedicine, home health care, direct to patient IMP, local pharmacies, local physicians and technology [different colours reflect patients choosing different options]. Each patient has the option to visit the investigator site in person for procedures, but it is not necessary to do so. This model allows for patient enrolment into clinical studies from remote geographies [concentric circles represent distance and time to travel to the investigator site].

Table 1. Definitions of DCT elements.

ELEMENT	
eConsent	eConsent is the use of digital consenting, sometimes supported by the use of telemedicine to encourage patients to discuss their understanding of the trial prior to signature. Patients may also be sent digital, language-appropriate media or videos to inform patient education and to give the patient the opportunity to discuss with family and friends
Telemedicine	Telemedicine leverages telecommunication devices (mobile phones, telephones, computers, and other internet-connected devices) to enable the investigator to provide oversight of the patient's medical care
Wearables	Wearables passively capture real-time data e.g., activity, sleep, and vital signs, (via an internet connection) through a provisioned device (PD) or a 'bring your own device' (BYOD). Patients are able to download validated software applications to the device, enabling data collection
Behavioural Nudges	Text messages, emails, and interactive voice calls can be sent as reminders to patients, primary caregivers or parents, 'nudging' participants to improve their adherence to the protocol e.g., completing an electronic patient diary, administering IMP
ePRO/eCOA	Electronic patient reported outcomes (ePROs) and electronic clinical outcomes assessments (eCOA) allow the remote reporting of data e.g., health, quality of life, or functional status, by patients, caregivers, or HCPs
Direct to Patient IMP/AxMP	Direct to Patient Investigational Medicinal Product (IMP) or Auxiliary Medicinal Product (AxMP) is couriered from the investigator site or a central depot, directly to the patient or to a local pharmacy
Home Health Care	HCPs or specialist nurses provide services e.g., sample collections, intravenous infusions, injections, observations of vitals and other signs, patient education or administration of IMP in the patient's home

3. VALUE FOR STAKEHOLDERS

A clear understanding and articulation of the intended value that DCTs will provide to all stakeholders is an essential requirement when developing a compelling business case to justify investment. There are four main stakeholder groups who benefit.

Patient

Real value and the perception of value to a patient need to be distinguished. The patient's condition and individual circumstances will determine whether there is value from the DCT elements, and a recent recommendation paper by the European Commission (EC), the Heads of Medicines Agencies (HMA) and the European Medicines Agency (EMA) emphasises this point by ensuring that the patient understands their options and that patients who are less technology savvy are not discriminated against[5]. That said, engagement of patients, patient advocates and other patient groups in clinical trial design will help identify which elements are likely to be truly valuable to the clinical trial participants. The value to a broader patient population comes from the generation of evidence resulting in the successful commercialisation of the product.

Investigator and Site Staff

Elements of DCTs e.g., wearables, will provide investigators with real-time information about the medical health of the patient. This enhanced visibility through dashboards may aid the investigator with the medical care of the patient and support decision-making and timely interventions. Whilst site staff will need to adapt to new technology and ways of working, this brings the ability to interact, albeit virtually, with patients on a more frequent basis. There would also be the expectation of less administration and management of patient flow by engaging patients remotely.

Sponsor

The promise of DCTs and a more patient-centric clinical trial design is that it will drive efficiencies and productivity. However, there is a paucity of evidence to support this and the return on investment must be carefully considered. DCTs may attract and retain more participants in the clinical study, with greater patient recruitment, patient retention and geographical reach[6]. The theoretical outcome for the sponsor is an accelerated time-to-market and an increased opportunity for product revenue.

Regulatory Authorities and Ethics Committees

In 2020, during the first wave of the COVID-19 pandemic, the FDA published guidance on modernising evidence generation and conducting clinical trials with IMP during the public health emergency. The non-binding recommendations introduced the possibility of adopting DCT elements to ensure that ongoing and new clinical trials could run, whilst adhering to COVID-19 measures. By example:

> "If scheduled visits at clinical sites will be significantly impacted, certain investigational products, such as those that are typically distributed for self-administration, may be amenable to alternative secure delivery methods. For other investigational products that are normally administered in a health care setting, consulting FDA review divisions on plans for alternative administration (e.g., home nursing or alternative sites by trained but non-study personnel) is recommended. In all cases, existing regulatory requirements for maintaining investigational product accountability remain and should be addressed and documented.[7]

[5]European Commission (2021). Recommendation paper on decentralised elements in clinical trials.

[6]Sommer et al. (2018). Building clinical trials around patients: Evaluation and comparison of decentralized and conventional site models in patients with low back pain. Contemporary Clinical Trials Communications.

[7]FDA (2021). FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency.

The European Commission (EC), the Heads of Medicines Agencies (HMA) and the European Medicines Agency (EMA) more recently published a recommendation paper in December 20225. This is a far-reaching paper that outlines expectations in a 33-page document.

Through these recommendation papers, both agencies set-out clear expectations with respect to transparency of DCT elements within clinical trial documents, extension of responsibilities for sponsor companies and an emphasis on enhanced risk management practice, data privacy and security, and adherence to local legislations – ensuring the safety of patients and the maintenance of data integrity.

4. DCT CHALLENGES

Patient safety must be prioritised

One of the essential requirements for a clinical study is to ensure patient safety. First established in the Declaration of Helsinki[8], it outlines key ethical principles in medical research. These principles form the basis of ICH GCP guidelines (a global standard for conducting clinical studies) and have been incorporated into regional and country legislation. Publications by the FDA and EMA provide guidance on how these regulations will be applied when a DCT element is employed on a particular clinical study. Patient safety remains of paramount importance[5, 7].

Over and above a more traditional clinical study, a DCT requires additional considerations with respect to patient safety. These include, but are not limited to:

- Outlining in the protocol how the investigator and the DCT provider will manage (serious) adverse events in a timely manner,
- Ensuring that participants and the DCT provider are trained on the management, reporting and timings associated with (S)AEs,
- Outlining in the protocol any requirement for additional equipment for IMP storage and to provide clear instructions to the patient on storage requirements in advance of a HCP visit,
- Providing adequate training to participants in the case where the participant is responsible for performing study-related tasks.

While the points above are not comprehensive, they do emphasise the continued high expectations of Regulatory Agencies regarding patient safety.

Data management and governance becomes more complex

There are two main challenges with respect to data captured in a DCT. The first is the complexity of data privacy and data protection requirements. The second is the step-change in quantity of data that a sponsor will be required to govern, collect, analyse and report.

Sponsors have the challenge of interpreting what sometimes feels like competing legislation. Within European Union countries, the Clinical Trials Regulation EU No 536/2014 is now fully implemented. In addition to adapting to this new framework, sponsors must also interpret correctly and incorporate the General Data

[5]European Commission (2021). Recommendation paper on decentralised elements in clinical trials.

[7]FDA (2021). FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID-19 Public Health Emergency.

[8]World Medical Association (2018). WMA Declaration Of Helsinki – Ethical Principles For Medical Research Involving Human Subjects.

Protection Regulation EU No 2016/679 into their processes and procedures. Individual countries and US states, for example, have different standards and legislation, adding to the complexity faced by sponsors.

The international rules on the transfer of data between geographies also must be understood. Practical considerations include:

- The validation of data acquisition tools e.g., a wearable,
- Controlled access to study data with defined access rights,
- The type and scope of personal data to be collected,
- Confidentiality measures for remote access of source data,
- Encryption and enhanced security levels for digital devices.

The second main challenge is due to the increase in data quantity. Whilst data sources and quantities of data have increased because of patient diaries, ePRO and eCOA, the scale is not comparable with wearables and their continuous data feeds. Historically, sponsors generally have a complicated data systems landscape and the inability to collect, analyse and store these increased levels of data. As with any large, complex biopharmaceutical organisation, the governance of such data continues to be debated.

The inclusion of wearables in clinical trials is perhaps the most challenging of all the elements within DCTs. A Lucid Consulting analysis of clinicaltrials.gov shows that the inclusion of wearables in industry-sponsored Phase I to IV clinical studies is rare, and in its infancy.

Less than 0.1% of ongoing industry-sponsored clinical development studies include a biopharmaceutical intervention and a wearable in the study design.

Operational challenges increase

Due to their unique operational challenges, DCTs and hybrid clinical studies are likely to require additional resources to achieve key milestones on-time, as compared with more traditional clinicals studies. In addition, there are practical challenges to overcome:

- Inclusion of specialist, capital equipment e.g., MRI, Computerised Axial Tomography CAT or X-Ray procedures will require an in-person visit to a secondary or tertiary care-setting,
- Selection and contracting additional vendors,
- Distribution of Direct-to-Patient IMP with challenging storage conditions or delivery mechanisms may be unsuited to the home-setting,
- Missed visits or missed deliveries will need to be rescheduled and comply with visit windows,
- Complete access of data to enable the investigator to fulfil their responsibilities.

5. DEFINING A DCT OPERATING MODEL

A framework to design an operating model is shown in Figure 3. The framework is hierarchical, with interdependencies between each of the operating model components. Considering the interdependent parts of the model and taking a more holistic approach develops a more robust and integrated operating model design.

Figure 3. Operating model framework

Vision & Strategy

The organisation's overall approach for DCTs should be decided and clearly communicated both internally and externally with partners. Leaders should consider nuances of the organisation's R&D portfolio, and formulate relevant high-level objectives, such as whether they will focus on full DCTs versus hybrid, and whether they want to bring DCT capabilities in-house or fully outsource. Suggested target milestones may include when the first patient is enrolled on a DCT, and when execution of DCTs at the organisation is considered "business as usual".

Process

The end-to-end clinical study process will be impacted by the introduction of DCT elements, and some SOPs, work instructions and support tools may require adaptation. There is a need for incorporation of new or different process flows which require adaption of established business processes. In addition to new, and differentiated, roles and responsibilities within the sponsor and vendor companies, ownership of decisions needs to be clear.

Capabilities & Resources

New capabilities to support DCTs will need to be defined and resourced. On the demand side, consideration must be given to the patient population and their ability to engage with technology and any potential benefits to them. From a supply perspective, applicable knowledge of technology e.g., eConsent, eCOA, wearables, data integrations expertise and access to up-to-date country requirements with respect to ethical, regulatory and data privacy insights will be essential to guide a study team. Building in resource flexibility and scalability is essential as the demand for DCTs can vary substantially across the portfolio. In addition, a transformation capability will be needed to engage and influence stakeholders, drive the design, work across organisational boundaries and maintain the organisational focus on the implementation.

Information Management

Over many years, a biopharmaceutical company will have developed a data collection and analysis process, designed to be efficient and compliant based on an Electronic Data Capture

(EDC) backbone. DCTs will add complexities, not least from the potential step-change in the quantity of data being obtained from wearable devices. New process flows will need to be defined, systems integrated, tested and configured, and the new data validated and analysed. Data privacy and data security will also need to be ensured.

Organisation Structure

Often reporting lines are the focus for companies, however, this operating model framework considers the other components of the operating model first, only determining the organisational structure once all the other components are understood. Organisational design will be affected by the sourcing strategy, workload forecast, new processes, new capabilities, digital elements of DCTs being considered, geography, and budget and resource constraints. Operating in a matrix isn't unusual in a biopharmaceutical company, however, there will be new interfaces to consider and a need to determine whether budget ownership and decision-making lies with a function or a study team.

Performance Management

Performance management is critical for effective implementation of DCTs. Implementation measures should be defined, tracked and governed, to drive informed decision-making. In addition, measures should focus on ensuring that the expected benefits of DCTs are realised, such as patient and investigator satisfaction, patient recruitment and retention, clinical trial population diversity and improvements to operational timelines. A return on investment calculation will also establish the validity of the original business case.

6. CRITICAL SUCCESS FACTORS FOR SUCCESSFUL IMPLEMENTATION OF DCTS

Biopharmaceutical companies often struggle to implement change effectively. The industry is highly regulated, there are long product development cycles and the culture of large organisations tends to promote the established way of doing things.

To help sponsor companies embrace patient-centric DCTs, eight critical success factors have been identified.

1. Design the operating model with your portfolio in mind

It is beneficial to conduct a detailed, objective assessment of the clinical study portfolio to determine opportunities for DCTs, including understanding the patient view, characteristics of their medical condition, the complexity of the clinical study design and additional interventions to manage risk and ensure patient safety. This will aid identification of early-adopter clinical studies to build momentum and provide flexible DCT options to patients.

2. Align senior management sponsorship

The cost and resources required to implement an effective DCT platform are not insignificant. In addition, political will needs to sustain a move from a portfolio of traditional clinical trials to a portfolio of clinical trials where DCT is an integral part of the protocol. Evidence from multi-year surveys across multiple industries shows a clear and positive correlation between the successful outcome of change initiatives and the effectiveness of a project sponsor or coalition[9]. A clear strategy and a visible, sustainable commitment to DCTs by senior management, are key factors in successfully mobilising the broader organisation.

[9]ProSci (2020). Thought Leadership Articles: Primary Sponsor's Role and Importance.

3. Leverage your existing operating model

The approach to developing a DCT capability will likely be different for each biopharmaceutical company and will very much depend on the strategic operating model. If clinical operations are in-house at the global and local level, then there is a strong benefit in developing an internal DCT capability. Conversely, if the strategic operating model is to outsource clinical operations (full-service), then leveraging preferred relationships with Contract Research Organisations (CROs), their technology investment, patient networks and their partners is likely to be the most effective way to build a DCT portfolio. A critical factor will be the robust evaluation of the CRO and its partners to establish if, for example, their capability is sufficiently developed in order to deliver a full or hybrid DCT in the specific patient population, indication and geographical location.

4. Engage patients

Industry is increasingly recognising that patients in clinical trials should be actively involved in the trial, rather than treated as mere 'subjects'. Early and routine patient involvement will drive efficient design of fit-for-purpose protocols and may reduce the number of protocol amendments.

5. Support investigators and site staff

As with all clinical trials, the goodwill of investigators and site staff is essential for the successful adoption of components of DCTs. Investigators and site staff work in a highly pressured and challenging environment, with sponsor-initiated clinical trials being one of many responsibilities. The frustration caused by poor performance or failure of technology should not be underestimated. To mitigate the impact on sites, sponsors must ensure adequate site staff training, IT support and troubleshooting, single sign-on, intuitive IT systems, technology and user-friendly interfaces.

6. Actively explore digital innovation

Technological innovation is an enabler of patient-centric clinical trials, and today, we have multiple digital devices validated for use in clinical trials by patients.

The critical success factor is for biopharmaceutical companies to continually be searching for, and investing resources in, those digital technologies which are patient-orientated, simple-to-use, and generate data insights and evidence to support product characterisation, regulatory submissions and, ultimately, marketing of the product. To achieve this aim, a digital device needs first, regulatory approval as a device, and second, validation in the patient population to be considered for use as a study endpoint.

7. Understand regulatory and ethical challenges

Understanding the regulatory and ethical environment is complex and challenging for any biopharmaceutical company, especially when we are considering innovative approaches, not conceived when regulations were initially drafted. Again, there must be a significant investment by sponsor companies in understanding the local regulatory and ethical environment with respect to conducting a DCT. This is an ongoing intelligence gathering process required to have the full picture of what is achievable in a particular country. Equally challenging to understanding clinical trial requirements is the data privacy and data protection legislation landscape, in particular, legislation such as the General Data Protection Regulation; the scope and reach of which extends far beyond the European Union.

8. Implement an effective change management plan within the sponsor organisation

Perhaps the most unexpected challenge facing biopharmaceutical companies when trying to implement patient-centric clinical trials is the need to change the mindset of colleagues within the company. At a philosophical level, the vast majority of employees within a biopharmaceutical company would agree that a patient-focus, and co-creating a clinical trial design, is positive. However, there will be concerns about budget, delaying the start of the clinical trial, whether patients can provide any more insight than their medical professional, loss of influence, technical challenges which invite risk, risk-benefit for

the patient, process changes, regulatory and data privacy concerns and how to manage an exponential increase in data, to name but a few. Many individuals and organisations are struggling to fully adapt or embrace the opportunity that patient-centred clinical trials provide. To overcome resistance and move to patient-centric clinical trials, it is critical to design, implement and reinforce, an effective holistic and engaging change management strategy.

7. CONCLUSIONS

Although initial implementation of DCTs was limited by regulatory acceptance, the Covid-19 pandemic has shown that DCTs may provide industry with larger geographical reach, faster data collection and enhanced patient recruitment. To establish a truly patient-centric approach and patient adoption of DCTs, patients will need to be consulted and their needs anticipated, when incorporating DCT elements into a protocol.

However, DCTs also present new challenges which must be taken into careful consideration and opportunities balanced with the potential to increase, as opposed to decrease, patient and investigator and site staff burden. There are also patient safety, data and operational challenges in addition to regulatory and data privacy requirements which need to be understood, with risks managed and mitigated.

Finally, the use of DCTs has the potential to transform the industry and ultimately improve outcomes for all stakeholders, especially patients. However, the return on investment for sponsors remains unproven, and for sponsor companies with constrained budgets and finite resources, demonstrating a positive business case is both necessary, and a key success factor, for systematic adoption of DCTs.

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