

Bringing the Trial to the Patient:

A Quality-by-Design Manual for Decentralized Clinical Trials

ACRO Decentralized Clinical Trials Working Party
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ACRO

ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

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Executive Summary

The [Association of Clinical Research Organizations \(ACRO\)](#) represents the world's leading, global clinical research and technology organizations, which provide specialised services that are integral to the development of drugs, biologics and medical devices. ACRO and its members advocate on a global basis for safe, ethical, high-quality medical research so patients can benefit from the development of new treatments and therapies. ACRO members are dedicated to helping bring efficiency, innovation and value to the clinical research process.¹

As part of its broader initiative to support ACRO member company innovation in the clinical trial enterprise, ACRO has focused on supporting the greater adoption of decentralized clinical trials (DCTs) in clinical research. In traditional clinical trials, participants typically have to make frequent visits to clinical sites for interventions and monitoring. Often participants drop out of trials due to logistics such as the travel distance to the site and frequency visits. With digital capabilities such as wearable devices, telemedicine, real time data collection, it is now possible for participants to participate in trials and be monitored remotely. This allows patients to be included in trials from different geographies and from groups that are typically under-represented in trials.

In October 2019, ACRO established the Decentralized Clinical Trials Working Party (ACRO DCT WP) – composed of ACRO member experts on DCTs – to examine barriers to adoption of DCTs and to study the benefits to clinical trial participants and gains in efficiency. The Working Party quickly came to consensus on a broad variety of DCT topics, including:

- The need to address stakeholder hesitation regarding modernization and change – and how the creation of end-to-end best practices could help mitigate this hesitation
- The need to identify and help resolve change-management burdens on stakeholders – for example, initial site burden and initial investment in a new model

The ACRO DCT WP team developed a work plan that included two primary objectives and deliverables:

- **A Customized Map for Decentralized Clinical Trials**

The Working Party comprehensively examined a “map” of each step – from beginning to end – that must take place in all clinical trials. This examination of every step in the beginning-to-end clinical trial process, enabled Working Party members to answer a key question about each step:

Is this specific step largely the same in both a “decentralized” trial model and a “conventional” (“traditional”) clinical trial model? Or, alternatively, does this specific step create brand new considerations and challenges when a decentralized model is adopted. *The exercise allowed Working Party members to highlight and illuminate those specific steps in the clinical trial process where unique and new considerations and concerns emerge under a decentralized clinical trial model.*

- **A Toolkit Dedicated to Decentralized Clinical Trials**

The ACRO DCT Working Party then began its work on two important new tools dedicated to decentralized clinical trials. The DCT Toolkit is comprised of two distinct, *interdependent* tools that complement each other and are designed to be used together. These two tools that together make up the Toolkit are :

- **A new Quality-by-Design Framework Dedicated to Decentralized Clinical Trials**

This document – called *Bringing the Trial to the Patient: A Quality-by-design Manual for Decentralized Clinical Trials* – provides stakeholders with much-needed quality-based, beginning-to-end guiding principles for the construction of DCTs. The goal of this new framework – dedicated to the design of decentralized clinical trials – is to propel greater adoption of the DCT model.

It should be noted that the Customized Map for Decentralized Trials (referenced above) is a key component of this QbD Manual.

- **A Risk-Assessment Tool**

The second, companion document – *Decentralized Clinical Trials (DCT) Risk Assessment Considerations* – is a key component of the overall quality-by-design framework.

The DCT Risk Considerations document is designed to complement (rather than replace) an organization’s current risk assessment tools. It provides questions, considerations and potential mitigations to facilitate a quality-by-design and risk management approach to decentralized trial design. It is intended to supplement an organization’s existing risk assessment process by providing DCT-specific questions which can be added to an existing risk management workbook.

This companion risk-assessment spreadsheet tool is a separate document in the form of an Excel spreadsheet, and is a companion document to this QbD Manual. This Manual and the corresponding, companion Spreadsheet are complementary, interdependent tools that should be used together. This risk-assessment tool has adapted the organizational categories developed by TransCelerate.²

The ACRO DCT Working Party recognizes the important global variations and the absence of any harmonization regarding legislation and regulation on clinical trials. However, an actual geographical “starting point” was needed in order to begin this important work on decentralized clinical trials. Therefore, the approach of the ACRO DCT WP has been to engage country by country with authorities at a national level.

The ACRO DCT Working Party made the decision that this first country to examine in beginning this work would be to look specifically at decentralized clinical trials within the *United Kingdom*.

As the ACRO DCT Working Party conducted its work on decentralized trials, the Working Party was able to have several informal conversations and discussions with the Innovation Office at the UK’s Medicines and Healthcare Products Regulatory Agency (MHRA) and UK’s Health Research Authority (HRA).

Please note: While ACRO’s thinking and work products were informed, and greatly improved, by multiple conversations with the MHRA and HRA, it must be explicitly noted that these were only informal conversations and discussions with MHRA and HRA. These informal listening sessions should not in any way be construed as a formal collaboration with, or a formal endorsement from, either MHRA or HRA. ACRO is the sole author of this Manual and solely responsible for its content. We would like to thank both the MHRA and the HRA for their generous time and for the opportunity to share and informally discuss ACRO’s work with them.

Over the course of this work, the DCT Working Party team studied and catalogued differences in process between a “decentralized” clinical trial model, on the one hand and a “conventional” (or “traditional”) clinical trial model, on the other. And, while the focus of this Quality-by-Design Manual is decentralized clinical trials, there are sections of this document that are applicable to both trial types. While it may seem – at times – that this dedicated DCT Manual strays from a focus on DCTs to a more universal discussion applicable to across all clinical trial designs, this occasional discussion of universal issues is intentional. This more general, universal content has been purposefully retained in this Manual in order to provide helpful suggestions for modernization across all clinical trial designs (both decentralized and conventional).

1.0 Introduction to Decentralized Clinical Trials

1.1 What is a Decentralized Clinical Trial?

Many different phrases are used when discussing decentralized trials (DCTs) – for example, “virtual,” “remote,” “direct-to-patient,” “site-less,” and “hub-and-spoke” trials. For the purposes of common terminology, this document will use the term ‘decentralized clinical trials (DCTs)’.

The ACRO DCT Working Party defines a Decentralized Clinical Trial as a trial that:

“Brings the trial to the patient by utilizing local healthcare providers, optimizing digital health technologies, and enabling the voice of the patient in order to accelerate medical product development, speed delivery of therapies to patients, and create efficiencies across clinical research processes.”

There are a variety of approaches to DCTs depending on the trial type, spanning from fully decentralized clinical trials to hybrid clinical trials, which is a traditional clinical trial that uses some aspects or technological strategies of a decentralized trial, and which could be considered a partially decentralized trial. Decisions related to whether a trial is fully or partially decentralized (hybrid) may be driven by factors such as:

- **Trial population** – the perception of decentralized approaches. Whilst many patients may react favourably to the flexibility of decentralized solutions such as remote visits, and use of technologies such as wearables, some populations may prefer more traditional approaches and less confident with technology use.
- **Geography** – Some aspects of DCTs may be feasible in some countries but not others, enforcing the need for a hybrid approach. This may be the result of differing regulations between countries or practical considerations such as the availability of reliable internet connections in country
- **Indication** – Some technologies and DCT activities may be more appropriate or easy to adopt within given indications than others
- **Study Phase** – The financial and time cost of implementing DCT solutions may be inappropriate for some early phase studies.
- **Investigational Product** – Storage and administration of IP at a participant’s home will influence the ability of a decentralized approach to be taken.

There are many well documented benefits of decentralizing clinical trials to all stakeholders involved from participants, monitors and investigators and sponsors.³

The expectation is that by combining local healthcare providers and digital health technologies, medicinal product development will be accelerated through enhanced recruitment and retention during DCTs which result in faster study completion times, increasing the speed of delivery of therapies to patients and creating efficiencies across clinical research processes. Greater use of aggregated data with analytical capabilities can derive greater insights; for example, leveraging wearable devices and other innovative technology to collect patient data in real-time conducted at the point of care.

'Pragmatic and hybrid clinical trials, including decentralized trials that are conducted at the point of care and that incorporate real world evidence (RWE) can help clinical trials become more agile and efficient by reducing administrative burdens on sponsors and those conducting trials, and can allow patients to receive treatments from community providers without compromising the quality of the trial or the integrity of the data that's being collected.' **FDA commissioner Scott Gottlieb 2019**

2.0 COVID-19 and use of DCT approaches

The COVID-19 pandemic revealed the urgency for a more flexible approach to clinical trials with the ability to allow participation remotely while retaining all of the expectations of GCP and other relevant regulations and laws. Regulatory authorities have acted quickly in response to the pandemic and have published updated guidance for the pandemic period to support management of clinical trials.

The COVID-19 pandemic revealed the urgency for a more flexible approach to clinical trials with the ability to allow participation in clinical trials remotely

- Risk assessment development for decision-making around continuing or halting a trial
- Remote visits versus onsite sites - clearly patient safety is the primary concern, sponsors should determine whether it is safer for patients to participate in assessments via phone, virtual visits, or at an alternative location, if COVID-19 is a concern and the process is acceptable for the trial there is an endorsement, where appropriate, to manage aspects of trials remotely.
- Centralized and remote monitoring - If on-site monitoring visits are no longer possible, sponsors should consider centralized and remote monitoring programs and document any inability to access or delayed monitoring of a site.
- Direct to patient supply of investigational products.

All of these areas are fundamental to a decentralized trial. COVID-19 is essentially forcing a paradigm shift, leveraging technologies such as social media, electronic consenting, telemedicine, apps and biosensors to name a few. Technology coupled with supporting operational strategies are making it possible for patients to participate in studies from the comfort of their homes and so reducing or eliminating the need to travel to sites. Additionally, monitors and investigators have access to tools to engage and interact with participants remotely and processes by which data can be captured real-time and analyzed in an accelerated manner.

3.0 Bringing the Trial to the Patient

3.1 Benefits of Decentralized Clinical Trials

Deploying decentralized trials reduces the practical, financial and geographical barriers to participation. This can positively impact recruitment, retention, study duration, and cost – which ultimately benefits patients. DCTs also provide the opportunity for a greater diversity of trial participants, many of whom would not usually participate in clinical trials, either due to geographical constraints or insufficient time to attend clinical visits.

The ACRO DCT Working Party team carefully identified and analyzed the key benefits of decentralized clinical trials, building upon and complementing the CTTI Recommendations⁴ on clinical trials:

- Faster trial participant recruitment
- Improved trial participant retention
- Reduction on patient burden
- Greater control and comfort for participants
- Increased participant diversity
- The opportunity for home administration and direct to patient supply
- Improve data quality
- Improved patient experience
- Improved clinical trial continuity

70% of potential participants live more than 2 hours away from their nearest study centre which limits recruitment and retention.

Research has shown that:

- Of 40,000 clinical trials recruiting in the US, 80% were delayed due to recruitment challenges.⁵
- 70% of potential participants live more than 2 hours away from their nearest study centre which limits recruitment and retention.⁶
- 85% of clinical trials fail to retain enough patients.⁷
- Across all clinical trials the average drop-out rate is 30%, when more than 12,000 people were asked “Compared to traveling to a study clinic for all of your study visits, how appealing is each of the following options?” More than 75% responded that collecting all data on their own at home or having nurses come to their home for all study visits were appealing choices.⁸

3.2 Improved patient experience with decentralized clinical trials

Conventional clinical trials are subject to strict validation rules for data gathering and analysis. Trial data generally flows from investigators back to the drug company/sponsor, instead of to/from the patients who were participants in the trials. This latter characteristic of clinical investigations is clearly changing.

Trial sponsors and clinical investigators are exploring ways to engage and immerse patients in trials including consideration of their perspectives and making improved information available to them about risks, benefits, and disease progression.

The objective of a standard clinical trial is no longer to just determine whether the drug causes the intended biochemical and pharmacological effects. Investigational drugs must be safe, effective and produce positive outcomes for patients in general. Investigators, regulators and pharmaceutical marketers are increasingly interested in outcomes as measured from the patient’s perspective. “Outcome” more broadly referring to the improvement in the trial participant and general patient wellness or quality of life, and not just reversal

of disease or extension of longevity. As patient experience is an important consideration in trial design, organizations that sponsor and conduct trials are identifying best practices and testing methods to improve the patient experience, resulting in improved participant recruitment, participation and lower drop-out rates.

3.3 Patient Centricity by Design

One of the primary benefits of decentralized clinical trials is their potential to be a patient-friendly model for clinical trials. In order to optimize and maximize the patient-centricity of decentralized trials, ACRO recommends the following:

In the same way that a “Quality-by-design” approach optimizes the benefits of decentralized trials, so too a “Patient Centricity by Design (PCbD) approach will increase the value and benefits of these clinical trials. This PCbD approach ensures that the patient perspective is baked into all aspects of a decentralized trial from the beginning of the design and planning process – rather than as an afterthought. PCbD is both a methodology and also a mindset.

‘Time - A key concept for patients is time – and the valuable, efficient use of time. A Patient Centricity by Design approach helps ensure that the time-reduction potential of DCTs is fully realized’

Given the importance of software development in decentralized clinical trials (e.g., the creation of patient portals), the goal of PCbD is to build in the patient perspective so that there is no longer the scenario of fixing software after the fact (after development). Under PCbD, software development becomes an iterative process, with the patient perspective continually built in – which is much more efficient. Of course, PCbD is important for all clinical trials (both “conventional” and “decentralized”). Therefore, it is important to ask what unique and distinctive issues emerge regarding PCbD in the specific context of a decentralized clinical trial. As the normal face-to-face, in-person interaction between patients and clinical trial staff in a traditional/conventional model is dramatically reduced in a decentralized clinical trial model, two key elements of the relationship between clinical trial staff and patients become absolutely vital under a DCT model—

Transparency and consistent, clear communications/connections. The goal of transparency and consistent, clear communications is to ensure the following:

- **Trust** clinical trial staff need to help ensure clarity about what work/tasks in a DCT model are transferred to the patient – and why
- **Value Exchange** - This also needs to be clear and transparent throughout all phases of a DCT of the value exchange
- **Connection/Communication:** While “inter-patient” (i.e., patient-to-patient) communication is important via various online forums/platforms, it is necessary for patients to be connected to the clinical trial team so that they are not isolated from these teams who can provide valuable, expert information
- **Education and availability of a virtual helpline** is one element to help ensure consistent, reliable connection to clinical care and clinical trial team.
- **Time** - A key concept for patients is time – and the valuable, efficient use of time. A PCbD approach helps ensure that the time-reduction potential of DCTs is fully realized.

3.4 Being connected to decentralized clinical technology

Almost 4.57 billion people were active internet users as of April 2020, encompassing 59 percent of the global population. Almost 92% of these were unique mobile internet users.

The use of smartphones is nearly universal in developed countries. Globally, there has been an explosive proliferation of apps; a large percentage of smartphone and tablet users are accustomed to downloading and using them not just to consume data, but also to enter it for a variety of purposes. And for app developers, the costs of developing and deploying them via mobile networks is low compared to the cost of conventional enterprise software tools. According to recent data from STATISTA, almost 4.57 billion people were active internet users as of April 2020, encompassing 59 percent of the global population. Almost 92% of these were unique mobile internet users.⁹

Smartphones are more than just pocket-sized computers. They contain onboard biometric and global positioning systems that make them uniquely powerful passive data collection devices. These features have been put to work in clinical investigations to monitor patients' vital signs, activity levels and mobility.

The platforms that support decentralized trials will have the option for a user to login from a household computer as well as a mobile phone option, so there will be a variety of aspects for DCTs that are simply computer-based and mean that participants who do not have a smartphone can still participate. Additionally, not all studies will need smartphones to be used as passive data collection devices, key aspects of making studies patient-centric is improve the ability to participate in studies by making them more accessible, especially for participants that are working or have other commitments that would limit their ability to attend clinical visits.

DCTs should improve recruitment as they can target a wider selection of potential participants, improve retention in studies by being more "user-friendly" so the drop-out rates are lower and as a consequence studies will complete more quickly as they are losing fewer participants.

Clearly outlining patient safety as being the primary concern and the use of more flexible pragmatic approaches, such as the use of alternative strategies and technologies, with more activities occurring at a trial participant's home or local environment. As consumer expectations evolve, trial participants will be demanding a more patient-friendly clinical trial experience. This is also being recognized by the pharmaceutical industry as many of the target participants for clinical trials are not able to commit to taking time out of work or daily schedules to attend clinical sites.

The convenience of a decentralized approach makes this much more attractive and will lead to improved recruitment and participation, ultimately benefiting both participants, drug developers and future patients in the longer term. Importantly, the ability to access online medical information means that participants are becoming more informed and involved in their conditions and treatments prior to and during clinical trials and a higher level of interest in the results of clinical development.

3.5 Early Engagement with stakeholders

‘Early engagement should be considered at the soonest possible point and planned from the outset.’

Throughout the process of this ACRO initiative, and regardless of the type of trial being executed, there has been a common theme arising between members around earlier engagement of stakeholders. Early engagement should be considered at the soonest possible point and planned from the outset. The practical and operational aspects should be discussed from all perspectives

and subsequently built into protocol design discussions and cross functional risk management decisions. Sponsors are encouraged to reach out to vendors, investigators and patient groups to assess the risk-benefits to critical data and processes from utilizing planned decentralized methodologies and tools, taking into account the study phase, size, disease indication, patient population, planned country distribution and proposed decentralized trial elements for adoption. Early engagement with stakeholders is also referenced in the recent ICH E8 Revision 1.¹⁰ The use of the quality-by-design framework of this Manual enables the potential ‘critical to quality’ aspects of the trial design, patient safety and trial integrity to be identified and mitigated against at the earliest opportunity.¹¹

4.0 Methodology Quality-by-design Manual

4.1 End to end process review

The ACRO DCT WP leveraged the UK’s National Institute Health Research (NIHR)¹² Clinical Tool kit¹³ as the foundation for the end to end process review.

The NIHR Clinical Trials Toolkit maps the clinical trial process and navigates through the legal and good practice arrangements surrounding setting up and managing a Clinical Trial of an Investigational Medicinal Product. The ACRO DCT WP team reviewed each route stop (clinical process) on the map and discussed in detail what additionally would need to be considered for a DCT versus a traditional conventional clinical trial. There were some clinical processes where a DCT would have a significant impact, for example remote monitoring, and other processes where there would be no change, for example assignment of a unique trial number.

Each clinical process was reviewed end to end from Trial Planning and Design to Archiving and prioritized in terms of DCT impact. The clinical processes were prioritized and areas considered included:

- Processes around traditional clinical trial compared to a DCT
- Quality-by-design considerations for DCTs
- Additional risk criteria considerations for DCTs
- Data Management
- Regulatory criteria, acknowledgement of gaps for verification, collated list of questions for the authorities

4.2 Quality-by-design Manual for DCTs

This document outlines the quality-by-design considerations of DCTs and highlights risk areas for generic clinical trials. ACRO’s organizational framework for this QbD Manual has been adapted from the Clinical Trials Transformation Initiative (CTTI) Quality-by-design Project Critical to Quality (CTQ) Factors Principles.”¹⁴

5.0 Regulatory Landscape

5.1 Regulatory Overview

The regulatory landscape surrounding the conduct of DCTs is complex and fragmented. There are several aspects pertinent to DCTs being progressed and some of these are outlined below, (please note this is not an exhaustive view).

- Dr. Scott Gottlieb (former FDA commissioner) discussed the importance of decentralized trials in a 2019 speech.¹⁵
- The industry is awaiting the output of the ICH GCP renovation project, which, it is hoped will address considerations related to the conduct of DCTs but the first part of this is not expected to reach step 4 until November 2022.
- An EMA guidance document on Electronic Systems and Electronic Data in Clinical Trials, currently in development, is believed discuss e-technologies which support decentralized trials, but does not address all aspects such as Direct to Patient IP shipment or utilization of Home Healthcare Professionals.
- FDA have issued Guidance on the Use of Electronic Health Record (EHR) / Electronic Source. In 2018 the Clinical Trials Transformation Initiative (CTTI) released their [final recommendations](#) on overcoming the legal, regulatory, and practical hurdles for planning and conducting DCTs. This provides useful industry guidance but is US centric in content and is not formally endorsed under any regulatory framework.

...in general, there is no cross–industry end to end regulatory guidance document on this topic at the current time of writing.

In general, there is no cross–industry regulatory guidance document on this topic at the current time of writing. In addition to the lack of any formal clinical trial regulatory guidance in this area, the DCT landscape is further complicated by the complexity of other laws outside the GXP area which influence the ability to conduct decentralized activities, e.g. data privacy laws or other local laws related to the management of medical records may preclude the site monitor from having access to unredacted medical records outside of the clinical trial site (either via an Electronic Health Record system) or through a document reviewing portal, or electronic signature laws e.g. eIDAS, may prevent formally agreeing to consent to a clinical trial through an e-consent system.

The relevant country agencies (e.g. National Competent Authorities and Data Protection Authorities) may not be well versed in the respective agency’s laws and at times the respective legislation may directly be too high level or ambiguous for easy interpretation. Advice from National Competent Authority and Regional oversight bodies of clinical trial is required to help individual companies navigate the complexity of these interlinked laws. Without such clarification, Sponsor organizations are likely to remain cautious in fully adopting DCT principles for fear that the study data may be rejected or breach laws they are less well-versed in. Currently, it requires sponsors to check in with multiple agencies in multiple countries to determine whether a decentralized approach would be permitted. There is also the issue that not all countries are aligned resulting in different approaches needing to be implemented in different countries, raising the risk of data integrity issues resulting from country-specific approaches.

5.2 Common Regulatory Requirements

All clinical trials regardless of whether a conventional or a decentralized trial should be in accordance to the guidelines, regulations, directives and local laws pertinent to the region and country of where the trial is being executed. Regardless of the approach conventional or DCT, the investigator and sponsor responsibilities do not change²:

- The risks to the quality and integrity of the study and the data that's being collected lie within these sponsor and investigator responsibilities
- The sponsor's and investigator's due diligence is necessary to ensure all of these responsibilities are met and the integrity and quality of the clinical trial data.

5.2.1 International Guidelines on Good Clinical Practice

The International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use, brings together the regulatory authorities and pharmaceutical industry to collaborate and develop technical ICH guidelines that are harmonized regionally. ICH responds to global developments in the pharmaceutical sector and these ICH guidelines are applied by a growing number of regulatory authorities. ICH's mission is to achieve greater harmonisation worldwide to ensure that safe, effective and high-quality medicines are developed, registered and maintained in the most resource efficient manner whilst meeting high standards.

The work carried out by ICH under the 'Efficacy' heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/ pharmacogenomics techniques to produce better targeted medicines. The ICH E8 The Principles of Clinical Trials guideline is currently going through a modernization and the E6 Good Clinical Practice Procedures guideline is also being renovated.¹⁶ It is hoped that the topic of DCTs will be addressed in this update and that appendix 2 of the revised ICH E6 will cover non-traditional interventional trials, including decentralized trials.

In addition, there are certain regional guidance's developed from the ICH standards which provide additional clarity on key aspects of GCP, for example the EMA has provided guidance in the form of questions and answers on GCP and is based on discussion and agreement by the EMA GCP Inspectors Working Group. For example, question 10 of the 'GCP Matters' section confirms that any contractual arrangements between healthcare providers going into a subject's home should be with the Investigator.¹⁷

5.3 Data Privacy and Security

The EU General Data Protection Regulation (GDPR), along with the new UK Data Protection Act, governs the processing (holding or using) of personal data in the UK and similarly respective to other national laws in the EU. Some of the key applicable concepts of the GDPR are below:

- **Accountability and Data Protection Impact Assessments:** Controllers must account for how they process and protect personal data. Best in class capabilities will provide uniform materials for digital products and business processes to assist with accountability and data protection impact assessment obligations, namely, for example security certifications and reports (e.g., SOC 1 and SOC 2 audit reports, ISO/IEC 27001:2013 Certification) and Privacy Shield certification.
- **Privacy by Design:** The GDPR requires systems to be designed from the outset based on data protection principles, such as restricting the processing of personal data to only that which is necessary for the purpose of the processing.

- **Rights for EU individuals:** The GDPR provides expanded rights for EU individuals such as deletion, restriction of processing, and portability of their personal data. Some of these rights (such as the “right to be forgotten”) are likely excluded in clinical trials context;
- **Security:** data protection and security standards are confirmed by rigorous third-party compliance audits for security, confidentiality, availability, processing integrity, and privacy controls. Robust platforms provide encryption in transit (Transport Layer Security (TLS) with minimum key length of 256 bits); encryption at rest for EDC data using AES (256-bit keys)

In the UK the operational guidance has been produced for researchers and study coordinators on the implications of the GDPR for the delivery of research in the UK. It has been prepared in collaboration with a range of stakeholders and reviewed by the Information Commissioner’s Office.¹⁸

5.4 Validation of Electronic Systems

With a DCT more parts of a clinical trial are using electronic systems and tools for data capture and analysis. All the electronic systems leveraged for this use must be in compliance to ICH GCP and local laws and guidelines. The EMA has recently provided a notice that highlights the requirements for validation and qualification of computerized systems used for management of clinical trial data, as well as an earlier reflection paper on electronic source data and data collection tools.¹⁹

Any clinical data generated by these systems must be done in a robust and structured manner and makes sure the data created is reliable and has integrity and that the tools are fit for purpose.²⁰

During its 2020 GCP Symposium, the MHRA offered suggestions on Electronic Data Capture Systems and Digital Health Technology Tools:²¹

- Sponsors/CROs should – Ensure that electronic systems (owned and controlled by sponsors/CROs) employ data security and integrity controls (e.g., access controls, audit trails, encryption, risk-based approach to validation)
- Use of centralized monitoring is encouraged to identify and proactively follow-up on missing data, inconsistent data, data outliers, and potential protocol deviations that may be indicative of systemic or significant errors

5.5 Electronic Signatures

With a DCT there is the possibility for signatures and informed consent to be performed remotely and within a specific validated and secure system. In the EU the ‘eIDAS’ Regulation (EU) No 910/2014 establishes an EU-wide legal framework for electronic signatures. The Regulation, which is supplemented by the UK eIDAS Regulations (SI 2016/696), defines an electronic signature as ‘data in electronic form which is attached to or logically associated with other electronic data and which is used by the signatory to sign.’²²

The eIDAS Regulation allows for three different types of electronic signatures: basic, advanced and qualified. In the case of qualified electronic signatures, eIDAS requires the appointment of a trust service provider to create, verify, validate and preserve electronic signatures/ The MHRA and HRA have laid out their guidance within their joint statement and permit the use of electronic signature within the UK.

Expectations for electronic signatures associated with informed consent (GCP) are covered in alternative guidance.²³

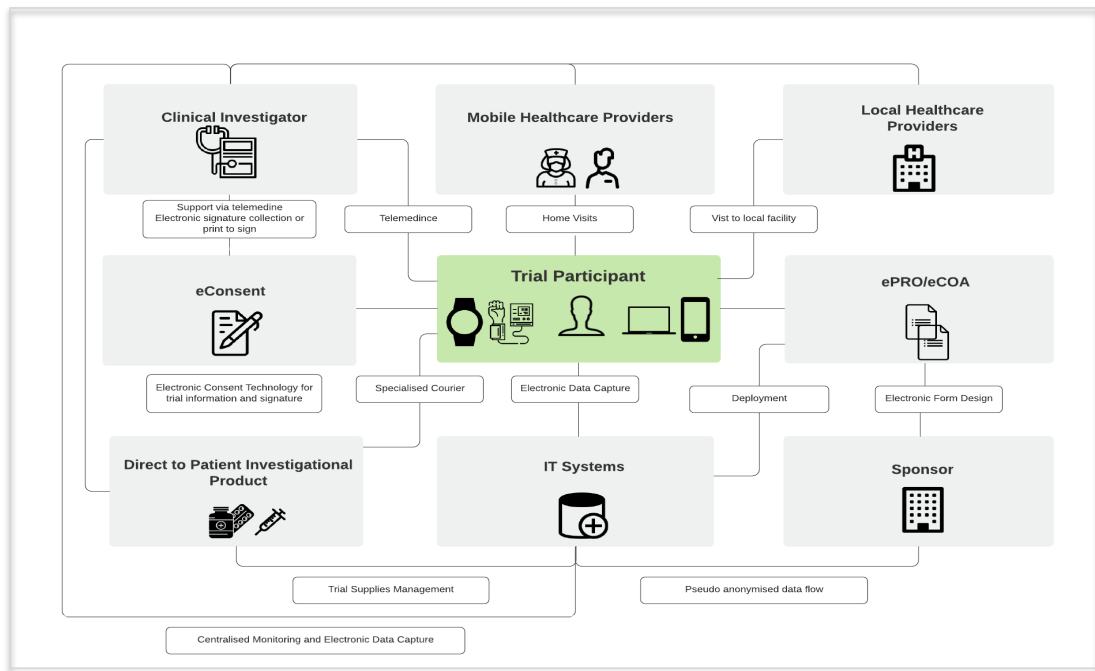
6.0 High level Aspects of a DCT Design

Diagram 1 indicates the high level aspects of a DCT where the trial participant is at the heart of interactions and some of the stakeholders involving the clinical investigator, mobile healthcare providers, local healthcare providers, direct to patient investigational product delivery, some of the IT technologies involved such as eConsent and eCOA/ePRO and other electronic data capture processes.

...the investigator is always responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

Regardless of type of clinical trial the investigator is always responsible for supervising any individual or party to whom the investigator delegates trial-related duties and functions conducted at the trial site.

Diagram 1 – High level Aspects of a DCT



6.1 Data Collection, Handling, and Management Processes and Procedures

As part of a DCT data collection via electronic means will be increased compared to a traditional trial. There is guidance around data collection and management outlined below:

Sponsors/CROs should have:

- Robust and well-defined data collection, handling, and management procedures
- Detailed understanding of the data flow: – A data flow diagram that includes from whom and to whom the data are transferred or transmitted, including all third-party vendors contracted for data collection, data handling, data management and/or data processing

The protocol and /or investigator plan should describe the:

- Data flow
- All electronics systems used in the study
- Source data that are transcribed or manually entered in the EDC System
- Source data that are transferred via an automated system -to-system level exchange
- External data that are transferred to the EDC system (and process for transferring the data)
- Handling of external medical records.

7.2 General IT and Systems Consideration

Description/Rationale: Decentralized Clinical Trials require an IT systems infrastructure that allows for traditional site-based data input by study teams as well as allowing participants to review content and contribute data remotely. This inherently creates opportunities for external systems breach by bad actors and therefore should maintain the same system security provisions and procedures as other clinical systems, financial systems, or confidential data systems. Clinical systems which support DCTs will fall under the same regulatory requirements as all other clinical data systems, including ICH GCP E6 (R2), 21 CFR Part 11, Annex 11, ERES and other local or international regulations. As DCTs may also collect Identifiable Data Concerning Health, these systems may also be subject to data protection and privacy laws and regulation regulating those types of data.²⁴

Potential Considerations in Evaluating Relative Importance of CTQ Factors

Consider connectivity and robust infrastructure of the DCT network, ensuring:

1. The integrity and security of electronic records.
2. The accuracy and precision of remote sensor measurements.
3. Systems and IT solutions are fit for purpose and in accordance with computer systems validation principles.
4. A document is in place outlining the data flow and data collection for a DCT.
5. Business continuity and back up plans are in place and testing procedures are documented and followed.
6. Storage, archival, and availability for retrieval of source documents and electronic information during and after the trial.
7. A process in place for the scenario in case the device fails, outlining how the participant gets a replacement or has an equivalency in accessing the systems.
8. In the case of 7 above how to manage the data collection in the meantime
9. Technology support provision of adequate training and support for all stakeholders involved see 10.
10. Training is provided to all new and current stakeholders involved in the DCTs. Depending on the operational model, this includes but is not exhaustive, participants, site staff, call centres, sponsor staff and provision of insight to regulators and EC/IRBs.
 - a. Investigators should clearly articulate procedures and train staff on processes unique to decentralized clinical trials.
 - b. Trial participants must know what to do especially in the case of experiencing an adverse event.
11. Consider climate change and use of DCTs which can add efficiency, cost savings and reduce waste.

Examples of Issues to Consider in Evaluating Risks to CTQ Factors

1. A risk of resistance to change, users, such as sites and or trial participants can't or don't want to use a new process or technology and preference is to maintain current established traditional methods.
2. A risk that infrastructure is poorly designed.
3. A risk that there a lack of or no connectivity or sub optimal unstable internet at the patient's location.

4. A lack of interoperability between systems; for example, risks with using multiple technologies that terminologies are not the same and there is mis-interpretation, challenges with data integration across applications into EMR or eCRF, etc.
5. Lack of training on new processes and systems to all users pertinent to their role.
6. Risk of outsourcing to numbers of technology vendors.
7. Risk around maintaining oversight of all vendors, optimal governance structure should be in place
8. For multi country trials and ability to translate Apps, eCOA, Consent, ePRO to other languages? Low risk as this already exists.
9. Risk of hybrid approach with a paper back up option for if a device fails.
10. Risk of overburdening site e.g. multiple studies with multiple technology systems.
11. A risk that initially moving to a new DCT would involve too much change and cost despite potential to have longer term patient centric, efficiency gains.

7.3 Trial Planning and Design

Description/Rationale: A robust trial design is essential to ensure a successful outcome. The trial design should be considered before developing the protocol and relevant stakeholders should be consulted in these discussions. This will help ensure that all necessary practical requirements are identified early so that the subsequent protocol design is both scientifically robust and operationally feasible by those who are involved in its execution, either as clinical trial participants, investigators or vendors. A well-documented study plan will facilitate the process of investigator selection, ethics committee and R&D approvals / NHS permissions, and any necessary regulatory approvals. This will help to avoid substantial amendments within the clinical trial potentially impacting the patient and the efficiency of the trial.

Potential Considerations in Evaluating Relative Importance of CTQ Factors

1. In considering the planning and design of a decentralized trial the expected goal, objective and benefits to the different stakeholders should be outlined and well thought through, including trial participants, relevant third parties etc.
2. It is essential for sponsors to engage early with all stakeholders to support understand any operational barriers to adoption and provide insight to specific expertise to support the downstream quality of the trial. Consider early dialogues with the regulators, Ethics Committees and IRBs to outline the decentralized approach. How to engage and provide insight to IRBs/ECs on the new DCT process and technology.
3. Critically question whether there are benefits of running a DCT in comparison to a traditional model; it must be considered that just because a DCT *can* be performed doesn't necessarily mean it might add value in some scenarios.
4. Consider any additional safety risks that may be brought with a DCT.

Potential Considerations in Evaluating Relative Importance of CTQ Factors

5. When considering all stakeholders involved in the planning and design of a decentralized trial the expected goal, objective and benefits to the different stakeholders should be outlined and well thought through.
6. Complete an analysis of the study phase of a DCT including
 - a. the patient population being studied and demographics.
 - b. the planned country distribution and relevant regional and national legal requirements, site requirements.
7. Understand the criticality/sensitivity of the data such as:
 - a. Having in place a specific data management plan/diagram and privacy impact assessment for DCTs to show how the data flows, data ownership, and protection.
 - What data is collected and which party own/control which type of data?
 - how data flows between systems and parties involved in the conduct of the DCT
 - General implications of proposed technical solutions for confidentiality, integrity, availability and non-repudiation of data
 - How the data will be monitored and queried/corrected if necessary?
 - b. Determining whether any new technologies are fit for purpose and validated in line with computer systems validation principles.
 - c. What data won't be used from certain technologies (i.e. telemedicine)?
 - d. What are the different country regulation that will need to be adhered to for different technologies and data?
 - e. Identify where multiply generic technologies will be used?
 - f. How will raw and normalized and extracted data will be stored, routed, and tracked?
 - g. Where will machine learning/ai will be applied and what algorithms will be used
 - h. Will technologies be able to meet patient impairments (colour-blind, blind, deaf, etc) – will there be any impact to data collection
 - i. Who needs access to the data for review (DM, Patient, Site, CRA, PM, Investigator, etc)?
 - j. How are any data clarification done with a direct device collection?
8. Determine and make clear in the protocol/participant information sheet which elements of the trial can be decentralized.
9. Design communication models and scenarios; what these look like could depend on the trial, such as: patient interfaces with investigators and health care professionals, call centre models, video, phone, telemedicine, trial participant interacts or travels to a local site.

Examples of Issues to Consider in Evaluating Risks to CTQ Factors

1. Lack of detail in the planning and design phase which steps through the end to end process of a DCT, for example handling and structuring of data.

2. Planned country distribution and infrastructure limitations to full adoption; consider the risks and costs associated with hybrid solutions e.g. use of a technology solution to collect data from patient in one country and use of paper tools in another.
3. Consider translation requirements.
4. A risk of a lack of engagement with patients and stakeholders who will be involved in the operational aspects of a trial or that are involved far too late in the process:
 - a. Need to consider impact of decentralized approach on all stakeholders e.g. are telemedicine visits welcomed by patients to facilitate their participation or do they prefer direct contact with investigator? Do technologies support site or add further burden? We need to be careful not to assume technology is welcomed by impacted stakeholders in all cases.
 - b. Does the technology inadvertently discriminate against or exclude some participants e.g. to their ability to access or use the technology?
5. Protocol (or associated document) must detail any data for which CRF is the source (important for when e-source is in use).
6. Risk in terms of not thinking about the wider trial and accounting for impacts throughout the trial and impact on overall data integrity/quality

7.4 Early Patient and Stakeholder Engagement

Description/Rationale: most of the technology developed for decentralized studies has been designed to facilitate the patient experience by reducing travel needs (eConsent, ePRO), facilitating and maintaining patient engagement (apps.) and enhancing compliance (real-time analysis of data). Early engagement with all stakeholders will ensure that study participants needs as well as those of the investigator and study sponsor are met and also promoting a study design and strategy that is more likely to succeed.

Potential Considerations in Evaluating Relative Importance of CTQ Factors

1. Analyze protocol procedures to evaluate which of these can be decentralized.
2. Consider all stakeholders involved including trial participants, relevant third parties at the earliest possible point etc.
3. It is essential for sponsors to engage early with all stakeholders to support understand any operational barriers to adoption and provide insight to specific expertise to support the downstream quality of the trial. Consider early dialogues with the regulators, Ethics Committees and IRBs to outline the decentralized approach. How to engage and provide insight to IRBs/ECs on the new DCT process and technology.
4. Understand consequences for patients; involve patient/patient association to review patient journey
5. Consider capabilities and qualification/validation of systems that will support DCT strategies, early engagement with relevant stakeholders such CROs and computer systems vendors who have developed these platforms will be important in determining strategy.

Examples of Issues to Consider in Evaluating Risks to CTQ Factors

1. Risk associated with progressing too far forward without having engaged with all necessary stakeholders and specific expertise.
2. Failure to engage with or listen to the stakeholders early on. This can impact the clinical trial in terms of operational challenges, additional amendments, potential time delays, increase in costs and in-efficiencies and reputational impacts and generally supporting patients get the treatments they need.
3. Requirement for use of technology not built into feasibility assessments, and not identified until too late that site / participants struggle with use of technology as expected

7.5 R&D Consultation and Peer Review

R&D Consultation - Description/Rationale: In the UK an NHS R&D Office must ensure all relevant approvals are in place before a research project can take place within their organization: When acting as the sponsor, NHS R&D offices will be involved in the oversight of the trial by guiding the Chief Investigator and managing the risks associated with any trial initiated. When acting as a host organization, NHS R&D offices facilitate the timely set up of externally sponsored trials and support the Principal Investigators participating in those trials ‘Whichever scenario applies, these offices need to be aware of all projects that involve their organization’s staff or resources.

Peer Review Description/Rationale: A number of 'experts' examine the proposed trial to consider aspects such as design quality, feasibility, acceptability and importance of the topic etc. ‘Experts’ in this context will usually include views from relevant clinicians, allied health professionals and other professional groups, methodologists, patients and members of the public.

Potential Considerations in Evaluating Relative Importance of CTQ Factors

1. Ensure that all new processes and technologies are clearly and transparently documented and understood by the R&D approvers

Examples of Issues to Consider in Evaluating Risks to CTQ Factors

1. Risk that sponsors don't engage adequately or early enough with third parties and patients
2. Risk that new processes and technologies are not understood and approvals are subsequently blocked or rejected
3. Risk that impact of technology on site is not adequately explained to R&D office in submission so impact on site is not fully assessed

7.6 Protocol Development, Protocol Approval

Description/Rationale: The Guideline for good clinical practice E6(R2) outlines a clinical trial protocol as: “A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.” The protocol will describe all aspects of the trial but should also be written to be clear and concise and should also ensure that the trial avoids ‘unnecessary complexity’. Protocols should include a definition of the ‘end of the trial’ and information on post-trial care. Protocols (and many other documents produced as part of a trial) should be controlled documents; version numbered and dated using a formalised convention, involvement of patients and the public helps to shape fundamental aspects of the protocol to ensure it takes into account the needs of participants.

Therefore, all additional aspects of a DCT or hybrid trial should be described from the end to end perspective.

Special considerations need to be made to ensure that no additional risks to participants occur by applying DCT methods to the protocol. This should be addressed in the risk benefit section of the protocol along with risk mitigation measures. There should be a high degree of stakeholder engagement during the trial design which will result in specific callouts in the protocol development to ensure patient safety and accurate collection of any digital endpoints. The Early Engagement recommendation is also referenced in the Guideline ICH E8 R1: “facilitate the ability to design quality into the study protocol”. Additionally, “the design should also consider the relevance of the study results for regions other than the one(s) in which the study is conducted.”²⁵ The ICH E6 R3 Concept Paper points out the development of an annex 2 which will address “additional considerations for non-traditional interventional clinical trials which include DCTs.”²⁶

Potential Considerations in Evaluating Relative Importance of CTQ Factors

1. Prior to designing a trial, a triage process is recommended to assess the suitability of a DCT approach. Those include patient burden, patient safety, integrity of data as well as IMP requirements which also results in a positive impact on patient recruitment/retention and/or compliance.
2. Describe the early engagement mechanisms with stakeholders.
 - a. Engage with all stakeholders whom may be involved in designing the trial and building in feedback early on. This will subsequently help to avoid protocol amendments later on. Stakeholders will include for example CROs, Patient Advocacy groups, regulators, MHRA.HRA and third parties and experienced vendors.
3. Description of Process and Procedures
 - a. Outline the different scenarios and trial specific procedures for the DCT including the activities occurring at the investigative site verses what is occurring remotely
 - b. Outline the role of additional resources that will be now supporting the DCT, for example the role of the mobile and local Health Care Provider (LHCP) in the DCT in conducting study-related activities and evaluating adverse events.
4. Define process/ guidance on what triggers an interaction between HCP, homecare nurses and patient.

Potential Considerations in Evaluating Relative Importance of CTQ Factors

5. Outline clearly the accountability of the stakeholders or reference the contractual obligations.
6. Outline the process for informing LHCP of the participant's participation in the research, including upfront confirmation that the LHCP is available and understands that the participant will be in a research study.
7. Outline the process/procedure for communicating information to and from LCHP and the clinical investigator
8. Outline the accountable parties at each step in the supply chain, from the requisition to distribution to the study participant to destruction or return of used and unused study drug.
9. Technological and data considerations including
 - a. A detailed overview of the technology used in the DCT (all electronics systems and technologies to be used in the study to be described. Outline the types of technology solutions and mobile solutions to be used across the end to end DCT)
 - b. Map the data flow, data collection and data storage considerations with a DCT (outline which systems/solution are being used such as mobile technologies, telemedicine, and other ensure that it is made clear how the data flows, is captured and stored)
 - c. Describe how data will be captured, frequency of data collection, the impact on the patient are critical to evaluate and address in the protocol as part of its development.
 - d. Source data that are transcribed or manually entered in the EDC System
 - e. Source data that are transferred via an automated system to system level exchange
 - f. External data that are transferred to the EDC system (and process for transferring the external data)
 - g. Handling of external medical records and recording of home care nursing notes and diaries
 - h. Validation, UAT, back-up, licensing of applications used for monitoring activities.
 - i. Describe the provisioning to the trial participant and investigational sites
 - j. Not all mobile technologies and apps are suitable to be used in a DCT. Ensure relevant technologies used are in line with applicable data protection and privacy laws and regulations; Information Security standards and/or applicable and security laws
 - k. Ensure there is suitable documented evidence that the relevant technologies have been suitably validated
 - l. Describe additional risks there may be regarding DCTs in the risk benefit section of the protocol along with risk mitigation measures.
10. Describe any additional requirements around study participant compliance including:
 - a. training on electronic systems, telemedicine apps and any other technology that study participants, mobile health care practitioners/providers, clinical investigators and participants, mobile health care practitioners/providers, clinical investigators and other study personnel, and LHCP will be required to use in the clinical trial other study personnel,

Examples of Issues to Consider in Evaluating Risks to CTQ Factors

1. Lack of suitability to protocol/patient population to a DCT approach may be related to:
 - Patient profile
 - Medical assessment
 - DCT schedule
 - Country considerations
2. Lack of early engagement with stakeholders
3. The inability to effectively describe the new DCT process and technologies gain insight from experiences third party vendors and experts in supporting the development of the protocol.
4. Instruments that will be used to collect data directly from the patient need to be evaluated and addressed with the instrument license holder to determine if the mode of collection can be validated in a BYOD environment to ensure data accuracy
5. Poor protocol design and lack of clarity around the DCT process and technology being used
6. Lack of documents governance and oversight
7. For protocol approval ensuring the relevant personnel are familiar with

7.7 Trial Monitoring and Management

Description/Rationale: Appropriate planning before the trial and adequate oversight and monitoring during the trial will help ensure that trial participant safety is maintained throughout the trial and that there is accurate reporting of results at its conclusion. The sponsor is responsible for ensuring that robust trial management systems are put in place. The monitoring of a trial is one of the key activities undertaken as part of the trial's management. Risk-adapted trial management taken by the MHRA addresses the question: What are the critical processes and critical data for this trial and how best can any risks and/or vulnerabilities identified in these areas be mitigated? DCTs helps mitigation as the technology expedites the capability to monitor, thus allowing for data driven decisions in real time.

Potential Considerations in Evaluating Relative Importance of CTQ Factors

1. Technological and data considerations
 - a. Outline responsibilities for 21CFR part 11, EMA and UK compliance in regards to validation, UAT, back-up, licensing of applications used for the patient, sites and operations.

Potential Considerations in Evaluating Relative Importance of CTQ Factors

- b. Determine strategy and training for BOYD, provisioned device scenarios and wearables
 - c. Evaluate the data flow to efficiently access participant's data
 - d. Outline key data requiring monitoring and how technology will support oversight. Determine data access and impact of roles defined within the technology
2. Description of process and procedures
- a. Determine monitoring activities required onsite verses the ability to use technology for central monitoring
 - b. Ability to monitoring patient compliance and notifications to allow for timely follow up
 - c. Define the investigator access to data to ensure oversight/ control/ access is appropriately maintained
 - d. Define process for recording of home care nursing notes
 - e. Define triggers for key interaction and information sharing between site, homecare nurses and patient
 - f. Outline communication mechanisms to ensure the obligations of all parties are being met
 - g. Roles and responsibilities are defined to ensure individuals are appropriately qualified and competent to perform necessary functions for a DCT
 - h. Define monitoring oversight and governance required for a DCT due to varies technology being utilized for the study

Examples of Issues to Consider in Evaluating Risks to CTQ Factors

1. Choosing the right vendor, that has effective access rights and controls in place and can demonstrate and provide suitable documentation
2. Multiple technology vendors within a study creates complexity for understanding data flow and ensuring appropriate oversight
3. Gaining access to the right data for monitoring activities (e.g. not having access to the EHR (or records outside the EHR) which prevents ability to perform task
4. Participant is on a trial just to get a provisioned device
5. Clear understanding of expectations for MHRA inspections (i.e data from sensors)?
6. Oversight of homecare providers, ensuring the right credentials
7. Understanding data flow to allow for oversight
8. Lack of guidance on monitoring of eConsent
9. Continued access to participant data by investigator after study closeout
10. Changes to the type of support needed for sites and monitoring team

Examples of Issues to Consider in Evaluating Risks to CTQ Factors

11. Active engagement in starting and stopping access to systems
12. Site burden due to systems variability and multiple vendors for trial

7.8 Clinical Trial Supplies

Description/Rationale: Appropriate procedures and controls need to be in place for Direct-to-Patient and Direct-from-Patient trial delivery/dispatch. This includes clinical trial supplies (e.g. IP/device, Non-IMP/auxiliary medicinal products (AxMP) and other ancillary products such as lab sample collection kits, mobile or wearable devices, and bio-sample dispatch

Decentralized trials are designed to be participant-centric and reduce the burden on participants to attend clinical sites; use of Direct-to-Patient shipment reduces the need for participants to visit sites for the collection, accountability and return of IP supplies and, with combined involvement of Home Healthcare Providers, may also facilitate the administration of IP. The option to provide DtP supplies has been permitted for some time now under current regulations, but as an integral component of a DCT, this requires careful control to ensure appropriate chain of custody and stability of the IP throughout the shipment process. The ability to perform drug accountability during the course of a study as well as return or destruction of unused IP supplies at the end of a study requires consideration and development of appropriate procedures to address these.

Potential Considerations in Evaluating Relative Importance of CTQ Factors

1. Consider whether the IP is appropriate for home administration /storage -
 - For IP that is generally administered in a healthcare setting (e.g. infusions), Sponsors should consider the risk of home administration (e.g. is self- administration a possibility, use of home nursing staff who are trained but not study personnel)
 - Certain products may not be suitable for DTP shipment, for example if it is a controlled substance, or requires specific light or temperature storage conditions.
2. Consider if the planned DTP/DFP deliveries are appropriate for use by the participant population, development stage and trial design.
3. Clearly describe the supply and dispatch procedures either in the protocol and/or a study document for the investigator, patient, home nurse. This should include temperature monitoring during transportation, recording of temperature excursions and actions required if these occur; also participants should be clearly aware of any specific storage / administration requirements for the IMP and able to comply with these.
4. Obtain necessary EC / CA approvals for IP shipment process and any written information provided to participant to support handling of the IP.
5. Ensure that appropriate training is provided to all stakeholders and documented.

Potential Considerations in Evaluating Relative Importance of CTQ Factors

6. Evaluate any specific safety concerns associated with the use of the supplies and describe how these have been identified and managed in prior investigational or marketing experience.
7. Assess if DTP shipment is in compliance with applicable data protection and privacy laws and regulations in all considered countries. Ensure subject consent is obtained for release of personal information to courier.
8. Assess contracting and logistical requirements where depot is in use.
9. Evaluate the national legal and regulatory compliance of planned supply chains.
10. Consider using specialist vendors for DTP shipments to ensure IP stability is maintained and confirmation is obtained of delivery only to clinical trial subject

Examples of Issues to Consider in Evaluating Risks to CTQ Factors

1. Measures should be in place to obtain consent from participants and to document in source documents confirmation of their agreement to supply of their contact details to depot and /or courier and /or homecare nurses.
2. IP delivery method must be appropriate to the IP type (e.g. post, courier, delivered by home care nurse or collection from pharmacy) and should ensure delivery only to the clinical trial participant (or their nominated and approved delegate); use of services such as collection from local pharmacy or secure IP vending machine may facilitate this, especially when participant works and may not be at home to accept delivery.
3. Automated IP supply management should have capabilities to initiate requests for IP to new participants, track confirmation of receipt, usage and initiate resupplies.
 - a. Where shipment to subject is direct from a depot (rather than clinical trial site), the depot should be independent of the Sponsor.
 - b. IP should only be shipped to participant on confirmation of the participant’s verbal consent and receipt of a prescription from the investigator
4. Instructions for the documentation, filing and archiving of all relevant communications and other records that demonstrate oversight of the IP process should be developed including:
 - a. Shipment and delivery records of IMP directly to study participants, including any confirmation of stability requirements or temperature excursions
 - b. IP administration and accountability records where applicable
 - c. IP destruction /return records

7.9 Trial Documentation and Trial Master File

Description/Rationale: A Trial Master File (TMF) should be set up at the beginning of a trial. The essential documents that make up the file should be kept in a secure but accessible manner. A well-kept TMF is necessary for efficient trial management and to facilitate the reconstruction of the conduct of the trial during the audit/inspection process. The GCP Inspection Working Group have produced the ‘Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic)’ (6 December 2018), to assist sponsors and investigators to comply with the requirements of the Clinical Trials Regulation (EU) No 536/2014. In addition, the MHRA FAQs for Trial Master Files (TMF) and Archiving provide further guidance on their expectations when scanning paper documents for electronic archive.

Potential Considerations in Evaluating Relative Importance of CTQ Factors

1. Determine the owning party for documents / data required in the TMF, and where these will be retained both during and after completion of the trial. E.g. will all documents / data be sent to the TMF on an ongoing basis by all vendors or will any vendors retain responsibility for documents /

Potential Considerations in Evaluating Relative Importance of CTQ Factors

- data they create in a secondary location? E.g. data on vendor servers. This becomes more complicated with the more vendors involved in the process.
2. Ensure that details of which documents are stored in secondary locations are clearly detailed in the study TMF plan and vendor contracts as appropriate.
 3. Where documents are held in a secondary location, determine how all parties given access to them as needed? Where everything is held in the TMF what processes are in place for the timely loading into the TMF and accessibility to all parties?
 4. Consider how Investigators will retain responsibility for the management and oversight of source documents generated outside their direct control and what procedures they have in place for their maintenance and retention e.g.,
 - a. From local medical doctors and other local health care providers
 - b. Generated and collected at home visits by the study participants, clinical investigator, study personnel, or third-party contractors such as homecare nurses
 5. Ensure the vendor contract details how to manage data when companies go through changes. such as bankruptcy
 6. Management and recording of the metadata

Examples of Issues to Consider in Evaluating Risks to CTQ Factors

1. Risk data sets or documents never make it into the TMF and /or are not flagged in TMF index to indicate where they are stored
2. Risk that documents don't get to the investigator in real time or in timely manner
3. Potential risk through lack of clarity over
 - a. who is responsible for oversight of the home healthcare nurse?
 - b. how source documents generated by the home healthcare nurse are transmitted to the investigator and timelines for this transfer
 - c. who is responsible for the review and storage of the notes the nurse has generated by the investigator?
4. Who owns what part of the data risk to data standardisation due to involvement of multiple different vendors
5. Risk that vendors switch off systems without ensuring there is a mechanism for data to remain available to investigators throughout the archiving period
6. If the vendor retains and transfers all the relevant data, need retention policies in place.

7.10 Contracts and Agreements

Description/Rationale:

Many parties may be involved in the conduct and management of a clinical trial and it is important that each party has a clear reference of what is expected of them.

Contracts and agreements should be in place prior to the initiation of any trial and should be subject to periodic review to ensure that they remain up to date and relevant.

The content of contracts and agreements should include:

- The standards that are applicable (for Clinical Trials of Investigational Medicinal Product (CTIMPs) this would include the Clinical Trials Regulations)
- The roles and responsibilities of various parties
- The procedures to be undertaken
- The lines of communication.

Potential Considerations in Evaluating Relative Importance of CTQ Factors

1. Maintain a central listing in organization of all different potential vendor types involved within the DCTs
2. Leverage a standard template which nuances the differences in vendors I.e decentralized trials site contacts and vendor contracts.
3. Clarify where the contractual obligation lies with a DCT and who the appropriate signatories are?
4. Develop tools to outlining areas that vendor management need to consider when qualifying DCT vendors
5. Need to train sites and investigating team, who is responsible for providing the care.
6. Need to be very specific on roles and responsibilities of all parties involved in the DCT
7. Investigators push back as they didn't directly contract with a home care service for example request advice on this (supporting information on EMA GCP IWP Q&As – questions 10 and 11 addresses this or at least provides some guidance)
8. Weak area collectively in the context of CRO, sponsor, lack of clarity and responsibilities, major challenges have been highlighted by EU IWG.

Examples of Issues to Consider in Evaluating Risks to CTQ Factors

7.11 Feasibility and Site Selection

Description/Rationale:

Potential Considerations in Evaluating Relative Importance of CTQ Factors

1. The Investigator and the site resources need to be trained and well versed in the DCT process and use of DCT technologies and the ability to interpret the data collected via remote means.
2. The investigator and site resources need to show in their credentials use of/training in relevant DCT processes and technologies.
3. For a full DCT model the ability to recruit, engage and monitor via remote means.
4. Contractual between relevant parties to include DCT models.

Examples of Issues to Consider in Evaluating Risks to CTQ Factors

1. A lack of training and credentials in DCT approaches
2. Sites are not suitably equipped with the relevant technologies
3. Risk that processes and procedures are not in place to effectively run a DCT

7.12 Ethics Submission

Description/Rationale

The Health Research Authority (HRA) facilitates ethical research that is of potential benefit to participants. The Research Ethics Service (RES) is a core function of the HRA.

Potential Considerations in Evaluating Relative Importance of CTQ Factors

1. The submission process itself will not change with DCTs. However, it is important that the submission package (protocol, ICF, scripts, storyboards and views of software applications) clearly outline the way in which the trial will be conducted - I.e. use of telemedicine, wearable technologies, use of e-consent, ePRO/eCOA forms, Patient Portals, remote access to EHRs etc.
2. Make sure the process is transparent, about what is being done remotely, and who is involved.
3. Provide screen shots, videos or other evidentiary materials which outline any content or materials with which the participant will be presented.

Potential Considerations in Evaluating Relative Importance of CTQ Factors

4. Provide the opportunity to allow for comment and discussion.
5. Make sure that all relevant parties are involved in the submission and all aspects of the DCT are made available to the ethics committee ensuring the process is well described and understandable.
6. Where applicable, provide attestation documentation to explain the differences that may exist between electronic versions of a paper process or document. Be prepared to provide assurances and evidence of data collection, storage and access documentation to demonstrate patient safety, compliance with applicable data protection and privacy laws and regulations and implemented technical and organizational protection measures including methods for patient identification as well as for protection of patient identity when remote data is being collected.
7. Provide a sample of the final product of approved materials once the system is ready to go live. This will include copies of the final production video for informed consent as well as a recorded demo of the data collection tools.

Examples of Issues to Consider in Evaluating Risks to CTQ Factors

1. Insufficient clarity in the protocol for the ethics committee to understand the level of DC
2. Lack of training on the DCT process and technology
3. Insufficient clear guidance and policy on how to handle review of DCTs

7.13 Informed Consent

Description/Rationale: Participants must give their informed consent before being entered into a trial*. Consent should be obtained before the first trial-specific activity is undertaken. For Clinical Trials of Investigational Medicinal Products (CTIMPs), Schedule 1 of The Medicines for Human Use (Clinical Trials) Regulations 2004 describes the requirements for consent.²⁷ The HRA and MHRA have published a Joint Statement on Seeking Consent by Electronic Methods (September 2018)²⁸ which outline the expectations for conducting both site-based as well as remote electronic informed consent which should be the basis for eConsent in DCTs.

Potential Considerations in Evaluating Relative Importance of CTQ Factors

1. How the EIC is administered (e.g., by use of video, informed consent document)
2. How participants access the EIC (e.g., through a web-based portal, email etc.)
3. What methods are used to positively identify the participant?

Potential Considerations in Evaluating Relative Importance of CTQ Factors

4. What methods are used to obtain the participant’s signature?
5. How copies of EIC are provided to the participant (by email, through an online portal, mailed)
6. How amendments to the EIC are communicated to the participant
7. How the investigator/sub investigator plans to assess the participant’s understanding of the EIC

Examples of Issues to Consider in Evaluating Risks to CTQ Factors

1. Participant receptiveness to use of e-consent; is it appropriate for the planned trial population?
2. Risk of system ‘down-time’ and back-up process
3. Appropriate control systems to positively identify participants and protect patient data.
4. Ensuring investigator control of patient data and consent process

7.14 Inspection & Audit

Description/Rationale: European legislation (and SI 2004/1031) requires Member States to inspect organizations that hold clinical trials authorisations or conduct activities on behalf of the clinical trial sponsor, this will not change with the introduction of more decentralized clinical design. GCP inspections, and their conduct, will continue to evolve due to increasing complexity in contractual relationships, trial design, and technology solutions, but core elements such as inspection phases, types and locations are unlikely to change.

With more data being collected at the home or at the patient’s workplace, outside the traditional clinical setting, not only will managing the quality and the validity of those data become more challenging, but audit and inspection approaches may differ in order to evaluate tools and processes employed.

Potential Considerations in Evaluating Relative Importance of CTQ Factors

1. Contractual obligations must clearly define responsibilities that cover all required activities.
2. Contracts – ensure availability and/or provision of documentation during and after the trial (i.e. specific provision and level of documentation for inspection purposes)
3. Ensure data pertaining to new service lines/solutions is tracked in a way that can be reported.
4. Provide appropriate system access for the inspection, ensuring Inspectors have complete and direct access.

5. Demonstrate new systems or technologies to save time on training and issues with navigation
6. Availability of Critical data definition and identification, with documentation in place to show data flows and data ownership. For 'new' technologies, consider specific data management plans/diagrams (flow between Sponsor, Participant, Vendors, Site Staff, CRO (Data Management, Monitors etc.)
 - a. Data Lineage from source to report
 - b. Who what and how the data was touched?
 - c. All the different locations
 - d. How was the source data validated before collection?
 - e. Access to the data for inspection
 - f. Validation of programs that touch the data
 - g. Possibly who viewed the data
 - h. How is the data protected at rest and in transit?
 - i. Who owns the data and devices?
 - j. How were patients trained or ensured that they are using any technologies correctly?
 - k. How were any SAE or Safety events managed from technologies?
 - l. How were patients were supported for use of technologies
 - m. Who owns the data, what data did the participant get back?
7. Describe how new technologies are assessed as fit for purpose and validated in line with computer systems validation principles
 - a. Including implications for areas such as compliance with applicable data protection and privacy laws and regulations as well as implemented technical and organizational protection measures, especially if the trial involves social media.
8. Equipment/Materials – ensure availability at site/office of tools (and records of calibration, training etc.) used to perform remote activities (e.g. equipment used by Mobile Nurses)
9. TMF - ensure as a company you know all the systems that make up the TMF and ensure direct access for Inspectors.
10. Parties should be able to provide timely access to systems or data
11. Relevant responsible individuals (i.e., the investigator and DCT study personnel) should be available on site or by phone to answer any questions that may arise
12. Inspections may need to take place at other facilities (e.g., local clinics and pharmacies) where trial-related activities occurred, according to prior arrangements between the investigator and these facilities.

Examples of Issues to Consider in Evaluating Risks to CTQ Factors

1. Party erroneously omits to include contracted activities in the inspection dossier due to a lack of operational tracking for reporting. Increased complexity for answering, for example:
 - a. “eSystems information (e.g. CRF/diaries/ePRO/BYOD/eConsent) systems: If the trial is using any electronic CRFs, esource data collection tools or diaries (e.g. eCRFs, ePROs, BYOD, eConsent etc.) please enter details (e.g. use, name and version of system(s)).
2. Contracted party does not provide documentation in a timely manner due to ambiguity or a lack of contractual requirement.
 - a. Vendors or teams providing technology or services for Inspection support (e.g. validation and testing documents, access logs) were unavailable or unable to provide documentation or access in a timely manner
 - b. Validation
 - c. Time-stamped audit trail
 - d. Legacy systems
 - e. Copies of records
 - f. Protection of records (retention and availability)
3. Contracted parties did not include description of method for electronic data and data collection methods in the protocol
4. Contracted party did not ensure sites had access to the or source documents and did not maintained access for the required data retention period.
5. Project teams did not updated study plans to describe how electronic data would be monitored remotely
6. Lack of understanding of critical data how it was captured (primary source document), data flow or integration and final reporting in eCRF.

7.15 Archiving

Description/Rationale: The Clinical Trials Regulations and specifically, Regulation 31A of the Medicines for Human Use (Clinical Trials) Amendment Regulations 2006, define the archiving requirements for Clinical Trials of Investigational Medicinal Products (CTIMPs). All essential documents should be archived and this includes essential documents held by investigators, sponsors and others involved in the conduct of a clinical trial (including services departments such as pharmacy, laboratories and radiology).²⁹

Potential Considerations in Evaluating Relative Importance of CTQ Factors

1. Determine how the investigator can access the data during the trial and once the trial has closed
2. Consider how to pull all the documents together and how to signpost to alternative storage locations where these exist (e.g. TMF index)
3. Determine who is responsible for archiving which data and being very clear in the contract regarding the roles and responsibilities

Examples of Issues to Consider in Evaluating Risks to CTQ Factors

1. Risk that the data is not available to the investigator and relevant teams throughout the archive period, process in place to ensure any documents data in electronic systems are available to investigating teams and regulatory authorities where appropriate
2. Risk that 3rd party vendors are still in business and able to support archive retrieval and that there are processes in place to correctly transition.
3. Making sure the due diligence is performed

8.0 Appendix 1 – Areas not/minimally impacted by a DCT

Areas of a clinical trial not/minimally impacted	
Sponsorship	Safety Reporting
Funding Proposal	Progress Reporting
GCP & Serious Breach Reporting	Ongoing Management and Monitoring
Funding Secured	Addition of new sites and investigators
Unique Trial Number	Substantial Amendments
EudraCT Number	Urgent safety measures
Confirm Sponsor	Temporary Halt or Early Termination
Final Protocol	Trial does not commence
CTA Submission	Audit
R&D Submission	End of study declaration
Approvals	Statistical Analysis
Final Trial Management Documentation	Clinical Study Report
Trial is abandoned	Dissemination of Results

9.0 Appendix 2 – References

¹ Association of Clinical Research Organizations (ACRO) website

<https://www.acrohealth.org/>

² The ACRO “Decentralized Clinical Trials (DCT) Risk Assessment Considerations” is a companion to the ACRO Quality-by-Design Manual.

This ACRO risk assessment template and spreadsheet has been adapted from the general categories of TransCelerate BioPharma.

ACRO’s *DCT-focused* template is meant to supplement, complement, and be used alongside a company’s currently existing risk tools (such as the TransCelerate Risk Assessment and Categorization Tool (RACT)).

See General Process Here:

<https://transceleratebiopharmainc.com/rbminteractiveguide/how-does-clinical-trial-site-monitoring-work-under-a-risk-based-monitoring-approach/the-transcelerate-model/>

See TransCelerate BioPharma Tool here:

[TransCelerate’s Risk Assessment and Categorization Tool \(RACT\)](#)

³ Clinical Trials Transformation Initiative (CTTI) Decentralized Clinical Trials Project

<https://www.ctti-clinicaltrials.org/projects/decentralized-clinical-trials>

⁴ Clinical Trials Transformation Initiative (CTTI) Decentralized Clinical Trials Project

<https://www.ctti-clinicaltrials.org/projects/decentralized-clinical-trials>

⁵ Clinical trial delays: America’s patient recruitment dilemma; Clinical Trials Arena, 18 July, 2012

<https://www.clinicaltrialsarena.com/analysis/featureclinical-trial-patient-recruitment/>

⁶ Ben Adams, “Sanofi launches new virtual trials offering with Science 37,” FierceBiotech, March 2, 2017.

<https://www.fiercebiotech.com/cro/sanofi-launches-new-virtual-trials-offering-science-37>

⁷ Considerations for Improving Patient Recruitment Into Clinical Trials; Clinical Leader

<https://www.clinicalleader.com/doc/considerations-for-improving-patient-0001>

⁸ 2019 Perceptions and Insights Study – Engagement Preferences – CISCRP

<https://www.ciscrp.org/wp-content/uploads/2019/12/Engagement-Preferences-04DEC.pdf>

⁹ STATISTA – “Global digital population as of July 2020”

<https://www.statista.com/statistics/617136/digital-population-worldwide/>

¹⁰ INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE GENERAL CONSIDERATIONS FOR CLINICAL STUDIES E8(R1)
https://database.ich.org/sites/default/files/E8-R1_EWG_Draft_Guideline.pdf

¹¹ ACRO’s analytical categories for this QbD Manual have been inspired by and adapted from the Clinical Trials Transformation Initiative (CTTI) Quality-by-design Project – Critical to Quality (CTQ) Factors Principles” which can be found at:

https://www.ctti-clinicaltrials.org/files/principles_document_finaldraft_19may15_1.pdf

¹² National Institute for Health Research (NIHR)

<https://www.nihr.ac.uk>

¹³ The ACRO Decentralized Clinical Trials Working Party has adapted the NIHR Routemap (which is applicable to all clinical trials) into a new Map dedicated specifically to DCTs in order to illuminate those specific steps in a decentralized model where new challenges and concerns arise.

National Institute for Health Research (NIHR) Clinical Trials Toolkit “Routemap”

<http://www.ct-toolkit.ac.uk/routemap/>

¹⁴ ACRO’s organizational framework for this QbD Manual has been adapted from the Clinical Trials Transformation Initiative (CTTI) Quality-by-design Project – Critical to Quality (CTQ) Factors Principles” which can be found at:

https://www.ctti-clinicaltrials.org/files/principles_document_finaldraft_19may15_1.pdf

¹⁵ US FDA website, Speech by Scott Gottlieb, M.D., “Breaking Down Barriers Between Clinical Trials and Clinical Care: Incorporating Real World Evidence into Regulatory Decision Making,” JANUARY 28, 2019

<https://www.fda.gov/news-events/speeches-fda-officials/breaking-down-barriers-between-clinical-trials-and-clinical-care-incorporating-real-world-evidence>

¹⁶ Please see both:

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE GENERAL CONSIDERATIONS FOR CLINICAL STUDIES E8(R1)

https://database.ich.org/sites/default/files/E8-R1_EWG_Draft_Guideline.pdf

Final Concept Paper -- ICH E6(R3): Guideline for Good Clinical Practice

Dated 17 November 2019 -- Endorsed by the Management Committee on 18 November 2019

https://database.ich.org/sites/default/files/E6-R3_FinalConceptPaper_2019_1117.pdf

¹⁷ EMA Human Regulatory website page— Q&A: Good clinical practice (GCP)

<https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp>

¹⁸ Please see both of these two documents:

NHS Health Research Authority

Data protection and information governance

Last updated on 4 Aug 2020

<https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/>

UK Data Protection Act 2018

<https://www.legislation.gov.uk/ukpga/2018/12/contents/enacted>

¹⁹ European Medicines Agency

Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials

09 June 2010 -- EMA/INS/GCP/454280/2010

GCP Inspectors Working Group (GCP IWG)

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/notice-sponsors-validation-qualification-computerised-systems-used-clinical-trials_en.pdf ,

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-expectations-electronic-source-data-data-transcribed-electronic-data-collection_en.pdf.

²⁰ Please see both of these documents:

Medicines & Healthcare products Regulatory Agency (MHRA)

'GXP' Data Integrity Guidance and Definitions

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf

EMA Notice to sponsors on validation and qualification of computerised systems used in clinical trials

07 April 2020 – EMA/INS/GCP/467532/2019

Inspections Office, Quality and Safety of Medicines Department

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/notice-sponsors-validation-qualification-computerised-systems-used-clinical-trials_en.pdf

²¹ FDA/MHRA Considerations for the Design and Conduct of Decentralized Clinical Trials:

Regulatory perspectives – FDA/MHRA GCP Symposium 2020

<https://mhrainspectorate.blog.gov.uk/2020/06/16/good-clinical-practice-symposium-2020/>

²² Please see:

European Commission—

Regulation (EU) No 910/2014 of the European Parliament and of the Council of 23 July 2014 on electronic identification and trust services for electronic transactions in the internal market and repealing Directive 1999/93/EC

https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv:OJ.L_.2014.257.01.0073.01.ENG

UK Law—Statutory Instruments 2016 No. 696 ELECTRONIC COMMUNICATIONS
The Electronic Identification and Trust Services for Electronic
Transactions Regulations 2016

https://www.legislation.gov.uk/uksi/2016/696/pdfs/uksi_20160696_en.pdf

Medicines & Healthcare products Regulatory Agency (MHRA)
'GXP' Data Integrity Guidance and Definitions

https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf

²³ Joint statement on seeking consent by electronic methods (September 2018)
(This Joint Statement on Seeking Consent by Electronic Methods (September 2018) outlines the expectations for conducting both site-based as well as remote electronic informed consent which should be the basis for eConsent in DCTs)

<https://www.hra.nhs.uk/documents/1588/hra-mhra-econsent-statement-sept-18.pdf>

²⁴ Please see the following documents:

EMA Reflection paper on expectations for electronic source data and data transcribed to electronic data collection tools in clinical trials

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/reflection-paper-expectations-electronic-source-data-data-transcribed-electronic-data-collection_en.pdf

EMA Notice to sponsors on validation and qualification of computerised systems used in clinical trials

https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/notice-sponsors-validation-qualification-computerised-systems-used-clinical-trials_en.pdf

Please also see recent updates to EMA GCP Q&As, 'GCP Matters' numbers 8 and 9

<https://www.ema.europa.eu/en/human-regulatory/research-development/compliance/good-clinical-practice/qa-good-clinical-practice-gcp>

²⁵ INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE GENERAL CONSIDERATIONS FOR CLINICAL STUDIES E8(R1)

https://database.ich.org/sites/default/files/E8-R1_EWG_Draft_Guideline.pdf

²⁶ Final Concept Paper -- ICH E6(R3): Guideline for Good Clinical Practice

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²⁷ NHS health Research Authority

Clinical Trials of Investigational Medicinal Products (CTIMPS)

<https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/clinical-trials-investigational-medicinal-products-ctimps/>

²⁸ Joint statement on seeking consent by electronic methods
September 2018

<https://www.hra.nhs.uk/documents/1588/hra-mhra-econsent-statement-sept-18.pdf>

²⁹ Please see EMA guidance: Guideline on the content, management and archiving of the
clinical trial master file (paper and/or electronic), Dec 2018

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-archiving-clinical-trial-master-file-paper/electronic_en.pdf