DCT POSITION PAPER

Decentralized Clinical Trials (DCT) – A Landscape Assessment with Recommendations for Growing the Ecosystem by Indian Society for Clinical Research (ISCR) 2022

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This position paper was written by the ISCR DCT Working Group (2022) and comprises of Accredited Member Organization Representatives and Lifetime Members of ISCR.

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ABOUT ISCR:

The Indian Society for Clinical Research (ISCR) is an association of Indian clinical research professionals registered under the Societies Registration Act (1860) in India. The Society brings together all those who are engaged in clinical research activities in India and provides a forum for the exchange of information and learning. ISCR aims to build awareness of clinical research as a specialty in India and to facilitate its growth in the country while helping to evolve the highest standards of quality and ethics.

ABOUT ISCR's DCT WORKING GROUP (2022):

The ISCR DCT Working Group (2022) is an independent group formed under the leadership of the executive committee of ISCR to evaluate the current state, challenges, benefits and opportunities for the conduct of decentralized clinical trials (DCT) in India. The working group aims to evaluate areas and issues pertaining to the implementation of the decentralized clinical trial capabilities and to provide perspectives and recommendations for successful implementation of DCT capabilities in India, for consideration by all stakeholders in the clinical research industry. This Working group has representation from sponsors, contract research organizations (CROs), technology service providers (both clinical research and healthcare), academia, and investigators and with invited outreach opportunities with Indian Regulatory agency.

CONFIDENTIALITY STATEMENT:

The information presented in this position paper draws upon the combined current understanding and knowledge of ISCR DCT Working Group and is provided as an aid to evaluate the decentralization capabilities for clinical trial conduct in India. The opinions of the author(s), ISCR, and the DCT Working Group do not necessarily reflect the position of individuals or organizations (academia/industry). Users should assess the contents and opinions in the light of their own knowledge, needs, and experience as well as interpretation of relevant guidance and regulations.

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

The concept of implementing patient-centric components in clinical trial conduct is described as Decentralized Clinical Trials (DCT), or decentralized studies. Similar to the swift adoption of the virtual approach for providing continued clinical care for patients during the COVID-19 pandemic, the need for adapting clinical trial processes more to the preferences of participants rather than sponsors or study sites has gained renewed traction and focus. Pharmaceutical and allied organizations in sync with major regulatory agencies have rapidly mobilized to preserve trial participant's care and trial data integrity by the implementation of capabilities and "decentralized elements" such as telemedicine, sensory-based technologies, wearable medical devices, home nursing visits, patient-driven virtual healthcare interfaces, and direct delivery of study drugs and study related materials to participants' homes.

The objective of ISCR in undertaking this DCT initiative was to review the current state of DCT capabilities in India, provide clarity on the awareness, assess challenges, benefits and opportunities for DCTs in India through this position paper. The position paper intends to serve as a tool to build an ecosystem that can support decentralized elements in the clinical trial conduct at all levels of stakeholders in India viz. regulatory agency, pharmaceutical and research organizations, study investigators, ethics committees, and study participants. The DCT Working Group highlights the need for regulations/guidance on DCT within the ambit of the existing regulations/guidance pertaining to clinical trials/medical care. This would address various aspects concerning all the stakeholders in the clinical research industry, for a successful implementation of DCT capabilities in India.

Elements of DCT in study designs should address patient-centric data capture and analysis, additional support and monitoring system for the participant, investigator and sponsor including use of home nursing in clinical trials (HNCT) and telemedicine. India's existing telemedicine guidance can have additional clauses encompassing its use in the clinical trial setting [Telemedicine Practice Guidelines 2020]. Clarity can be provided within the existing Information Technology (IT)/Digital Health Rules (2018) regarding the use of digital and social media for participant recruitment, alongside addressing ethical concerns and India-specific nuances. It is recommended to extend the use of electronic signatures (e-signatures) and electronic consenting (e-consent) as part of the trial conduct under the existing IT/Digital Health regulations. Industry stakeholders should endeavor to set up standards for use of outsourced healthcare vendors, direct-to-participant supplies, remote data and safety monitoring, and participants' feedback mechanisms should be established. Industry with other stakeholders should set up robust mechanisms to allow remote source data verification (remote monitoring or source data verification). Sharing of health/medical records available electronically and source documents electronically without divulging participant's privacy and confidentiality would be a key factor in furthering DCT conduct. Use of electronic clinical outcome assessment (eCOA) devices and integration of electronic health/medical records for allowing electronic reporting of trial participant assessments will lead to faster and robust patient data reporting in clinical

trials. The ecosystem for HNCT and its related elements needs to be strengthened by collaborating with NABH/QCI to bring in standards for these services. Stakeholders need to be sensitized for the use of advanced digital technology for data collection, transmission, and storage; thus, addressing data security, data privacy and data integrity for DCTs. Industry stakeholders should implement within DCT the extent of data sharing and access in line with existing IT policies in the country along with regular audit considerations. Awareness and training requirements for various elements of DCT at all stakeholder levels is required on an ongoing basis so that best practices can be implemented. Involvement of patient-centric groups viz. patient groups/forums, patient advisory and advocacy groups to promote trial participant's awareness and gain insights into their choices and feedback, would be critical to the success of these DCT elements.

A significant benefit that DCT capabilities ushers is the ease and flexibility for trial participant. The major challenges include integrating DCT into existing regulations governing IT / Medical care, finding the right balance between decentralization and traditional approaches, participant's accessibility and understanding of technology and availability of stable internet connectivity. The need to increase technical literacy when compared to the rising digital penetration in the country is a matter of concern for all stakeholders. Challenges around regulatory, legal, privacy, and data confidentiality and integrity aspects will also need to be considered. Considering a hybrid approach in these trials while dedicated helpdesks support participants for better technological understanding at all levels via trainings is important.

This DCT initiative is an attempt of the ISCR working group to collaborate with all stakeholders to build an ecosystem for implementing these capabilities in India. The DCT Working Group intends to sensitize different stakeholders regarding the concepts of DCTs and aims to dispel any misconception around these capabilities. The position paper and the subsequent advocacy by ISCR in collaboration with other stakeholder organizations in clinical research in India will aim to bring in regulations that is fit for purpose to ensure appropriate oversight and similar standards of ethics, data quality and participant protection are available in DCTs as is currently present in the setting of traditional clinical trials. The key positive aspects backing this attempt are evolving regulatory understanding, acceptance and direction; progress towards technological maturity; investment and capability development; and most importantly, continued focus on patient-centricity.

1 INTRODUCTION

1.1 Rationale for the DCT Initiative by ISCR

Clinical trials are inevitable in the pursuit of developing new safe and effective medicinal products for improving patient health across the globe. Traditionally, the conduct of clinical trials has been centered around physical trial sites and study Investigators while trial participants travel to the sites. This has a significant impact on the cost and effort for the study conduct, while also bringing in inefficiencies in certain elements of the process that involves trial participants to travel for study visits, impacting their recruitment and retention [Fogel 2018]. The duration and number of clinic visits have been a known factor to impact protocol adherence; about 30% of trial participant dropouts have been reported across clinical trials [Levitan 2017]. In a survey by the Center for Information and Study on Clinical Research Participation (CISCRP), about 60% or more respondents reported a lack of patients' awareness and their location and distance from study sites as major barriers to patients' participation in clinical studies [CISCRP 2017]. Moreover, the need for being in the same geography in a conventional clinical trial narrows down eligibility criteria for patient participation, and thus, the clinical trials may not fully reflect a broad patient population for which the investigational medicinal product is intended raising concerns of poor diversity, equality & inclusion in clinical trials. This implies that real-world patients who receive specific therapeutic intervention would be generally more diverse in terms of race, ethnicity, the severity of disease and comorbidities when compared to the corresponding pool of clinical trial patients [Hill 2008, Blumenthal 2017, Heneghan 2017]. This points towards a missing link between clinical research and clinical practice.

Globally, the pharmaceutical fraternity had already recognized a need for transformational changes in the way clinical trials have to be conducted, so as to address the traditional conduct challenges as well as safeguard trial participants' interests. This challenge was heightened during the COVID-19 pandemic which disrupted the conduct of most ongoing clinical trials overnight, delaying the evaluation and release of potentially beneficial medicinal products. The total number of clinical study initiations monthly declined by 50% from January 2020 to April 2020, and 60% of investigators reported a significant reduction in trial activities in May 2020 [Xue 2020]. The COVID-19 pandemic restricted travel and reduced patients' access to clinical trial sites by almost 80% [Medidata Perspective 2020, Agarwal 2021]. With minimal options at disposal, the pandemic has offered an opportunity to redefine the way trials could be conducted, keeping trial participants at the core. Aspects like swift adoption of the virtual approach for providing continued clinical care for patients while maintaining physical or social distancing between patients and doctors, the need for adapting clinical trial processes more to the preferences of participants rather than sponsors or study sites gained focus. Pharmaceutical organizations across the globe have rapidly mobilized to preserve the continuity of care and data integrity by adopting remote consent and trial participant monitoring, assessments through videoconferencing, and at-home phlebotomy [Agarwal 2020].

The two major regulators globally – the European Medicines Agency (EMA) and the US Food and Drug Administration (US FDA) – first implemented measures and guidance to enable trial continuity during the pandemic [EMA 2020, US FDA 2021]. Elements of home visits for laboratory tests and drug infusions, direct shipment of study supplies to trial participants, telephonic follow-up for safety monitoring, remote data and trial participant monitoring, online assessment for patient-related outcomes etc. were measures implemented so as to mitigate the risk of skipped doses, missing data, dropouts or early study discontinuations. Rapid implementation of technology and "virtual elements" such as telemedicine, sensory-based technologies, wearable medical devices, home visits, patient-driven virtual healthcare interfaces, and direct delivery of study drugs and materials to participants' homes has grown multi-fold in parallel with acceptance of "virtual medicine," accelerating shifts in clinical trial design that was long overdue [Van Norman 2021]. The concept of implementing such virtual components in the clinical trial conduct is described by various terms like decentralized clinical trials (DCT), direct-to-participant studies, and virtual studies [Dorsey 2020].

Today, the focus of trial activities and conduct has shifted from conventional research-site setup to being more "patient-centric" using technology at its best. Clinical trials now revolve around the participants in their homes and community through remote visits and monitoring through decentralization which facilitates continuity of trial operations [Van Norman 2021]. Additionally, decentralization also enables efficiency at other levels of study conduct – trial investigators' time and effort, drug administrations, patient-reported assessments, and data reporting, which can be performed remotely by study participants themselves [Agarwal 2021]. Implementing DCTs facilitate remote conduct of trial activities through home visits, remote consent and trial participant monitoring, video-conference assessments, at-home nursing, home sample collections, telemedicine consult, direct data capture through wearable devices, and electronic diaries [Ramasamy 2020, Agarwal 2021]. The ease of remote participation will positively impact the retention rate expected during clinical trials. In a fully DCT set-up, participant recruitment, delivery and administration of study medication, and acquisition of trial outcomes data can all proceed without involving in-person contact between the study team and the study participant. Home healthcare has been accepted widely in the commercial (licensed) medicines and general healthcare space throughout the Asia-Pacific region, and the inclusion of this concept in clinical trials was already widely accepted in the USA and Europe. As India also gears up to implement and conduct DCTs, pertinent regulations will be key to the greater implementation and use of decentralization in trial activities in the Indian clinical research ecosystem, which currently is lacking. As the pandemic accelerated the adoption of decentralized and hybrid clinical trials, there is strong reason for the Indian regulatory authorities to evaluate the need for new guidance which can make DCTs possible and implementable, while ensuring participant safety and trial transparency. This will also support extending the reach of clinical trials to the tier 2 and tier 3 cities of India, which otherwise are sparsely represented, or generally not accessible. In turn, this can become a mitigation strategy ensuring the smooth functioning of clinical research while addressing challenges associated with in-person

site visits, compliance to study standards, travel restrictions for trial participants and investigators, and concerns about COVID-19 exposure, among many others.

1.2 Objective of the DCT Initiative

The objective of ISCR in undertaking this DCT position paper was to review the landscape of DCT, its current understanding and awareness among the different stakeholders of clinical research in India.

ISCR intends to use this position paper as a tool to drive conversations and build an ecosystem that can support decentralized clinical trial conduct at all levels of stakeholders in India viz. regulatory bodies, pharmaceutical and research organizations, study investigators, ethics committees, and trial participants.

1.3 Purpose of the Position Paper

This position paper intends to provide clarity on the current state, challenges, benefits and opportunities for DCT in India.

The position paper also includes recommendations for successful and effective implementation of DCT capabilities in India, for consideration by all stakeholders in the clinical research ecosystem.

1.4 Development of the Position Paper

The executive committee of ISCR conceptualized and kick-started the DCT initiative in August 2021. Some of the traditional components of clinical trial conduct which were considered appropriate for a decentralized capability building were identified namely – *patients' perspectives; telemedicine; patient recruitment through digital and social media; electronic consent and electronic signature; direct-to-patient medicinal products; remote data and trial monitoring; e-clinical assessments; remote data capture through the use of wearables and digital biomarkers; home health care; and data security, privacy and ethical considerations*.

Ten workstreams were created and allocated with one capability topic under the stewardship of the executive committee members of the ISCR. Workstream participation was open to all member organizations of ISCR and nominations of individuals who were ISCR life-members was sought based on their domain knowledge, work experience and relevance of contribution to the workstream. Academic institutions, ethics committees as well as the regulatory agency were also approached for participation or inputs, as needed. Workstream members' details are included as part of the ISCR DCT Working Group 2022, refer to Section 5.

Individual workstreams were launched in August 2021 and worked towards creating a status report for the assigned capability topics over 3 – 4 months. Periodic meetings for deliberations and a central repository for collating inputs and recommendations within workstream members were implemented. Surveys with clinical trial sites and Investigators, and/or Ethics Committees were also initiated as relevant by some workstreams.

The workstreams considered the following areas/issues/perspectives on the assigned capability topic:

- Mapping of the current landscape on the virtual component for the capability considered.
- Current regulatory approach/environment.
- India-specific legal framework and challenges, if any.
- Anticipated solutions available globally versus India.
- Key technology-related challenges in implementing the virtual capability.
- Any ethics committee related challenge relevant from the Indian perspective.
- Challenges and adaptations anticipated at the investigator/site level (e.g. capacity, understanding, execution).
- Current role of institutions/pharmaceutical companies/CROs.
- Probable recommendations for successful implementation.

The individual workstream reports were provided to the Executive Committee of ISCR in December 2021. The reports were cumulatively analyzed to create this position statement for presenting the current status of DCTs in India and practical recommendations for implementation of the virtual elements in the trial conduct.

The executive committee of ISCR and the DCT Working Group also acknowledges that the topics currently covered under this position paper may not represent an exhaustive coverage of all DCT elements.

With advances in the DCTs globally, and expansion of our understanding and experience with the implementation of DCT as a research community in India, these existing topics and recommendations will be revisited and refined, and new elements will be addressed as part of the next versions of this position paper.

Additionally, following this position paper, ISCR also aims to publish full reports of the individual workstreams so as to provide complete details of assigned capability topic and present their groundwork to holistically conceptualize and implement DCTs in the Indian scenario.

2 ELEMENTS OF DECENTRALIZATION IN CLINICAL TRIAL CONDUCT

The pandemic has witnessed patient and the health caregiver behaviour adapt to digitization of most of their interactions using technologies that are well supported by high standards of security, encryption, and privacy compliance. Clinical research, being a subset of the healthcare domain, has also been impacted by these changes, leading to widespread use of e-consent, electronic case report forms (e-CRFs) and electronic patient-reported outcomes (e-PROs) being used for assessments of participants in trials, as appropriate. Parallel growth was also seen in the adoption of wireless and bluetooth-enabled devices or wearables to capture and transmit data to e-CRFs or e-patient diaries. Since the data is captured remotely and stored in centralized and secure e-repositories, accessibility of near-real-time data has become easier rendering unnecessary the need for clinical research personnel to travel to sites to monitor data. A host of methods like remote source data verification (rSDV), electronic trial master files (e-TMF) and the like are used to verify the data using various security layers, technology platforms and data analytics tools, making remote monitoring efficient and productive. It has also additionally enabled monitoring the performance and mitigating risks identified earlier, allowing them to be resolved earlier than traditional physical site visits by monitors.

All these technologies and changes have also led to newer initiatives like patient forums, patient advocacy groups, social media forums etc. to be more visible and discuss research access and participation much more than before. The above changes have made it obvious that the hitherto legacy model of healthcare that was doctor-centred has moved to becoming patient-centric. Patient-centricity has now become the hot-topic of the healthcare industry and has forayed into the rest of the support services to completely decentralize the healthcare model from a hospital towards home. Similarly, the clinical research industry has been influenced to change the model from an investigator/site-centric to decentralized model where various services are now provided to patients for their convenience, making trial participation experience more seamless and transparent than in the recent past.

As part of this initiative, the ISCR workstreams have dwelled in greater detail and depths as to how such changes helped clinical projects become decentralized and patient-centric during the pandemic. A systematic analysis under each capability is considered and consolidated for presentation in the different sections. Later this year, the ISCR workstreams intend to publish their individual detailed reports describing the researched elements of corresponding DCT capability.

2.1 The Patient's Perspective in DCT

In recent times, driven majorly by the COVID-19 pandemic in India, there has been a heightened emphasis on the use of digital health solutions centred on serving patient care remotely. This has signalled that the time is ripe to change the *status quo* of the clinical trial operational models the world over, and India is no exception. This disruptive thinking which began between 2008-2010, took roots and accelerated

during the pandemic to become the alternative model called DCT, which was also rightly termed as “Patient-centric trials”.

Though not all disease conditions or study designs are DCT-friendly, there are several that can use decentralization design by being either completely or partially virtual in a hybrid model. Employing digital capabilities like telemedicine and mobile health care can offer several potential advantages such as faster recruitment, improved retention, greater control and convenience for participants, enhanced communication between the trial participants and health care providers, and increased participant diversity, equality, inclusiveness, and transparency. Current trends in India also seem to be moving in this direction with over 25 studies registered under the Indian Council of Medical Research (ICMR)-owned Clinical Trials Registry of India (CTRI) database demonstrating decentralized or patient-centric approaches embedded in their designs. A recent public health “Barefoot Nurse” initiative of PHFI® [Sahu 2020] also showed that mobile health care (m-health) can be easily adapted to reach the hitherto unreachable population and geographical areas, thus employing and developing mobile primary healthcare skills at the grassroots, giving health and economy a much-needed growth in smaller-tier towns and decreasing the burden on the current health infrastructure that is concentrated in Tier-1 cities. This is a perfect match for bringing the two models, DCT and public mobile healthcare together to make the patient-centricity model be as effective as the traditional clinical trial model that was hitherto investigator/site-centric.

Clinical Trials Transformative Initiative’s (CTTI’s®) evidence-based and practical recommendations have been addressing barriers to DCTs in various country regulations, that include varying state medical licensing laws and issues with the drug supply chain custody hindering the widespread adoption of DCTs [CTTI 2018]. This helps identify burden/impact and formulate steps to help improve the patient experience and make current and future studies less burdensome. Together, these tools will provide patient insights and experiences of their participation.

More recently, the US FDA [Patient-Focused Drug Development, FDA, 2018], as well as the EMA [ICH reflection paper, 2021], have drafted regulatory guidelines for assisting the industry in the patient-centric approach. This guidance helps in recognizing DCTs as a better approach towards finding patient-friendly treatments by gathering patient usage and feedback data alongside scientific and clinical data points. These guidelines encourage DCT study designs to use standard treatment algorithms and modalities, and also include patient perceptions and feedback on how they eventually rate a product, early in the development cycle, thus paving a way for its future in the market.

The emphasis of these guidance is to provide the clinician with an alternative perspective and bring in further patient-oriented approach. Patient insights and discussions with patient-centric groups (patient groups/forums, patient advisory and advocacy groups) are especially relevant during the design phase, should be initiated early. These groups can partner with the sponsor study team to discuss clinical outcome expectations, patient-reported outcomes (ePRO), medication issues, travel

and logistics, build recruitment materials, facilitate site identification, diagnostics/laboratory facilities, participate in investigator meeting panels, and advise on wearables if necessary. Hence, the investigator-site operations model will also need to change to meet these changing logistics and operational aspects of study implementation.

Eventually, a truly patient-centric trial is about creating a personalized experience for every patient, from first contact through the end of the trial and future follow-up. It requires a fundamental shift in thinking about patients' role in clinical research and how sponsors can use existing data and technology to engage with them as active stakeholders whose needs and opinions are relevant to every touchpoint in the research journey [Bacheller 2021].

In the Indian scenario, the evolutionary journey from traditional clinical trial models to DCT will be possible with regulatory guidelines being laid down early and revised as the area develops from what was traditionally done with paper trials to e-trials. Elaborating the details and considering some local issues, e.g. regional, language, literacy infrastructure and reliability of medical care standards will help in not only improving the health care availability in the more remote areas but also provide more diverse, real-world evidence and feedback from the end-users With the internet and telecommunication becoming more widely available and improvement in reliability, and with transport infrastructure improvements, it would be possible to address the hurdles which hitherto were considered insurmountable.

Below are a few recommendations for patient-centric approach that will bring more transparency and benefit to the trial participants as the end-users of the fruits of research, and thus benefit the overall healthcare infrastructure by improving healthcare standards and expediting the spread of healthcare facilities to remote areas of the country.

A DCT guidance from regulatory authorities that:

- allows sites and investigators to use outsourced healthcare vendors that meet a minimum set of standards (accreditations/certifications) so that healthcare facilities that help remote participants do not compromise on the clinical monitoring, safety or efficacy of the drug products, participant privacy and confidentiality;
- includes DCT study design as one of the study methods in the Clinical Trial Registry database (CTRI), so as to differentiate it from the traditional and non-DCT models.

2.2 Telemedicine in Decentralization of Clinical Trials

Telemedicine has been available and used in healthcare practices for several years. However, its use to communicate with and monitor study participants enrolled in clinical trials has not been actively considered until recently. The COVID-19 pandemic has brought telemedicine to the forefront in clinical practice for communication and management of patients in various settings globally as well as in India [Telemedicine Practice Guidelines 2020], and its further use in clinical trial settings is also being

explored. Although there are several definitions of "telemedicine", the broadest one is a practice of interacting with the health care professional virtually from any location using a phone or video chat. It also includes services such as store-and-forward of images and reports while the consultation is completed via a telecommunication system. Telemedicine may offer several advantages leading to faster and more efficient conduct, and completion of a clinical trial [European Pharmaceutical Review 2018, Reites 2020, SignantHealth 2022].

Telemedicine can be used for accelerating capabilities of drug development including communication with patients who may be located at a distance. Telemedicine can enable patients to participate in clinical trials without a hospital site visit, or visit less frequently (in conditions managed in out-patient setting), provided patients have access to mobile and video communications with their clinician-investigator and research staff. This could enable patients with specific health conditions to participate in clinical trials regardless of their geographic location, and the clinician whom they seek advice from can become an integral part of a clinical trial. This can enhance clinical trial participation from different communities, those having limited transportation facilities or use, or limited access to health care facility/hospitals where clinical trials are conducted.

Telemedicine can enhance and broaden associations, collaborations, and partnerships among physician groups, medical associations, and patient advocacy and support organizations. These associations can help with more options for potential clinical trial participants, thereby overcoming otherwise existing barriers of location. This can lead to the enrollment of a diverse patient pool in clinical trials that enroll participants with specific health conditions (contribute to diversity, equity and inclusion initiatives as discussed *vide supra*).

Telemedicine also contributes to passive and longitudinal reporting which requires minimal or no effort to remember, document, or transmit data by the patient and the service provider. This will possibly reduce the number of patient visits, reduce staff time and numbers, and make data available much faster for decision-making. Patients can report safety-related information in real-time, along with the quality-of-life parameters.

The use of artificial intelligence as an integral part of telemedicine will aid in improving outcome measurements in a clinical trial setting and enable more direct participant reporting [Bookbinder 2017].

With the anticipated benefits, telemedicine does offer few challenges concerning all stakeholders, an important one being technology usage. Regulatory and legal challenges and issues around privacy and data confidentiality aspects will also need to be considered. The technology and data or platforms used to collect information would need to meet regulatory, legal and data privacy requirements i.e. acceptable and credible, access to records for an audit or inspection amongst others. From the participants' viewpoint, it needs to ensure privacy and confidentiality so as not to reveal information or data to non-intended recipients. Preventing the inadvertent or

purposeful misuse of telemedicine tools by non-trial members would also be a concern to address.

Overall, including telemedicine within the DCT framework would be an appropriate consideration to be made. It offers immense potential, especially for trials managed in less critical or out-patient settings. It aids patient convenience and participation regardless of the proximity to the hospitals. An enabling regulatory framework for use of telemedicine in clinical research will help decentralized trials to be implemented.

2.3 Patient Recruitment Through Digital and Social Media

Digital media is a form of communication that operates using various encoded machine-readable data formats and is broadcasted through a screen and/or a speaker [Smith 2013]. Social media (a form of digital media) is an interactive technology that allows the creation or exchange of information, ideas via virtual communities and networks [Kietzmann 2011, Preston 2022].

Considering about 40% of the clinical trial budget is allocated for patient recruitment, any delays in recruitment directly impact the increase in drug development costs. Conventional patient recruitment methodologies have resulted in delays in patient recruitments at 35% of investigator sites, and in about > 80% of clinical trials not meeting enrollment deadlines [Fassbender 2019]. Digital or social media may assist in increasing recruitment, and decreasing the cost incurred in patient recruitment in more than one way – by increasing the ability to reach a diverse and broad audience and facilitating better patient engagement and empowerment, as well as data capture.

Leveraging the capacities of digital or social media in a DCT for patient recruitment will, however, need to overcome some challenges – technological, regulatory, patient-related and ethical review boards. A patient-centric approach will be required in implementing the technology to enhance available recruitment methods and tools [Parkins 2021]. Making patients aware of the clinical trial in general, their rights and responsibilities during their recruitment process via digital/social media and engaging with patient advisory groups during the process of recruitment would be of utmost importance and help. The impact of social media usage patterns, language limitations, and the literacy rate of participants would also need to be considered. Regulatory concerns that need to be addressed while using digital or social media for DCTs include Privacy concerns - Relevant audience – Authentication - Mode of Dissemination (P.R.A.M). Operationally, the institutional review boards (IRBs) or ethics committees (ECs) generally tend to have a close watch while approving participants recruitment strategies through digital or social media. These may include but are not limited to: content or wording of the advertisement sent via social media; consent process; and whether the privacy and confidentiality of the participants' personal information is safeguarded enough or not.

Key points to be implemented for overcoming the challenges and effectively using digital or social media for patient recruitment are suggested below:

- Acknowledging and addressing India-specific nuances i.e. cultural, language, literacy rates, while recruiting patients via digital or social media.

- Involvement of patient support groups and/or investigators during the recruitment process.
- Engage and advocate through ICMR the need to disseminate information about clinical trials in public, possibly through the CTRI.

2.4 Electronic Signatures (ES) and Electronic Consent (e-Consent)

To have minimal disruption of clinical trial activities during the COVID-19 pandemic induced lockdowns and restricted movements, two critical processes evolved viz. the signature of documents for submissions to regulators, investigators sites, ECs, etc., and the informed consent process documentation. The focus is to ensure the safety and privacy of the clinical trial participants and the team members, and for maintaining the data integrity of the clinical trials. The traditional wet-ink signature on documents was replaced in India by electronic signatures (e-signatures/digital signatures). The regulators and the ECs started accepting documents submitted to them electronically with digital signatures. Important considerations for implementing e-signatures and e-consents as part of the decentralization of clinical trials are being discussed here.

E-signatures are already used in India and are governed by The Information Technology Act (ITA), 2000. The electronic signature is recognized if it is reliable, and authentication is done by e-KYC [ITA 2000]. However, e-signatures are vulnerable to potential technical challenges. They could be easily tampered with and cannot be verified unless known to the authorizer or done in front of the approver. E-signatures are unlike digital signatures which are more secure, validated, highly verified, and encrypted.

In order to mitigate these challenges for e-signatures the data entered or already fed should be encrypted and must be used only for and by the potential study participants. The e-signatures must be traceable and validated, the sponsor and the investigator must be able to prove the authenticity of the electronic signature. The e-signature tool used must be compliant with the applicable laws as per our (IT) requirement for e-signature and potential participant/guardian/signatory must have a KYC document to confirm their identity.

E-Consent: E-Informed Consent is an electronic medium of informed consent process used to provide information in the informed consent document, evaluate participant's comprehension and document consent from participant or participant's legally acceptable representative (LAR). There is an increasing interest seen in the research community to use electronic media to supplement or replace paper-based informed consent processes; participant/LAR consent and assent can be collected using electronic platform (guidance document for industry FDA,2016; Belgium, 2020; HSA, 2020, ICMR, 2020; MHRA, 2018). Though the e-source has been supported and adopted by the FDA, EMA and MHRA (UK) in clinical trials at various levels [Thread 2021], there is still a reluctance to adopt and implement e-consent among regulators, ECs, sponsors and investigators due to complications in usage of new or different technologies without denying the inclusion the time and cost factors. Adopting e-consents can bring several benefits [EUCROF 2021]; most common being improved

participant experience, efficiencies through digitization, improved patient retention, reduced regulatory risk and audit findings, and lowered site burden.

The workstream also conducted a brief survey amongst investigational sites pan India to understand the challenges that study sites would face if e-consent is implemented. The study sites expressed positively towards adaptations of e-consents but also evinced concerns related to lack of regulations, lack of technologically savvy site staff, and participants from remote places with limited internet connectivity, electricity outages, etc., and risk of a breach in confidential information and issues with data integrity. Training all stakeholders involved would be key to mitigating these risks.

Overall, the major challenge in the implementation of e-consent is the fact that the regulations related to e-Consent procedures are still very country-specific with the absence of any global consolidated stand. Only a handful of countries have taken an official stand on the use of e-consent in clinical research [guidance document for industry FDA,2016; Belgium,2020; HSA, 2020, MHRA, 2018]. There is no clear guidance on the use of electronic consent in clinical trials in India; regulations in India do not as yet address the concept of remote or e-consenting. Though there have been discrete instances of sponsors implementing the e-consent process, which were approved by the regulators and the respective sites' ECs in India, it was an add-on to the paper consent required by the existing laws. Clear guidance on the use of electronic consent in clinical trials from the Indian regulators will help implement this element of DCT by the investigator, sponsors, ethics committee, as well as participants.

Below are key points to be considered for facilitating e-consenting and allowing e-signatures in the clinical trial conduct:

- Print to Sign, where a conventional method of consenting to be used but with the content published electronically which could be printed by the participant (including LAR/impartial witness) for wet-ink signatures, could be the first step to bring all stakeholders on board and help them understand the possibility to explore more on this front like the complete electronic version of the consent form and e-signatures.
- The processes and devices used for e-signatures and e-consents should be compliant with regulations.
- Augment the regulations to validate the e-consent and e-signature procedures for clinical trials, for participant's safety and well-being and to maintain data integrity.

2.5 Direct-to-Patient – Medicinal Product

Direct-to-patient (DtP) supplies is an integrated supply chain system that makes investigational products and other clinical trial ancillary supplies delivered directly to participant's home. This includes dispensing, transportation and storage of therapeutic product in-home and return of investigational product and other supplies. The process of delivering clinical trial supplies directly to the patient had begun over a decade ago in cases of orphan or rare disease therapies possibly due to the patient's difficulty in

visiting the hospital or clinical sites frequently. During the COVID-19 pandemic where the participants had restricted access to the trial sites, this process helped to bring in healthcare and study treatments directly to the participant's home. It eased the burden on the participant to access the trial sites and thus enhanced participation and retention of participants in clinical trials even during the pandemic [Spillett 2018].

Seamless DtP is the key to the implementation of patient-centric DCTs. This includes management of supply chain logistics, participant engagement and education, adherence, trial data collection, oversight and regulatory compliance in the implementation of DtP. While some regulatory agencies provided a broad framework for implementation of DtP during the pandemic [FDA guidelines, EMA guideline in COVID pandemic], there is no concrete framework available for implementation of DtP beyond the pandemic, particularly in India. The workstream conducted a survey to understand the outlook and perspectives of various stakeholders on DtP in India; respondents included sponsor organizations, contract research organizations, pharmaceutical logistics companies, clinical site staff, investigators and EC representatives. The survey was designed to address all aspects critical for the implementation of DtP namely investigational product compliance; appropriateness of clinical trial supplies (CTS) for home administration and storage; participant's confidentiality; chain of custody including traceability; training of site staff and trial participants; CTS return, accountability; the role of regulatory agencies and ECs; vendors dealing with CTS supply chain logistics; role of sponsor in monitoring and oversight of DtP; and role of technology in investigational product (IP) tracking, IP shipment, IP accountability, administration and compliance.

The survey results were largely suggestive of benefits of DtP for all stakeholders involved in clinical trials. The responses were suggestive of most perceived benefits for clinical trial participants as DtP reduced their travel time to the sites and implied cost implications. This also reduced the number of visits thereby improving participant compliance and adherence to the trial; indirectly benefitting the sites and sponsor for the successful completion of the trial. The survey results also indicated that strategic planning is critical for the successful implementation of DtP in clinical trials. Major challenges anticipated include regulatory hurdles, logistics, IP accountability and IP compliance. Suggested solutions that can proactively identify the potential hurdles and would help in addressing these challenges effectively bearing in mind the rights, well-being and safety of the trial participants include:

- Engage and work with existing logistics/transportation partners (multi-regional/local) to have active presence across India so as to enable more seamless and robust implementation of DtP in clinical trials.
- Early assessment of the suitability of DtP in a particular clinical trial, appropriate planning, early engagement with key stakeholders and technology partners to ensure smooth implementation of DtP.
- Engage with ICMR/FERCI/Other organizations in order to sensitize, educate and train ECs in understanding the different ethical facets in the implementation of DCT capabilities.
- Guidance for smooth conduct of trials using these novel DtP models.

2.6 Remote Data Monitoring and Remote Source Data Verification

The monitoring of the clinical trial conduct is a crucial aspect to ensure that study protocol and standard operating procedures are adhered to, and the clinical data is collected per good clinical practice and regulatory requirements. By definition, source data verification (SDV) is the process of ensuring that the data reported for statistical analyses accurately reflect the source data at the clinical trial site by comparing data entered in case report form (CRF) against the patient records referred to as source data and source documents. The process of SDV ensures data accuracy by detecting errors if any, that are to likely have an impact on the results of clinical trials. Source data review (SDR) is the review of source documents in relation to the clinical conduct of the protocol and focuses on areas that may not have an associated data field in the CRF or a system [Medidata Blog 2021]. The process of performing the SDV and SDR remotely by gaining access to the source data electronically is referred to as remote monitoring.

The US FDA [2013] and EMA [2020], ICH-E6 R2 have provided guidance encouraging the use of remote monitoring and remote data verification methodologies when appropriate. The pandemic circumstances accelerated the use of remote monitoring and remote data verification to a large extent, which was otherwise slower in adoption during the pre-pandemic times. Increased adoption of remote monitoring and risk-based monitoring (RBM) in combination with onsite monitoring by the sponsor was seen due to the constraints the pandemic has posed. ***Remote Monitoring*** involves off-site evaluation performed by the monitor away from the site at which the clinical trial is being conducted. The process may involve a remote review of the source data from sites using technology platforms, depending on the available access to data. ***Risk-based monitoring*** is the process of ensuring the quality of clinical trials by identifying, assessing, monitoring and mitigating the risks that could affect the data integrity and participant protection during the conduct of a study. This can be done through centralized monitoring team and involves analytical evaluation carried out by sponsor personnel or representatives at a central location other than the site at which the clinical trial is being conducted. Remote monitoring and RBM have offered tremendous advantages during the pandemic for ensuring continuity in monitoring and reducing the costs/risks of travelling to the study sites. This also brings up key capability areas to focus on, in India, across the stakeholders' end viz. study sites, ECs, and regulators.

Implementing remote monitoring capabilities would need a substantial upgrade at the study site infrastructure and processes to manage most of the activities virtually. In India, given that electronic health records (EHRs) are rather rare, study centers would also need technology adoptions and shift to EHRs where possible which, in turn, will aid in better penetration of these methodologies.

Ethics Committees and regulators in India also need to develop mechanisms to oversee the conduct of DCTs with the same rigor as that is done for the conventional trials, keeping data privacy and patient safety at the core. The EMA and FDA's global regulatory guidelines consider the centralized monitoring and rSDV approaches as

acceptable monitoring methods during the COVID-19 pandemic crisis and experience during pandemic had certainly laid a foundation for usage of rSDV/SDR.

Upskilling for the investigators, research staff, and ECs on the technology and DCT trial nuances and providing standard reference to participants on DO's and DON'Ts or their rights and data privacy would be required. Regulatory guidance on the usage of remote SDV/remote monitoring should be implemented as acceptable monitoring methods. Sharing of electronic source documentation without divulging privacy and patient confidentiality should be permitted. The use of automated subject data review tools should be explored.

2.7 Electronic Clinical Outcome Assessments

Electronic clinical outcome assessment (eCOA) refers to measuring a patient's symptoms, overall mental state, or the effects of a disease or condition on how the patient functions [US FDA 2009]. eCOAs encompass electronic patient-reported outcomes (ePRO), Performance Outcomes (PerfO), Clinician Reported Outcomes (ClinRO) and Observer Reported Outcomes (ObsRO) [Guidance for Industry: PRO FDA.gov., 2022]. ePRO measurements directly come from the patients without amendment or interpretation of outcomes by a clinician or anyone else. An eCOA may support either direct or indirect evidence of treatment benefits and risks. The objective of eCOAs is to measure the clinical outcomes and improve the interpretation of study results. The ePRO Consortium was established in 2011 to advance the quality, practicality, and acceptability of electronic data capture in clinical trials for endpoint assessment [eCOA consortium, 2011]. The US FDA [Guidance for Industry: PRO FDA.gov., 2022], the EMA [EMA draft guideline computerized systems electronic data clinical trials. 2022], and the ICH Good Clinical Practice [ICH E6 R2 Addendum, 2018] supports the use of eCOAs as electronic data.

The sponsor can use various web-based solutions to receive and/or send files to clinical study sites. Many such solutions, document sharing platforms are available in the market ('Off-the-Shelf') which can be deployed in the study or sponsor can develop trial specific platforms for document sharing. Sponsor can give 'Study level' or 'Site level' accesses to adhere to US FDA Part 11 regulations. Once the Site/Study Team uploads the documents in the system, an alert is sent to clinical research associates (CRA), who can review the documents, raise queries on the documents after completing data verification with electronic data capture (EDC) information. Once the data review process is completed, the files uploaded will be deleted in timeframe that is mutually agreed between site, CRA and sponsor. Such data sharing and review systems help in remote data review in absence of availability of Electronic Medical Records systems.

eCOAs provide myriads of benefits over traditional paper-based measurement systems [Alper 2019]. Patients can complete eCOAs from their homes irrespective of geographical location increasing their willingness to participate, and thereby improving retention in the clinical trial. eCOAs save time and cost of logistics, and ultimately avoid disruptions in data collection during times like the COVID-19 pandemic. eCOA tools are password protected which creates a sense of confidentiality, and privacy when

trial participants enter sensitive information. eCOA/ePRO provides a real-time, continuous measurement of health status. An additional patient perspective of the effect on health and functioning enhances the quality of collected data. eCOA can transfer real-time data between the system/device, sponsor, and site which opens the lines of communication, and as a result, builds the patient's trust in both the study process and their care team. eCOAs create patient-centricity by sending reminders to the patients to complete their assessments. Skip patterns or branching the logic of questions presents shorter questionnaires giving personalized experience for the patients. The eCOAs may enable the development of better patient-centric endpoints and outcome measures.

The implementation of eCOA as part of DCTs requires consideration of regulatory requirements and patient perspectives. The eCOA tools need to meet the regulatory requirements of reliability, content and construct validity, and the ability to detect the change in the reported assessments. From the patient perspective, the challenge is to design patient-centric tools that suit their needs without any additional burden and ensuring the protection of privacy and confidentiality. The eCOA tools empower patients with access to everything they need as they progress through a clinical trial, including survey instruments, personalized reminders for visit schedule information, multimedia reference tools, as well as direct-from-site communications. Effective eCOAs are tailor-made to patient demographics, disease symptoms, treatment effects, and endpoints to be measured. They enable the collection of frequent and multidimensional data throughout the clinical trials.

In India, there are no regulations that differentiate between the medical-grade devices used in clinical trials and consumer devices. Current regulatory requirements mandate the same certifications for both devices. The import process of eCOAs regulatory requirements ought to be updated to improve and simplify the existing complex, time-consuming process. Intensive training of all the stakeholders (sponsor, ECs/ regulator/ investigators, and patients) is imperative to understand the eCOAs.

Operational challenges anticipated with eCOAs are access to smartphones and the internet for participants, availability of validated PROs in vernacular languages, and literacy of patients. However, the technical adaptation of the vernacular languages in user-friendly smartphone applications and user-friendly adaptation to accommodate illiterate patients can be perceived as developmental opportunities. Additionally, a potential risk is sharing patients' sensitive health and personal information over the internet. Literacy, accessibility to devices, internet are determinants of eCOA application in clinical trials. These might exacerbate or create health inequities or disparities. The Indian landscape needs to evolve and embrace it to help faster trial conduct.

- To ease the importation requirements of eCOA devices, there should be an active collaboration between the industry and regulators.
- There is a huge "Make in India" opportunity in partnership with global players in supporting the global initiative of eCOA.
- Future opportunities of integration with HER and Electronic Medical Records for eCOA will open even more opportunities for faster clinical trial conduct.

2.8 Remote Data Capture, Wearables, and Digital Biomarkers

Remote data is data that is electronically transmitted from the clinical trial participant, from outside the clinical setting to a data repository [Seltzer 2022]. Such data may include laboratory data, safety data, or outcome measures reported by the participant, the clinician or the observer. The workstream conducted an online survey to assess the use of remote data capture in clinical trials being conducted during the COVID-19 pandemic. Responses were received from 80 respondents including clinical research stakeholders from across India. Respondents included stakeholders such as investigators, academicians, professionals working in clinical research, and regulatory authorities.

A total of 70.2% of the respondents had prior experience on remote data capture, wearables and digital biomarkers. Also, 67.3% of the survey participants reported that upto 25% of their trials were decentralized. 68.4% of the participants reported implementation of remote data capture into their clinical trials and 58.2%, into their observational studies. Overall, 59.3% of the participants have indicated wearables/devices as the commonest method used for remote data capture; of which wrist-worn wearables (18 [90%]) were the most used. Thirty-six of the respondents mentioned that the current regulatory guidance surrounding decentralized trials and data capture in India is unclear.

The Government of India has formulated IoT Policy structure for appropriate governance of IoT activities and its implementations [Govt of India, IoT Policy document, 2022]. The policy is yet to be finalized. Meanwhile, the existing framework for data protection in India includes the following [Saksena 2021]:

- Information Technology Act, 2000
- Personal Data Protection Bill, 2019
- National Digital Health Blueprint, NDHM Health Data Management Policy, NDHM strategy overview
- Report by the committee of experts on Non-Personal Data Governance Framework

When asked to rate ***the ease of use of existing medical devices/wearables*** by participants. Over 90% of the respondents found ***access to real-time data and insights as one of the key benefits*** of wearables and remote data capture technology. The participants also reported that it saved time and was convenient for the site staff, the patients), and for the sponsors. The key concerns regarding remote data capture and use of wearables as per the respondents were lack of standardization of data, data protection and data privacy and quality of data

Most participants were open to using remote data capture in the near future. When asked about the impact of adoption of DCTs in their technology requirements/current environment, the most frequent responses were “Must have the ability to integrate with other platforms”, “Must ensure compliance”, and “Must have the ability to reconcile inconsistent data formats”.

Overall, less than a quarter of all current studies in India have moved toward DCTs and remote data capture. Most clinical research stakeholders are still unaware of the regulatory guidelines and standards governing remote data capture. The government of India is drafting an IoT Policy that is likely to make things more standardized soon. The workstream's survey tried to identify the key concerns and difficulties faced by the stakeholders in capturing data remotely. Based on the results, it is recommended that we need to:

- create more awareness about remote data capture and its applicability in DCTs;
- discuss with the regulatory agency on need for creating India-specific guidance and standards; and adopt device agnostic technologies.

2.9 Home Health Care (Home Nursing in Clinical Trials)

The need to transition clinical trial conduct from the sites to participants in their homes and community through e-consent, remote data monitoring, telemedicine consults, and bringing the trial activities to the patient have been well-emphasized in sections above, be it, for drug administration, sample collection, or direct data capture through wearable devices, and electronic diaries [Schwamm 2014, Ramasamy 2020, Agarwal 2021]. The positive impact of this shift on recruitment rates, improved compliance and participant retention, fewer protocol deviations, and lesser delays or missed visits [Khozin 2019, Van Normal 2021].

Facilitating home health care is, however, a challenge in the Indian scenario where access to healthcare is already limited in smaller towns and villages. Besides this, home nursing services need resources that are trained to deliver trial activities according to set protocols while maintaining participant confidentiality. These and several other factors may limit the implementation of home nursing in clinical trials (HNCT) in India. The workstream conducted semi-structured qualitative interviews with experts from diverse domains involved in clinical trial conduct such as researchers from academia and industry, clinicians, investigators, nursing staff, patient research advocates, EC/IRB members, legal, patients, and trial participants to collect their opinion and the ground realities of such HNCTs in India. These interviews focused on the critical factors contributing to improve home health care in the Indian scenario. Major areas that would facilitate HNCT setting for India are identified and recommendations are discussed here for the key aspects of HNCT: (1) health care ecosystem; (2) regulatory environment and guidance; (3) training and oversight; (4) supply logistics; (5) safety monitoring; and (6) data privacy.

Health care ecosystem: DCTs may necessitate home visits by the mobile nursing staff and healthcare professionals to ensure that trial procedures are carried out in compliance to the protocol consistently. To ensure this, there is a need:

- for a robust ecosystem that includes healthcare professionals trained for remote visits, trial operators, trial investigators, industry sponsors, and home health care service providers;
- to engage effectively with patients and other stakeholders (trial experts, healthcare staff trained in HNCT, service providers, trial sponsor, research staff

and community care teams) through targeted interactions, that will also help generate awareness, explaining benefits and acceptance of HNCT, gaining clarity and buy-in on roles and responsibility of each stakeholder.

Regulatory environment and guidance to facilitate the adoption of HNCT are currently lacking. It would be imperative to embed the essential components of HNCT pertaining to trial documents, data collection activities, investigator responsibilities, and practical conduct of trial activities within holistic guidance for DCT conduct in India.

- The existing laws governing clinical trials, medical practice, data privacy, and telemedicine [Telemedicine Practice Guidelines 2020] can be expanded to be inclusive of the needs of HNCTs.
- Acknowledging home health care as a distinct segment of healthcare and developing dedicated systems to register home nursing service providers, review of HNCT solutions via site standard operating procedures (SOPs) and monitoring mechanism by IEC/IRBs, and adequate risk coverage by insurers, government, trial sponsors, and employers needs to be addressed from regulatory point of view.

Training and oversight will be critical to HNCT. An acute shortage of experienced providers who have technical knowledge about HNCTs and are trained for basic procedures, equipment handling, treatment administration, and effective communication is recognized.

- Adequate training of skilled nurses and technicians along with oversight from investigators can further enhance the feasibility of using home care and nursing in clinical trial conduct.
- Partnership between key stakeholders to build synergistic team of trial experts supporting HNCTs would be crucial.

Supply logistics for home nursing services entails greater complexities around shipping of supplies, management of remote activities, ensuring drug stability and appropriate storage facilities at the patient's home, minimizing unauthorized access to trial products, and ensuring that the integrity of the trial is maintained.

- Equipping home nursing staff with required technical and material support to manage remote healthcare delivery would be essential.
- Introduction of remote methodologies within traditional trial protocols will allow the investigators and sponsors to gain logistics experience, evaluate user compliance and compare the quality of data with traditional methodologies.

Safety monitoring procedures in a remote environment are challenging but critical for home nursing in DCTs. This is especially true in a new drug trial or in critical patients who need extensive monitoring with medical devices.

- Enhanced efforts will be needed for HNCT-specific safety-related training to the trial personnel, participants, and their caregivers.
- A protocol safety monitoring plan in view of the remote environment; a simple, user-friendly safety reporting system using mobile technology; robust team for timely review of safety data; and ensuring participant feedback through trial data design and implementation would be the key points for consideration.

Data privacy: All stakeholders involved in HNCTs would need to handle the collected data remotely through e-systems, thus raising concerns about data confidentiality and patient privacy. As discussed in the sections above, it would be imperative to have guidance around remote handling of data, data protection, integrity, and patient privacy, particularly addressing the HNCT set-up. It would be important to build confidence in the participant/caregivers through transparent and simple processes, such as the options to participate via home nursing in clinical trials or traditional clinical trials, continuous feedback and communications with options to change from one to the other.

- Engaging patient advocacy groups and participant voices in such discussions that involve patient choice would be core to the success of these elements.

Overall, a slow and focused change is needed from all stakeholders for the success of HNCT with a patient-centric approach. Quality assurance and confidence building measures need to be established by all stakeholders alike across the spectrum. Participants must be given options to participate with feedback mechanism in place with an option to revert to site must be available. Emphasis should also be on developing clear regulatory framework, trained HNCT personnel, remote infrastructure, robust safety monitoring systems, effective communication between trial stakeholders and patients, and developing specific guidance for all stakeholders on conduct of HNCTs are key to achieving successful DCTs. Engaging the Indian regulator proactively to discuss practical barriers, develop and establish a strong regulatory framework to oversee the processes of HNCT, conducting DCTs is important step.

2.10 Data Security, Data Privacy, and Ethical Considerations

The CTTI recommends that “technology selection should occur after the identification of the aspect or experience that the assessment is intended to measure and should offer a value over existing measurement approaches” [CTTI, 2018]. Data has become the new currency in today’s technologically advanced world. This, in turn, has made data security, data privacy, and ethical consideration some of the key challenges towards implementing a DCT.

As things stand today, the US FDA and EMA have clarified their guidance on key modalities of DCT. In India, the New Drug and Clinical Trial (NDCT) rules 2019 provides trial participants with the right to privacy and confidentiality through the Informed Consent Form (ICF) [CDSCO 2019; Singh et al, 2020]. When considering a DCT in India, these rules are no different. However, when it comes to any legislation

governing data protection or privacy, the country still has a lot to ponder on and wait for any such legislations to be implemented. There is still a need to legislate specific laws that can specifically address the challenges imposed by DCT. This includes: the risk of loss of data or its corruption and data attribution due to abundance of data from different sources including metadata and remote data collection; increased responsibility on patients and site staff due to remote/less frequent site visits; mapping the flow of data; clinical validation of wearable biometric devices; protecting patient privacy at source and during its transmission (e.g. Telemedicine, HNCT); and drug distribution to trial participants and its management.

Strengthening local laws for data collection, transmission, and storage; digital capability building and acquaintance of technology, training for use of advanced digital technology by all stakeholders would be a key to mitigate these risks and overcome the concerns with data privacy and security.

3 PATH FORWARD FOR DCT IN INDIA

Adopting decentralization in clinical trial conduct is accompanied by several advantages and opportunities that must be considered in order to fully leverage the advantages of a DCT. DCTs is touted to simplify clinical trial participation for trial participants as well as sites. It also improves the trial participant experience as well as decreases the burden on the patient. Sponsors can look forward to improving diversity and inclusion in clinical trials, improved data collection and data quality. The trial efficiency also can be improved with DCT (faster enrollment, generation of endpoints etc.). In the case of regulators and policy makers, DCT provides with the opportunity to better inform regulatory/reimbursement decisions and be confident in the increased applicability of research findings. The important challenges are defining the right balance between use of decentralized capabilities vs. onsite visits, interoperability of data capture systems used in DCT, training of sites, ECs, patients, participant's accessibility and understanding and availability of internet, or technology. Challenges around regulatory, legal, data privacy and confidentiality aspects will also need to be considered. The path forward is to enable a hybrid approach in trials where professionals trained in DCT capabilities provide help and acquaint participants, enhance technological understanding at all levels via trainings, access and awareness will be of immediate help, alongside gaining regulatory guidance and acceptance.

India is home to significant advances and talent in the areas of Information Technology, use of artificial intelligence/machine learning (AI/ML) and automation. The Government of India has been instrumental in leveraging the technology and implementing various reforms through its campaigns like *Make in India, Digital India, Start-Up India, Skill India*. The inherent advantages that India offers in clinical research such as skilled healthcare professionals, disease burden, medical infrastructure and balanced regulations, makes the ecosystem conducive for the conduct of DCTs. With the use of technology, one can follow '*Stay Local and Work Global'* approach. Decentralized trials will also open up employment opportunities for Indian clinical research professionals who can support various global roles through remote monitoring. India has clinical research professionals with required skillsets and talent, and this can lead to new roles being created or upgradation of the existing roles to serve the purpose of DCT.

In this post-COVID era, several capabilities within DCT domain are here to stay. There will be a gradual but directional shift from site-focused to patient-centered trials. Key potential opportunities will be collaborative approaches and incentives involving sponsors, researchers, patient advocacy groups, patients living with the particular condition being studied, and health systems – including regulations, quality measures and outcomes, or reimbursement strategies. Increased participation of India in globally conducted clinical trials using decentralization methods would also imply that Indian patients benefit from participation in the research of new molecules for unmet medical needs. Despite the operational challenges that may arise during decentralization, the benefits for all stakeholders has potential to outweigh the increased investment and associated risks.

With this DCT initiative, the ISCR intends to collaborate with all stakeholders to advocate, support and build an ecosystem for implementing these capabilities in India. This position paper attempts to sensitize and socialize different stakeholders regarding the concepts of DCTs, and dispel any misconception around these capabilities so as to bring in regulations that ensure appropriate oversight and similar standards of ethics, data quality and patient protection similar to the traditional trials. The key positive aspects backing this attempt are evolving regulatory understanding, acceptance and direction; progress towards technological maturity; investment and capability development; and most importantly, continued focus on patient-centricity.

4 SUMMARY OF RECOMMENDATIONS

The ISCR DCT position paper highlights the need of a comprehensive set of actions that needs to be taken to build the DCT ecosystem: *for example*, sensitization and awareness building across stakeholders; developing the necessary infrastructure, skillsets, capabilities; and India-specific regulatory guidance for the relevant DCT components, as highlighted in this document. This position paper can also serve as a guidance for all the stakeholders who intend to implement the decentralization components to the clinical trials.

General principles of DCT applicable to all components: ○ Building awareness and imparting necessary training to all stakeholders (Sponsors, Sites, ECs, Patient Advocacy Groups) on an ongoing basis. ○ Sensitize stakeholders on patient privacy and confidentiality, data privacy and integrity. ○ Invest in upskilling stakeholders involved in clinical trial design, conduct, and reporting so as to embrace DCT as the way forward for patient-centricity in clinical trials.
Specific recommendations on key components of DCT:
○ Global and local sponsors can evaluate whether a study is an appropriate fit for DCT capabilities to be embedded and include elements of DCT in appropriate clinical study protocols as appropriate. ○ Work with ICMR to enable CTRI to be user friendly so that it can effectively disseminate information about DCT capabilities in clinical trials to lay public.
○ Sensitize and socialize among all stakeholders existing framework of telemedicine (Telemedicine Practice Guidelines - Enabling Registered Medical Practitioners to Provide Healthcare Using Telemedicine, Medical Council of India, 25 March 2020) and work within its ambit for using telemedicine as a capability in a clinical trial (short term). ○ Advocate on inclusion of broader use of telemedicine in clinical trials with the policy makers (long term).
○ To work within the ambit of existing IT Rules governing the use of digital and social media for participant recruitment. ○ To make information available to all stakeholders with regards to the guardrails available for participant recruitment and retention; how to addresses ethical concerns; use of advertisements; data privacy; and other India-specific nuances i.e. cultural, language, literacy rates.
○ Augmenting the existing regulations to allow e-signatures and validate the electronic consenting (e-consent) for clinical trials' participants. ○ Technology partners providing e-signature solutions to have e-KYC-based authentication that is compliant with applicable Indian IT regulations (IT Act 2000).
○ To bring in regulations/guidance to ease the importation requirements for eCOA devices (short term).

○ Facilitate and promote “Make in India” opportunities for eCOA tools (software and hardware) by Indian players through MSME (long term). ○ Sponsors to explore integration of Electronic Health/Medical Records for eCOA for faster and robust assessment reporting in clinical trials.
○ To work with relevant organizations (as applicable) to bring in standards and processes governing scope, operations and registrations of service providers for DCT (for e.g. home nursing, direct-to-patient provision of drug and allied supplies) in India.

5 ISCR DCT WORKING GROUP 2022

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